**NATURE REVIEWS IMMUNOLOGY – SCIENCE AND SOCIETY**

# The changing face of rheumatoid arthritis: sustained remission for all?

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## Preface

Earlier diagnosis and treatment, plus biological therapies, have transformed the outlook for many patients with rheumatoid arthritis. In the future new biomarkers for diagnosis, prognosis and therapeutic response will further improve outcomes. Additionally, pre-clinical diagnosis and tolerogenic therapies could provide sustained remission for some individuals, although ethical and societal challenges must also be addressed before rheumatoid arthritis becomes 'yesterday's disease'.

## Introduction

Rheumatoid arthritis affects 580,000 people in the United Kingdom, with a further 26,000 people developing the disease annually [1]. Similar

prevalence and incidence figures apply to most developed countries. Over the past decade, new treatment paradigms and therapeutic approaches have transformed the disease from a chronic, disabling condition, frequently requiring palliative measures, to a potentially curable illness wherein sufferers retain their independence, quality of life and contribution to society [2]. However, despite this dramatic turnaround in outlook , several scientific, societal and ethical issues must be resolved before rheumatoid arthritis becomes a disease of the past. These encompass the need for early recognition, the ability to provide a firm diagnosis and prognosis in the earliest disease stages and the ability to optimise treatment for the individual patient.

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In this article, I review the changing face of rheumatoid arthritis treatment, the need for biomarkers to guide ever earlier diagnosis and treatment and attempt to predict the future approaches for the management of rheumatoid arthritis. My main focus is the societal implications of these changes, rather than the underpinning science, which has recently been reviewed elsewhere.[3]

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**The consequences of rheumatoid arthritis**

Rheumatoid arthritis is a chronic inflammatory disease of the synovium, a delicate membrane that lines the non-weight bearing surfaces of the joint [4]. In rheumatoid arthritis, the synovium becomes infiltrated with chronic inflammatory cells (Figure 1). The resident fibroblasts adopt a 'quasi-malignant' phenotype with up-regulation of oncogenes, inhibition of apoptosis and secretion of cytokines, chemokines and enzymes that reinforce the inflammation and catalyse joint destruction. The resulting

'pannus' acquires the ability to invade and destroy adjacent articular cartilage [5]. Activation of osteoclasts in peri-articular bone leads to resorption and 'erosions', a radiological hallmark of the disease [6]. Similar processes affect the synovium lining tendon sheaths resulting in tendon weakness and rupture, responsible for the characteristic deformities of rheumatoid arthritis. Rheumatoid arthritis can also involve organs such as the lung, leading to inflammation and fibrosis, and the systemic effects of rheumatoid arthritis include osteoporosis, anaemia, and profound fatigue. Serious collateral damage takes the form of premature atherosclerosis, which accounts for the reduced lifespan of patients with severe rheumatoid arthritis as a consequence of heart attacks and strokes [7].

Up to a third of patients with rheumatoid arthritis stop working within 2 years of disease onset as a consequence of these dramatic changes [8]. Reduced physical function initially reflects joint inflammation itself but, beyond the first few years, physical impairment correlates more closely with joint damage. Because damage is irreversible, functional loss is permanent and associated with a significantly reduced quality of life. In addition to heart attacks and strokes, rheumatoid arthritis patients also suffer frequent infections, a consequence of both the disease itself and the drugs used to treat it. Other iatrogenic complications include peptic ulcer disease, bone marrow suppression and liver damage. In short, rheumatoid arthritis is a devastating disease that affects the whole individual, reducing their contribution to society, destroying their quality of life and shortening their lifespan. In the UK, the estimated costs of rheumatoid arthritis include £560 million a year in healthcare costs plus

£1.8 billion in sick leave and work-related disability [1]. Until the disease is eradicated, there will remain a very significant unmet personal and societal need.

**Heterogeneity and biomarkers**

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Few clinically useful biomarkers exist for rheumatoid arthritis in terms of diagnosis, prognosis or treatment response (Box 1). It is a polygenic disease, probably with various environmental triggers [9] (Figure 2). Symptoms can develop at different rates and in different joints, from 16 years of age to old age. There are also several disease mimics, particularly post-infectious syndromes such as reactive arthritis but also other chronic joint diseases with a lesser propensity to cause rapid damage. The discovery of antibodies against citrullinated peptide antigens (anti-citrullinated peptide antibodies (ACPA)) has improved diagnostic accuracy for 'seropositive' rheumatoid arthritis patients (about two thirds of patients carry this autoantibody) but a significant proportion of patients who eventually develop rheumatoid arthritis cannot be diagnosed at symptom onset [10]. These individuals carry the label 'undifferentiated arthritis' until further disease progression allows them to be distinguished from other types of inflammatory arthritis.

Among patients with definite early rheumatoid arthritis there is a spectrum of disease outcomes, ranging from relatively benign disease to aggressive disease, in which x-ray damage appears within months of

diagnosis. Autoantibodies, particularly ACPA, tend to associate with more aggressive disease but this is by no means inevitable, and other prognostic markers are similarly non-specific. Consequently most patients cannot be given an accurate prognosis at disease onset with respect to ultimate joint damage.

Currently we cannot predict which patients will respond well to particular anti-rheumatic therapies. Therefore, each patient is managed according to a predetermined treatment algorithm until inflammation is adequately controlled (see below). Even with modern treatment approaches some patients will experience significant delay until their disease is brought under optimal control, when first-line drugs fail to provide relief.

**The changing face of treatment**

The traditional management of rheumatoid arthritis adopted the so-called pyramid approach. Initial symptoms were managed with non-steroidal anti-inflammatory drugs (NSAIDs), which relieved symptoms but did not prevent cartilage and bone damage. Damage on x-rays triggered the prescription of disease-modifying anti-rheumatic drugs (DMARDs), such as gold, penicillamine, hydroxychloroquine, sulphasalazine and methotrexate. To a greater or lesser degree these retarded (but didn't prevent) joint damage. A characteristic feature of rheumatoid arthritis is that even highly effective drugs tend to lose their benefit with time, and a succession of DMARDs would be prescribed until there were none left to try. The third and final tier of treatment involved cytotoxic chemotherapy with drugs such as azathioprine and cyclophosphamide, or experimental

approaches such as thoracic duct drainage. Glucocorticoids were the mainstay of treatment in long-standing rheumatoid arthritis, although their potent anti-inflammatory benefits were counterbalanced by numerous metabolic and immunosuppressive side effects [11].

During the 1980s and 1990s, with the recognition that joint damage was irreversible, DMARDs (usually sulphasalazine or methotrexate) were prescribed earlier in disease [12]. Failure of a DMARD signalled its replacement, or addition ('step-up' combination therapy) of an alternative drug. However, several trials demonstrated that effective inflammation control during early rheumatoid arthritis minimised subsequent joint damage and destruction, apparently transforming the disease to a milder phenotype. Because DMARDs take many weeks to work and the response of the patient is unpredictable, this 'window of opportunity' led to the use of 'step-down' therapy. To avoid missing the 'window', multiple drugs were initiated at diagnosis, including temporary glucocorticoids [13-15]. Once inflammation was suppressed, drug doses could be tapered.

The development of disease activity measures, such as the disease activity score utilising 28 joints (DAS28), has resulted in modified strategies whereby treatment is adjusted to maintain a target level of disease activity, usually remission or low disease activity (treatment-to-target strategies)[16]. Trials of different strategies have confirmed that initial combination therapy controls disease more rapidly with reduced x-ray damage in the medium term. Physical function is well preserved in the short-term, regardless of the exact strategy adopted, however,

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emphasising the overarching importance of tight disease control in optimising outcomes **[Au: OK?]** [17, 18].

The development of biological therapies heralded one of the most dramatic changes in outlook for patients with established rheumatoid arthritis. New pathogenic insights, alongside the monoclonal antibody revolution, led to the licensing of a succession of biological therapies that target specific aspects of the disease process. Following the advent of tumour necrosis factor (TNF) blockade in the early 1990s, B-cell depletion, co-stimulation blockade and interleukin-6 receptor blockade have each offered new, 'targeted' approaches to therapy (Box 2). These drugs effectively control the symptoms and signs **[au: what exactly do you mean by signs? Isn't this the same as symptoms?]** of rheumatoid arthritis, even in patients with relatively advanced disease. Of major significance, they substantially retard and frequently halt joint damage. Nonetheless, up to 50% of patients with established rheumatoid arthritis do not respond to these drugs, and only a relatively small proportion achieve complete remission of disease activity [19].

Initially biological therapies were reserved for patients who had failed all conventional DMARDS, but their potency and particularly their ability to arrest joint damage led to trials in early rheumatoid arthritis with remission rates as high as 50% [20]. However, these drugs are orders of magnitude more expensive than conventional DMARDs and their side effect profiles include serious and opportunistic infections. Furthermore,

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**Comment [n2]:** We tend to use signs to refer to objective features, such as joint swelling – as opposed to symptoms such as pain and joinst stiffness. Symptoms and signs is also a term used by drug regulators.

around 30% of patients with early rheumatoid arthritis achieve low disease activity with methotrexate alone [21, 22].

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**Early biologics for all?**

Until clinically useful biomarkers of diagnosis, prognosis and therapeutic response are identified, some rheumatoid arthritis patients will accrue early joint damage and downstream disability. Recent studies have attempted to determine the 'disability-equivalent' of a 'quantum' of x-ray damage and suggest that all damage matters [23]. Furthermore, several studies suggest that, for a given level of disease activity, more damage will accrue with traditional DMARDs than with biological therapy [24].

This has strengthened calls for the use of biological therapies in patients with early rheumatoid arthritis. Studies of such strategies indicate that a proportion of patients can discontinue the biological therapy within a year or two, maintaining disease remission on traditional DMARDs or perhaps not requiring further treatment at all [25]. Counterarguments focus on the costs of such an approach and the fact that a proportion of patients will be over-treated and exposed unnecessarily to the side effects of biological drugs.

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Control of rheumatoid arthritis in its early stages is associated with long-term financial savings, in terms of future drug therapy and a reduced need for in-patient rehabilitation and orthopaedic surgery on damaged joints [26]. Continued employment also can offset the up-front costs, depending on the type of economic modelling used [27]. Furthermore,

patients with well-controlled rheumatoid arthritis suffer fewer infections than those with active disease, potentially offsetting the risks associated with the early use of biological therapies. In addition, rapid and effective control of inflammation should minimise the incidence of premature heart disease and stroke, with additional significant cost savings. Therefore, the universal use of step-down biological therapy in early rheumatoid arthritis has several attractive features but remains highly controversial.

**'Pre rheumatoid arthritis'**

It has been shown repeatedly that the time to first treatment influences the ultimate outcome for patients with rheumatoid arthritis. In line with the 'window of opportunity', patients who present to a rheumatologist and receive treatment within weeks of symptom onset have better long-term outcomes than those that experience treatment delay [28]. Furthermore, studies are now starting to address whether the treatment of undifferentiated arthritis prevents, or delays the progression to, rheumatoid arthritis. For example, administration of methotrexate to patients with undifferentiated arthritis **OK?** delayed progression to rheumatoid arthritis, at least in those who carried ACPA, and the developing disease appeared less aggressive in those individuals [29]. Co-stimulation blockade also reduced autoantibody titres and, possibly, radiographical damage at this stage of disease [30]. In type 1 diabetes, a related autoimmune disease, administration of CD3-specific monoclonal antibody therapy at disease onset has been shown to delay progression of disease for at least 18 months, with many patients remaining effectively insulin independent during this time [31]. Such approaches could re-induce

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self-tolerance to autoantigen, switching off the disease process and offering a potential cure [32].

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The delay to treatment has a profound effect on the burden of rheumatoid arthritis to both the individual and society. At present in the UK, approximately 10% of patients with rheumatoid arthritis commence treatment within 3 months of symptom onset. Doubling that proportion to 20% should become cost-neutral to the UK National Health Service (NHS) after 9 years, in addition to significant productivity gains for the economy [1]. The factors responsible for treatment delay (the current median time is 9 months from first symptoms) reflect either patient delay in reporting symptoms to their GP, or GP delay in referral to secondary care [33]. In the UK, the second of these is being effectively addressed by appropriate GP education and rapid-access early arthritis clinics, and it is now the patient delay that most threatens an optimal outcome [34]. A public awareness campaign may address this but, because musculoskeletal pain is so ubiquitous and the presentation of rheumatoid arthritis so variable, the message must be carefully worded. In the US, the balance between patient and GP/internist delay varies by Centre and geographical location but managed care regulations may also discourage referral to a rheumatologist, potentially delaying treatment. **[Au: OK?]**

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Serum samples from individuals who ultimately develop rheumatoid arthritis clearly show that immune tolerance may be broken many years before clinical disease presentation. Thus, autoantibodies may be present in blood samples collected ten years or more prior to diagnosis, with a

subsequent rise in the expression levels of C-reactive protein and other pro-inflammatory mediators [35-39]. Arthroscopic studies have also demonstrated synovitis in clinically 'silent' joints at disease presentation [40]. So, even encouraging individuals to report early symptoms may miss the critical time period **[Au: for clarity, it might be worth specific exactly when the critical time period (at disease onset?)]** for restoring immune tolerance, which may be during the asymptomatic, pre-clinical disease stage.

If it were possible to identify individuals with 'pre-rheumatoid arthritis', several exciting possibilities would ensue. These include simple measures such as lifestyle advice, incorporating smoking cessation and healthy eating, although there is currently no evidence that modifying these rheumatoid arthritis risk factors would protect from disease development. [41]. Very early intervention with DMARDs or biological therapies recapitulates earlier arguments around early rheumatoid arthritis but, in preclinical disease, milder drugs could be effective. Recently, a brief intervention with glucocorticoids was shown to reduce autoantibody levels but did not inhibit progression to rheumatoid arthritis [42]. A particularly attractive option might be approaches such as the induction of mucosal tolerance using a mixture of joint antigens; although thus far not effective in established rheumatoid arthritis, this is potentially a safe and effective way to stop the developing disease in its tracks, [43, 44].

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Because the heritability of rheumatoid arthritis is less than that of type 1 diabetes, screening family members would identify just a small proportion

of those in the earliest disease stages. Population screening for ACPA would identify a proportion of those destined to develop seropositive rheumatoid arthritis but miss seronegative disease, and those in whom autoantibodies develop later [45]. Genetic screening for polymorphisms strongly associated with rheumatoid arthritis such as HLA-DRB1 shared epitope alleles, and the C1858T single nucleotide polymorphism in protein tyrosine phosphatase, non-receptor type 22 (PTPN22) could be incorporated into a 'risk equation' along with serological and demographic factors. However, such an approach would require robust validation, as well as substantial debate around the associated ethical issues. The accuracy would not be 100%, but the potential risk identified would be life-long, providing a cohort of at-risk but healthy individuals. Furthermore even therapies that appear safe, such as mucosal tolerance induction, may not be risk-free. The lack of in vitro models of rheumatoid arthritis immunopathology that enable risk prediction, or of animal models that provide an accurate risk assessment for human therapy are limiting in this regard, and therefore the optimal way forward may not be obvious [46].

**Imaging rheumatoid arthritis**

New imaging approaches are providing novel insights into rheumatoid arthritis pathogenesis, while also providing a window to early and pre-clinical disease. Similar to arthroscopy, ultrasound and magnetic resonance imaging (MRI) in early rheumatoid arthritis often reveals sub-clinical inflammation in apparently unaffected joints and may also provide sensitive prognostic indicators [47-51]. MRI is expensive and requires

significant infrastructure, but musculoskeletal ultrasound (MSUS) is becoming widely adopted by rheumatologists as a routine adjunct to clinical examination. In early arthritis clinics, MSUS provides a useful diagnostic aid and could provide a means of screening individuals at high risk of developing rheumatoid arthritis, perhaps annually. In this way, intervention could be targeted at patients with objective, albeit asymptomatic, evidence of early inflammatory joint disease.

**The future patient pathway**

So how might rheumatoid arthritis management look in the future (Figure 3)? Recent-onset joint symptoms and objective synovitis should trigger a screen for diagnostic, prognostic and treatment-response biomarkers. These parameters, along with imaging findings, will inform the most appropriate treatment plan. Patients with good prognosis rheumatoid arthritis and appropriate treatment response biomarkers may receive methotrexate and expect an excellent outcome. Others may require immediate biological therapy. In most patients, the symptoms will come under rapid control, at which stage additional biomarkers may inform the decision of whether treatment could be tapered or stopped altogether. Currently, about 40% of patients in remission experience disease flare after therapy withdrawal but biomarkers of true disease remission versus drug-induced disease suppression should facilitate targeted therapy reduction [52, 53].

Population screening may allow the identification of individuals at high risk of developing rheumatoid arthritis. After appropriate counselling, such

individuals could be offered lifestyle advice and perhaps specific therapies, including mucosal tolerance approaches, with the hope of permanent disease remission. **[Au: is this not a bit strong? Perhaps 'with the hope of permanent disease remission' is more accurate??]** Alternatively, such patients may undergo further annual screening with imaging. The identification of synovitis could then trigger prescription of drugs such as hydroxychloroquine, or a brief course of glucocorticoids, in an attempt to delay or prevent progression to rheumatoid arthritis [54, 55]. Clearly this area is ripe for research and these suggestions are highly speculative.

Compared to current management, economic resource will be invested in the early and pre-clinical stages of rheumatoid arthritis, including screening strategies and biomarkers, and away from palliative measures, including joint surgery. Our target for rheumatoid arthritis patients should be 'normal health' and the development of disability a signal of management failure. To achieve this, early and aggressive remission-inducing treatment, potentially incorporating tolerance inducing strategies, will become the norm. Earlier in this article I referred to the 'quasi-malignant' phenotype of rheumatoid arthritis. Our quest for managing earlier disease, and our evolving treatment strategies utilising drug combinations, now have strong parallels with oncological treatment paradigms.

**Conclusions**

Rheumatoid arthritis provides a model for potentially reversible autoimmunity **[Au: OK?]** which, inadequately treated, causes joint damage, long term disability, impaired quality of life, reduced lifespan and a large societal burden. Over the past twenty years earlier treatment and the use of biological therapies has greatly improved patient outlook but there still remains a large unmet patient need. Still earlier treatment will make a significant difference. However, scientific advances in terms of biomarker evaluation and preclinical disease identification could lead to a step change in prognosis. There also remain several fascinating questions around rheumatoid arthritis pathogenesis, the answers to which could also improve outcomes (Box 3).

**Comment [n5]:** I prefer immuno-inflammation because, in established disease, autoimmunity may be less relevant – there is now uncontrolled chronic inflammation. I haven't really emphasised this in the article, so use autoimmunity if you prefer

*Box 1. Current rheumatoid arthritis biomarkers and gaps in knowledge.*

**Diagnostic biomarkers**

- anti-CCP
- rheumatoid factor

Gaps:
Biomarkers needed for 'seronegative' RA

**Prognostic biomarkers**

- serological: ACPA, rheumatoid factor
- genetic: shared epitope (related to ACPA generation), sulphoxidation status[56]
- radiological: joint damage due to RA at first presentation
- other: high CRP at presentation

Gaps:
Lack of sensitivity and specificity.

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**Therapeutic biomarkers**

- autoantibodies: seropositive patients may be more likely to respond to rituximab and less likely to respond to TNFα blockade (ref – manuscript under review)
- other potential biomarkers (transcriptional profiles, synovial biomarkers, multi protein arrays) have been studied in relatively small patient numbers

Gaps:
None are validated or replicated.
Most associate with degree of response rather than response vs lack of response, eg at present there are no predictors for primary non-response to anti-TNF.
Synovial biomarkers of mechanistic interest but currently unlikely to be broadly useful clinically because few units perform synovial biopsy

**Remission biomarkers**

- Lack of synovitis on imaging (MSUS, MRI).

Limitations:
Requires infrastructure.
Does not correlate with ability to stop therapy without precipitating flare

**Tolerance biomarkers**

- None identified in autoimmune disease.

Gaps
Essential to develop/monitor tolerogenic therapies
May also be useful for monitoring disease tapering for patients in remission

*Box 2. Current biological therapies for rheumatoid arthritis*

**TNF antagonists:**
*infliximab*
chimeric monoclonal antibody
neutralises TNFα
binds soluble and cell surface TNFα
administered by intravenous infusion every 8 weeks following loading doses

*etanercept*
recombinant dimeric fusion protein of p75 TNF receptor and hinge, CH2 and CH3 of human IgG1
neutralises TNFα
binds cell surface TNFα with lower affinity than monoclonal antibodies
administered by weekly subcutaneous injection

*adalimumab*
fully human monoclonal antibody
neutralises TNFα
binds soluble and cell surface TNFα
administered by subcutaneous injection every other week

*golimumab*
fully human monoclonal antibody
neutralises TNFα
binds soluble and cell surface TNFα

administered by monthly subcutaneous injection

*certolizumab pegol*
PEGylated humanised FAB fragment. No Fc.
neutralises TNFα
binds soluble and cell surface TNFα
administered by subcutaneous injection every other week following loading dose

**Anti-B cell therapy**
*Rituximab*
Chimaeric monoclonal antibody
Binds to CD20 and lyses CD20-expressing target cells
Administered as a course of 2 intravenous infusions, which can be repeated according to disease activity (usually approximately every 6 months)

**Costimulation blockade**
Abatacept
Fusion protein between the extracellular domain of CTLA4 and a modified hinge, CH2 and CH3 of human IgG1
Binds CD80 and CD86 in competition with CD28, inhibiting T-cell activation (costimulation blockade)
Administered by monthly intravenous infusion after loading doses

**Anti-IL6 receptor therapy**
*Tocilizumab*
Humanised monoclonal antibody
Binds soluble and cell surface bound IL6 receptor, inhibiting IL-6 signalling
Administered by monthly intravenous infusion

Box 3. Unanswered aetiopathogenic questions in rheumatoid arthritis

Areas of current and future research with potential therapeutic impact

Improved markers of 'pre-RA' – early identification of 'at risk' individuals, enabling 'preventative' studies
Window of opportunity – what is/are the pathological correlates?
Therapeutic 'escape' – what underlies loss of therapeutic response. ?similar to tumour 'escape' in malignancy
Methotrexate – identification of mode of action and efficacy biomarkers, to optimise therapy with this 'anchor' drug and develop related compounds
Biomarkers of diagnosis to enable rapid diagnosis
Biomarkers of prognosis to assist targeted treatment
Biomarkers of therapeutic response to optimise choice of therapy
Biomarkers of true remission (imaging and blood) to assist with therapy tapering
Biomarkers of tolerance induction to inform withdrawal of therapy

**Figure Legends**

Figure 1. The Pathology of rheumatoid arthritis. In rheumatoid arthritis, the synovial membrane becomes infiltrated with a wide variety of inflammatory cell types, which synergise to cause joint destruction. T cells are clearly important, as evidenced by the genes associated with rheumatoid arthritis (see Figure 2) **[Au: associations of RA with what? Please specify]** [57]. In particular, TH17 cells may orchestrate synovitis and damage via interactions with dendritic cells, macrophages and B cells [58]. By contrast, the function of regulatory T cells appears to be impaired in rheumatoid arthritis **[Au: OK?]** [59]. Macrophages are also key players and their presence correlates with symptoms, perhaps via secretion of critical inflammatory mediators [60]. The success of B cell-specific antibody therapy attests to the importance of B cells in rheumatoid arthritis pathogenesis. In addition to autoantibody secretion, B cells present antigen to T cells and stimulate synovial fibroblasts via secretion of cytokines such as lymphotoxin-β (LTβ) and tumour necrosis factor (TNF). In some patients, well-formed lymphoid follicles are present in the synovium, suggestive of local antigen presentation, whereas in other patients B cells are present in aggregates and scattered more diffusely[61]. Synovial fibroblasts are key players in joint damage via the secretion of matrix metalloproteinases and cathepsins. Initially, they are activated by the inflammatory micro-environment but subsequently take on a semi-autonomous, 'quasi-malignant' phenotype [62]. Bone damage is caused by the convergence of multiple signals upon osteoclast precursors in the subchondral bone, inducing their differentiation and maturation [63].

**Comment [n6]:** Omit joints

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Important cells that are omitted from this Figure include synovial mast cells and plasma cells.

*Figure 2 – The aetiology of rheumatoid arthritis and timelines of disease onset.*

Several genetic susceptibility loci have now been associated with rheumatoid arthritis [57]. *HLADRB1* remains the strongest but other genes are associated with several different autoimmune diseases. Some of these (such as PTPN22 and CTLA4) are immunoregulatory, emphasising a primary disruption of immune regulation in families with autoimmunity. Cigarette smoking is strongly associated with seropositive (but not seronegative) rheumatoid arthritis. Several studies support a gene–environment interaction whereby smoking triggers the production of ACPA in individuals who carry the 'shared epitope' (A)[64]. Evidence associating caffeine consumption and obesity with rheumatoid arthritis is less consistent [41]. A 'Mediterranean' diet and diets rich in fruit and vegetables appear to protect against rheumatoid arthritis, possibly via a beneficial effect of olive and fish oils, and anti-oxidants, respectively. Alcohol may also protect [65], whereas evidence for a protective effect of oestrogens is inconsistent.

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Retrospective studies demonstrate the presence of rheumatoid factor and/or ACPA for up to 15 years before clinical rheumatoid arthritis (B). Levels of acute phase proteins, cytokines and chemokines start to rise during the final few years before the disease presents (D). The trigger(s) for this period of gradually increasing inflammation that culminates in

clinical rheumatoid arthritis has not been identified but, anecdotally, patients report infections, trauma and stress as preceding factors (C). At disease presentation, joint imaging will demonstrate inflammation in joints that are not yet symptomatic (E).

*Figure 3. The future rheumatoid arthritis patient pathway.*

Individuals presenting with joint pain will undergo joint imaging and will be tested for a range of biomarkers (column 2). If rheumatoid arthritis is confirmed they will receive biomarker-guided treatment, to ensure rapid and safe efficacy. Management will follow 'treatment-to-target' principles, aiming for disease remission (see text). Imaging may be used to confirm the lack of synovitis. At this stage, further biomarkers will guide the tapering of therapy, to avoid subsequent disease flares during the attainment of 'drug-free remission' in some patients.

Individuals with a strong family history of rheumatoid arthritis, or in whom screening has revealed a strong genetic predisposition with or without ACPA may choose to modify their lifestyles (column 1). They may also choose to receive a 'tolerogenic' intervention such as mucosal exposure to collagen or other joint autoantigens. Such therapy may be monitored using biomarkers of tolerance induction and followed by annual imaging.

Others may simply choose to undergo annual imaging of hands and feet (the most common target joints for rheumatoid arthritis). If such screening reveals early synovitis then they will follow the synovitis pathway outlined above (path A).

1. The National Audit Office in http://www.nao.org.uk/publications/0809/services_for_people_with_rheum.aspx (2009).
2. Strand, V., Kimberly, R. & Isaacs, J.D. Biologic therapies in rheumatology: lessons learned, future directions. *Nat Rev Drug Discov* **6**, 75-92 (2007).
3. Cooles, F.A.H. & Isaacs, J. Treating to re-establish tolerance in inflammatory arthritis - lessons from other diseases. . *Best Pract Res Clin Rheumatol* (2010).
4. Pratt, A.G., Isaacs, J.D. & Mattey, D.L. Current concepts in the pathogenesis of early rheumatoid arthritis. *Best Pract Res Clin Rheumatol* **23**, 37-48 (2009).
5. Chang, S.K., Gu, Z. & Brenner, M.B. Fibroblast-like synoviocytes in inflammatory arthritis pathology: the emerging role of cadherin-11. *Immunol Rev* **233**, 256-66.
6. Walsh, N.C. & Gravallese, E.M. Bone remodeling in rheumatic disease: a question of balance. *Immunol Rev* **233**, 301-12.
7. Gabriel, S.E. Cardiovascular morbidity and mortality in rheumatoid arthritis. *Am J Med* **121**, S9-14 (2008).
8. The National Institute for Healthcare and Clinical Excellence, in http://www.nice.org.uk/nicemedia/pdf/CG79NICEGuideline.pdf (2009).
9. Klareskog, L., Catrina, A.I. & Paget, S. Rheumatoid arthritis. *Lancet* **373**, 659-72 (2009).
10. Pruijn, G.J., Wiik, A. & van Venrooij, W.J. The use of citrullinated peptides and proteins for the diagnosis of rheumatoid arthritis. *Arthritis Res Ther* **12**, 203.
11. Hoes, J.N., Jacobs, J.W., Verstappen, S.M., Bijlsma, J.W. & Van der Heijden, G.J. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. *Ann Rheum Dis* **68**, 1833-8 (2009).
12. Fries, J.F. Current treatment paradigms in rheumatoid arthritis. *Rheumatology (Oxford)* **39 Suppl 1**, 30-5 (2000).
13. Mottonen, T. et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* **353**, 1568-73 (1999).
14. Landewe, R.B. et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. *Arthritis Rheum* **46**, 347-56 (2002).
15. Rantalaiho, V. et al. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. *Arthritis Rheum* **60**, 1222-31 (2009).
16. van der Heijde, D.M., van 't Hof, M., van Riel, P.L. & van de Putte, L.B. Development of a disease activity score based on judgment in clinical practice by rheumatologists. *J Rheumatol* **20**, 579-81 (1993).
17. Grigor, C. et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* **364**, 263-9 (2004).
18. Goekoop-Ruiterman, Y.P. et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* **146**, 406-15 (2007).
19. van Vollenhoven, R.F. Treatment of rheumatoid arthritis: state of the art 2009. *Nat Rev Rheumatol* **5**, 531-41 (2009).
20. Emery, P. et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid


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arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* **372**, 375-82 (2008).
21. van der Kooij, S.M. et al. Limited efficacy of conventional DMARDs after initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. *Ann Rheum Dis* **66**, 1356-62 (2007).
22. van Vollenhoven, R.F. et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. *Lancet* **374**, 459-66 (2009).
23. Smolen, J.S., Aletaha, D., Grisar, J.C., Stamm, T.A. & Sharp, J.T. Estimation of a numerical value for joint damage-related physical disability in rheumatoid arthritis clinical trials. *Ann Rheum Dis* (2009).
24. Aletaha, D. et al. Rheumatoid arthritis joint progression in sustained remission is determined by disease activity levels preceding the period of radiographic assessment. *Arthritis Rheum* **60**, 1242-9 (2009).
25. Quinn, M. et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomised, double-blind, placebo-controlled trial. *Arth Rheum* **52**, 27-35 (2005).
26. da Silva, E., Doran, M.F., Crowson, C.S., O'Fallon, W.M. & Matteson, E.L. Declining use of orthopedic surgery in patients with rheumatoid arthritis? Results of a long-term, population-based assessment. *Arthritis Rheum* **49**, 216-20 (2003).
27. van den Hout, W.B. et al. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. *Arthritis Rheum* **61**, 291-9 (2009).
28. van der Kooij, S.M. et al. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. *Ann Rheum Dis* **68**, 914-21 (2009).
29. van Dongen, H. et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* **56**, 1424-32 (2007).
30. Emery, P. et al. Impact of T-cell costimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: a clinical and imaging study of abatacept (the ADJUST trial). *Ann Rheum Dis* **69**, 510-6.
31. Keymeulen, B. et al. Insulin Needs after CD3-Antibody Therapy in New-Onset Type 1 Diabetes. *New Engl J Med* **352**, 2598-2608 (2005).
32. Isaacs, J. T cell immunomodulation-the Holy Grail of therapeutic tolerance. *Curr Opin Pharmacol* **7**, 418-25 (2007).
33. Feldman, D.E. et al. Delay in consultation with specialists for persons with suspected new-onset rheumatoid arthritis: a population-based study. *Arthritis Rheum* **57**, 1419-25 (2007).
34. Kumar, K. et al. Delay in presentation to primary care physicians is the main reason why patients with rheumatoid arthritis are seen late by rheumatologists. *Rheumatology (Oxford)* **46**, 1438-40 (2007).

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35. Nielen, M.M. et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum* **50**, 380-6 (2004).
36. Nielen, M.M. et al. Increased levels of C-reactive protein in serum from blood donors before the onset of rheumatoid arthritis. *Arthritis Rheum* **50**, 2423-7 (2004).
37. Jorgensen, K.T. et al. Cytokines, autoantibodies and viral antibodies in premorbid and postdiagnostic sera from patients with rheumatoid arthritis: case-control study nested in a cohort of Norwegian blood donors. *Ann Rheum Dis* **67**, 860-6 (2008).
38. Karlson, E.W. et al. Biomarkers of inflammation and development of rheumatoid arthritis in women from two prospective cohort studies. *Arthritis Rheum* **60**, 641-52 (2009).
39. Kokkonen, H. et al. Up-regulation of cytokines and chemokines predates the onset of rheumatoid arthritis. *Arthritis Rheum* **62**, 383-391 (2010).
40. Kraan, M.C. et al. Asymptomatic synovitis precedes clinically manifest arthritis. *Arthritis Rheum* **41**, 1481-8 (1998).
41. Oliver, J.E. & Silman, A.J. What epidemiology has told us about risk factors and aetiopathogenesis in rheumatic diseases. *Arthritis Res Ther* **11**, 223 (2009).
42. Bos, W.H., Dijkmans, B.A., Boers, M., van de Stadt, R.J. & van Schaardenburg, D. Effect of dexamethasone on autoantibody levels and arthritis development in patients with arthralgia: a randomised trial. *Ann Rheum Dis* **69**, 571-4.
43. Landewe, R.B. et al. Intranasal administration of recombinant Human Cartilage glycoprotein-39 as a treatment for rheumatoid arthritis: A Phase II, multicenter, double-blind, randomized, placebo-controlled, parallel group dose-finding trial. *Ann Rheum Dis* (2009).
44. Cooles, F.A.H. & Isaacs, J. Treating to re-establish tolerance in inflammatory arthritis - lessons from other diseases. *Best Pract Res Clin Rheumatol* **in press** (2010).
45. Bos, W.H. et al. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. *Ann Rheum Dis* **69**, 490-4 (2010).
46. Bykerk, V.P. & Hazes, J.M. When does rheumatoid arthritis start and can it be stopped before it does? *Ann Rheum Dis* **69**, 473-5 (2010).
47. Wakefield, R.J. et al. Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease. *Ann Rheum Dis* **63**, 382-5 (2004).
48. Sheane, B.J., Beddy, P., O'Connor, M., Miller, S. & Cunnane, G. Targeted ultrasound of the fifth metatarsophalangeal joint in an early inflammatory arthritis cohort. *Arthritis Rheum* **61**, 1004-8 (2009).
49. Tamai, M. et al. A prediction rule for disease outcome in patients with undifferentiated arthritis using magnetic resonance imaging of the wrists and finger joints and serologic autoantibodies. *Arthritis Rheum* **61**, 772-8 (2009).
50. Haavardsholm, E.A., Boyesen, P., Ostergaard, M., Schildvold, A. & Kvien, T.K. Magnetic resonance imaging findings in 84 patients with early rheumatoid arthritis: bone marrow oedema predicts erosive progression. *Ann Rheum Dis* **67**, 794-800 (2008).


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51. Hetland, M.L. et al. MRI bone oedema is the strongest predictor of subsequent radiographic progression in early rheumatoid arthritis. Results from a 2-year randomised controlled trial (CIMESTRA). *Ann Rheum Dis* **68**, 384-90 (2009).
52. ten Wolde, S. et al. Randomised placebo-controlled study of stopping second-line drugs in rheumatoid arthritis. *Lancet* **347**, 347-52 (1996).
53. Burgoyne, C.H. et al. Abnormal T cell differentiation persists in patients with rheumatoid arthritis in clinical remission and predicts relapse. *Ann Rheum Dis* **67**, 750-7 (2008).
54. Verstappen, S.M. et al. The beneficial effects of a 3 week course of intramuscular glucocorticoid injections in patients with very early inflammatory polyarthritis: Results of the STIVEA trial. *Ann Rheum Dis* (2009).
55. Machold, K.P. et al. The Stop Arthritis Very Early (SAVE) trial, an international multicentre, randomised, double-blind, placebo-controlled trial on glucocorticoids in very early arthritis. *Ann Rheum Dis* **69**, 495-502 (2010).
56. Emery, P., Bradley, H., Arthur, V., Tunn, E. & Waring, R. Genetic factors influencing the outcome of early arthritis--the role of sulphoxidation status. *Br J Rheumatol* **31**, 449-51 (1992).
57. Barton, A. & Worthington, J. Genetic susceptibility to rheumatoid arthritis: an emerging picture. *Arthritis Rheum* **61**, 1441-6 (2009).
58. Miossec, P., Korn, T. & Kuchroo, V.K. Interleukin-17 and type 17 helper T cells. *N Engl J Med* **361**, 888-98 (2009).
59. Ehrenstein, M. et al. Compromised function of regulatory T cells in rheumatoid arthritis and reversal by anti-TNF alpha therapy. *J Exp Med* **200**, 277-85 (2004).
60. Hamilton, J.A. & Tak, P.P. The dynamics of macrophage lineage populations in inflammatory and autoimmune diseases. *Arthritis Rheum* **60**, 1210-21 (2009).
61. Manzo, A., Bombardieri, M., Humby, F. & Pitzalis, C. Secondary and ectopic lymphoid tissue responses in rheumatoid arthritis: from inflammation to autoimmunity and tissue damage/remodeling. *Immunol Rev* **233**, 267-85.
62. Aupperle, K.R. et al. Regulation of synoviocyte proliferation, apoptosis, and invasion by the p53 tumor suppressor gene. *Am J Pathol* **152**, 1091-8 (1998).
63. Takayanagi, H. Osteoimmunology and the effects of the immune system on bone. *Nat Rev Rheumatol* **5**, 667-76 (2009).
64. Kallberg, H. et al. Gene-gene and gene-environment interactions involving HLA-DRB1, PTPN22, and smoking in two subsets of rheumatoid arthritis. *Am J Hum Genet* **80**, 867-75 (2007).
65. Kallberg, H. et al. Alcohol consumption is associated with decreased risk of rheumatoid arthritis: results from two Scandinavian case-control studies. *Ann Rheum Dis* **68**, 222-7 (2009).

~~1. Office, N.A. in http://www.nao.org.uk/publications/0809/services_for_people_with_rheum.aspx (2009).~~
~~2. Strand, V., Kimberly, R. & Isaacs, J.D. Biologic therapies in rheumatology: lessons learned, future directions. *Nat Rev Drug Discov* **6**, 75-92 (2007).~~
~~3. Cooles, F.A.H. & Isaacs, J. Treating to re-establish tolerance in inflammatory arthritis--lessons from other diseases. . *Best Pract Res Clin Rheumatol* (2010).~~


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4. Pratt, A.G., Isaacs, J.D. & Mattey, D.L. Current concepts in the pathogenesis of early rheumatoid arthritis. *Best Pract Res Clin Rheumatol* **23**, 37-48 (2009).
5. Chang, S.K., Gu, Z. & Brenner, M.B. Fibroblast-like synoviocytes in inflammatory arthritis pathology: the emerging role of cadherin-11. *Immunol Rev* **233**, 256-66.
6. Walsh, N.C. & Gravallese, E.M. Bone remodeling in rheumatic disease: a question of balance. *Immunol Rev* **233**, 301-12.
7. Gabriel, S.E. Cardiovascular morbidity and mortality in rheumatoid arthritis. *Am J Med* **121**, S9-14 (2008).
8. Excellence, N.I.f.H.a.C. in http://www.nice.org.uk/nicemedia/pdf/CG79NICEGuideline.pdf (2009).
9. Klareskog, L., Catrina, A.I. & Paget, S. Rheumatoid arthritis. *Lancet* **373**, 659-72 (2009).
10. Pruijn, G.J., Wiik, A. & van Venrooij, W.J. The use of citrullinated peptides and proteins for the diagnosis of rheumatoid arthritis. *Arthritis Res Ther* **12**, 203.
11. Hoes, J.N., Jacobs, J.W., Verstappen, S.M., Bijlsma, J.W. & Van der Heijden, G.J. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. *Ann Rheum Dis* **68**, 1833-8 (2009).
12. Fries, J.F. Current treatment paradigms in rheumatoid arthritis. *Rheumatology (Oxford)* **39 Suppl 1**, 30-5 (2000).
13. Mottonen, T. et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* **353**, 1568-73 (1999).
14. Landewe, R.B. et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. *Arthritis Rheum* **46**, 347-56 (2002).
15. Rantalaiho, V. et al. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. *Arthritis Rheum* **60**, 1222-31 (2009).
16. van der Heijde, D.M., van 't Hof, M., van Riel, P.L. & van de Putte, L.B. Development of a disease activity score based on judgment in clinical practice by rheumatologists. *J Rheumatol* **20**, 579-81 (1993).
17. Grigor, C. et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* **364**, 263-9 (2004).
18. Goekoop-Ruiterman, Y.P. et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* **146**, 406-15 (2007).
19. van Vollenhoven, R.F. Treatment of rheumatoid arthritis: state of the art 2009. *Nat Rev Rheumatol* **5**, 531-41 (2009).
20. Emery, P. et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* **372**, 375-82 (2008).
21. van der Kooij, S.M. et al. Limited efficacy of conventional DMARDs after initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. *Ann Rheum Dis* **66**, 1356-62 (2007).

22. van Vollenhoven, R.F. et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. *Lancet* **374**, 459-66 (2009).
23. Smolen, J.S., Aletaha, D., Grisar, J.C., Stamm, T.A. & Sharp, J.T. Estimation of a numerical value for joint damage-related physical disability in rheumatoid arthritis clinical trials. *Ann Rheum Dis* (2009).
24. Aletaha, D. et al. Rheumatoid arthritis joint progression in sustained remission is determined by disease activity levels preceding the period of radiographic assessment. *Arthritis Rheum* **60**, 1242-9 (2009).
25. Quinn, M. et al. Very early treatment with infliximab in addition to methotrexate in early, poor prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomised, double-blind, placebo-controlled trial. *Arth Rheum* **52**, 27-35 (2005).
26. da Silva, E., Doran, M.F., Crowson, C.S., O'Fallon, W.M. & Matteson, E.L. Declining use of orthopedic surgery in patients with rheumatoid arthritis? Results of a long-term, population-based assessment. *Arthritis Rheum* **49**, 216-20 (2003).
27. van den Hout, W.B. et al. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. *Arthritis Rheum* **61**, 291-9 (2009).
28. van der Kooij, S.M. et al. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. *Ann Rheum Dis* **68**, 914-21 (2009).
29. van Dongen, H. et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* **56**, 1424-32 (2007).
30. Emery, P. et al. Impact of T-cell costimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: a clinical and imaging study of abatacept (the ADJUST trial). *Ann Rheum Dis* **69**, 510-6.
31. Keymeulen, B. et al. Insulin Needs after CD3-Antibody Therapy in New-Onset Type 1 Diabetes. *New Engl J Med* **352**, 2598-2608 (2005).
32. Isaacs, J. T cell immunomodulation-the Holy Grail of therapeutic tolerance. *Curr Opin Pharmacol* **7**, 418-25 (2007).
33. Feldman, D.E. et al. Delay in consultation with specialists for persons with suspected new-onset rheumatoid arthritis: a population-based study. *Arthritis Rheum* **57**, 1419-25 (2007).
34. Kumar, K. et al. Delay in presentation to primary care physicians is the main reason why patients with rheumatoid arthritis are seen late by rheumatologists. *Rheumatology (Oxford)* **46**, 1438-40 (2007).
35. Nielen, M.M. et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum* **50**, 380-6 (2004).
36. Nielen, M.M. et al. Increased levels of C-reactive protein in serum from blood donors before the onset of rheumatoid arthritis. *Arthritis Rheum* **50**, 2423-7 (2004).
37. Jorgensen, K.T. et al. Cytokines, autoantibodies and viral antibodies in premorbid and postdiagnostic sera from patients with rheumatoid arthritis:

case-control study nested in a cohort of Norwegian blood donors. *Ann Rheum Dis* **67**, 860-6 (2008).
38. Karlson, E.W. et al. Biomarkers of inflammation and development of rheumatoid arthritis in women from two prospective cohort studies. *Arthritis Rheum* **60**, 641-52 (2009).
39. Kokkonen, H. et al. Up-regulation of cytokines and chemokines predates the onset of rheumatoid arthritis. *Arthritis Rheum* **62**, 383-391 (2010).
40. Kraan, M.C. et al. Asymptomatic synovitis precedes clinically manifest arthritis. *Arthritis Rheum* **41**, 1481-8 (1998).
41. Oliver, J.E. & Silman, A.J. What epidemiology has told us about risk factors and aetiopathogenesis in rheumatic diseases. *Arthritis Res Ther* **11**, 223 (2009).
42. Bos, W.H., Dijkmans, B.A., Boers, M., van de Stadt, R.J. & van Schaardenburg, D. Effect of dexamethasone on autoantibody levels and arthritis development in patients with arthralgia: a randomised trial. *Ann Rheum Dis* **69**, 571-4.
43. Landewe, R.B. et al. Intranasal administration of recombinant Human Cartilage glycoprotein-39 as a treatment for rheumatoid arthritis: A Phase II, multicenter, double-blind, randomized, placebo-controlled, parallel-group dose-finding trial. *Ann Rheum Dis* (2009).
44. Cooles, F.A.H. & Isaacs, J. Treating to re-establish tolerance in inflammatory arthritis - lessons from other diseases. *Best Pract Res Clin Rheumatol* **in press** (2010).
45. Bos, W.H. et al. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. *Ann Rheum Dis* **69**, 490-4 (2010).
46. Bykerk, V.P. & Hazes, J.M. When does rheumatoid arthritis start and can it be stopped before it does? *Ann Rheum Dis* **69**, 473-5 (2010).
47. Wakefield, R.J. et al. Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease. *Ann Rheum Dis* **63**, 382-5 (2004).
48. Sheane, B.J., Beddy, P., O'Connor, M., Miller, S. & Cunnane, G. Targeted ultrasound of the fifth metatarsophalangeal joint in an early inflammatory arthritis cohort. *Arthritis Rheum* **61**, 1004-8 (2009).
49. Tamai, M. et al. A prediction rule for disease outcome in patients with undifferentiated arthritis using magnetic resonance imaging of the wrists and finger joints and serologic autoantibodies. *Arthritis Rheum* **61**, 772-8 (2009).
50. Haavardsholm, E.A., Boyesen, P., Ostergaard, M., Schildvold, A. & Kvien, T.K. Magnetic resonance imaging findings in 84 patients with early rheumatoid arthritis: bone marrow oedema predicts erosive progression. *Ann Rheum Dis* **67**, 794-800 (2008).
51. Hetland, M.L. et al. MRI bone oedema is the strongest predictor of subsequent radiographic progression in early rheumatoid arthritis. Results from a 2-year randomised controlled trial (CIMESTRA). *Ann Rheum Dis* **68**, 384-90 (2009).
52. ten Wolde, S. et al. Randomised placebo-controlled study of stopping second-line drugs in rheumatoid arthritis. *Lancet* **347**, 347-52 (1996).
53. Burgoyne, C.H. et al. Abnormal T cell differentiation persists in patients with rheumatoid arthritis in clinical remission and predicts relapse. *Ann Rheum Dis* **67**, 750-7 (2008).
54. Verstappen, S.M. et al. The beneficial effects of a 3-week course of intramuscular glucocorticoid injections in patients with very early

inflammatory polyarthritis: Results of the STIVEA trial. *Ann Rheum Dis* (2009).
55. Machold, K.P. et al. The Stop-Arthritis Very Early (SAVE) trial, an international multicentre, randomised, double-blind, placebo-controlled trial on glucocorticoids in very early arthritis. *Ann Rheum Dis* **69**, 495-502 (2010).
56. Emery, P., Bradley, H., Arthur, V., Tunn, E. & Waring, R. Genetic factors influencing the outcome of early arthritis--the role of sulphoxidation status. *Br J Rheumatol* **31**, 449-51 (1992).
57. Barton, A. & Worthington, J. Genetic susceptibility to rheumatoid arthritis: an emerging picture. *Arthritis Rheum* **61**, 1441-6 (2009).
58. Miossec, P., Korn, T. & Kuchroo, V.K. Interleukin-17 and type 17 helper T cells. *N Engl J Med* **361**, 888-98 (2009).
59. Ehrenstein, M. et al. Compromised function of regulatory T cells in rheumatoid arthritis and reversal by anti-TNF alpha therapy. *J Exp Med* **200**, 277-85 (2004).
60. Hamilton, J.A. & Tak, P.P. The dynamics of macrophage lineage populations in inflammatory and autoimmune diseases. *Arthritis Rheum* **60**, 1210-21 (2009).
61. Manzo, A., Bombardieri, M., Humby, F. & Pitzalis, C. Secondary and ectopic lymphoid tissue responses in rheumatoid arthritis: from inflammation to autoimmunity and tissue damage/remodeling. *Immunol Rev* **233**, 267-85.
62. Aupperle, K.R. et al. Regulation of synoviocyte proliferation, apoptosis, and invasion by the p53 tumor suppressor gene. *Am J Pathol* **152**, 1091-8 (1998).
63. Takayanagi, H. Osteoimmunology and the effects of the immune system on bone. *Nat Rev Rheumatol* **5**, 667-76 (2009).
64. Kallberg, H. et al. Gene-gene and gene-environment interactions involving HLA-DRB1, PTPN22, and smoking in two subsets of rheumatoid arthritis. *Am J Hum Genet* **80**, 867-75 (2007).
65. Kallberg, H. et al. Alcohol consumption is associated with decreased risk of rheumatoid arthritis: results from two Scandinavian case-control studies. *Ann Rheum Dis* **68**, 222-7 (2009).

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Box 1: RA biomarkers

**Diagnostic biomarkers**

- anti-CCP
- rheumatoid factor

Gaps:
Biomarkers needed for 'seronegative' RA

**Prognostic biomarkers**

- serological: ACPA, rheumatoid factor
- genetic: shared epitope (related to ACPA generation), sulphoxidation status
- radiological: joint damage due to RA at first presentation
- other: high CRP at presentation

Gaps:
Lack of sensitivity and specificity.

**Therapeutic biomarkers**

- autoantibodies: seropositive patients may be more likely to respond to rituximab and less likely to respond to TNFα blockade (ref – soon to be submitted review)
- other potential biomarkers (transcriptional profiles, synovial biomarkers, multi protein arrays) have been studied in relatively small patient numbers

Gaps:
None are validated or replicated.
Most associate with degree of response rather than response vs lack of response, eg at present there are no predictors for primary non-response to anti-TNF.
Synovial biomarkers of mechanistic interest but currently unlikely to be broadly useful clinically because few units perform synovial biopsy

**Remission biomarkers**

- Lack of synovitis on imaging (MSUS, MRI).

Limitations:
Requires infrastructure.
Does not correlate with ability to stop therapy without precipitating flare

**Tolerance biomarkers**

- None identified in autoimmune disease.

Gaps
Essential to develop/monitor tolerogenic therapies
May also be useful for monitoring disease tapering for patients in remission

Box 2

Current biological therapies for rheumatoid arthritis

**TNF antagonists:**

*infliximab*

chimeric monoclonal antibody
neutralises TNFα
binds soluble and cell surface TNFα
administered by intravenous infusion every 8 weeks following loading doses

*etanercept*

recombinant dimeric fusion protein of p75 TNF receptor and hinge, CH2 ad CH3 of human IgG1
neutralises TNFα
binds cell surface TNFα with lower affinity than monoclonal antibodies
administered by weekly subcutaneous injection

*adalimumab*

fully human monoclonal antibody
neutralises TNFα
binds soluble and cell surface TNFα
administered by subcutaneous injection every other week

*golimumab*

fully human monoclonal antibody
neutralises TNFα
binds soluble and cell surface TNFα
administered by monthly subcutaneous injection

*certolizumab pegol*

PEGylated humanised FAB fragment. No Fc.
neutralises TNFα
binds soluble and cell surface TNFα
administered by subcutaneous injection every other week following loading dose

**Anti-B cell therapy**

*Rituximab*

Chimaeric monoclonal antibody
Binds to CD20 and lyses CD20-expressing target cells
Administered by a course of 2 intravenous infusions, which can be repeated according to disease activity (usually approximately every 6 months)

**Costimulation blockade**

Abatacept

Fusion protein between the extracellular domain of CTLA4 and a modified hinge, CH2 and CH3 of human IgG1

Binds CD80 and CD86 in competition with CD28, inhibiting T-cell activation (costimulation blockade)

Administered by monthly intravenous infusion after loading doses

**Anti-IL6 therapy**

*Tocilizumab*

Humanised monoclonal antibody

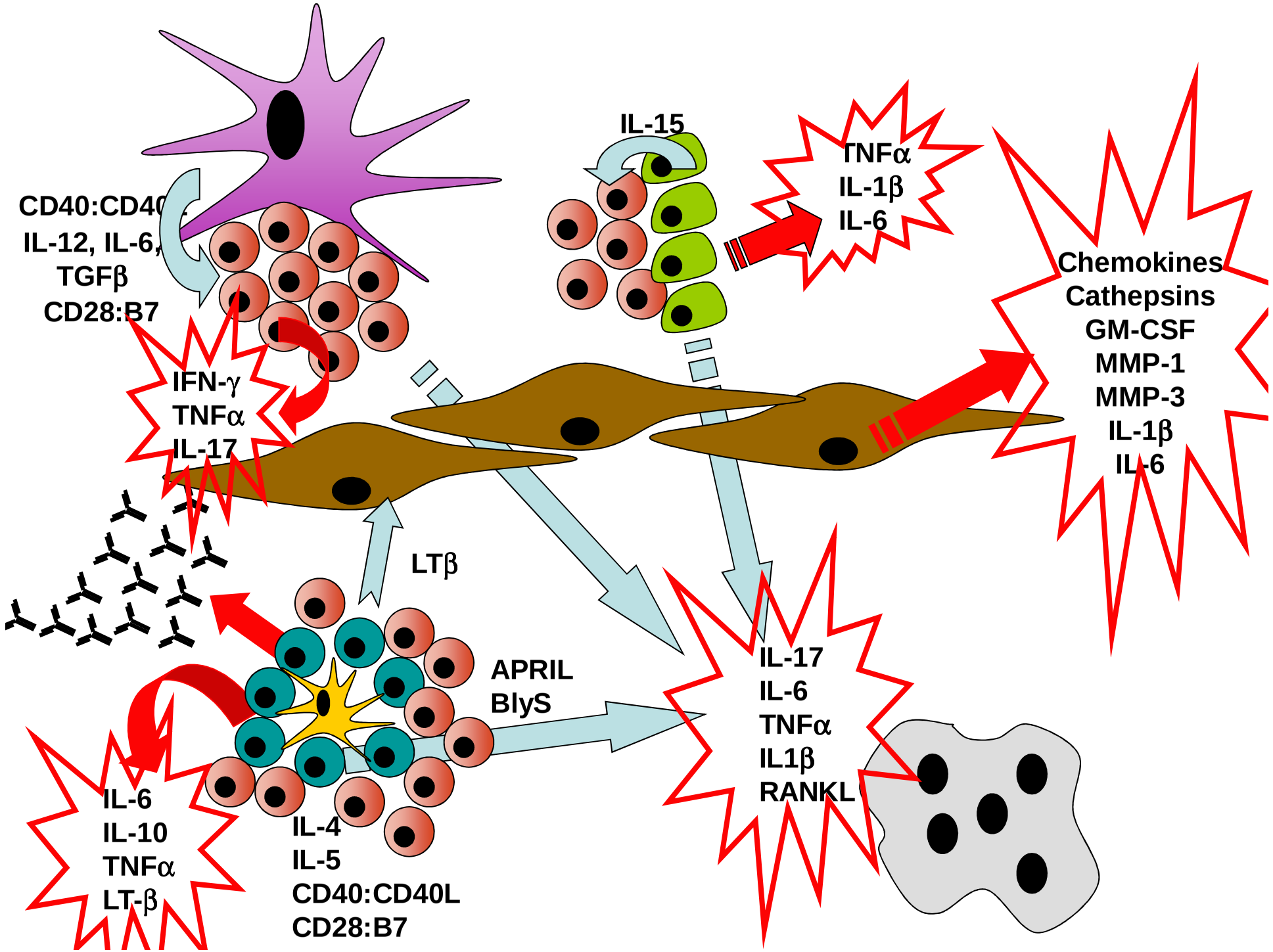
Binds soluble and cell surface bound IL6 receptor, inhibiting IL-6 signalling

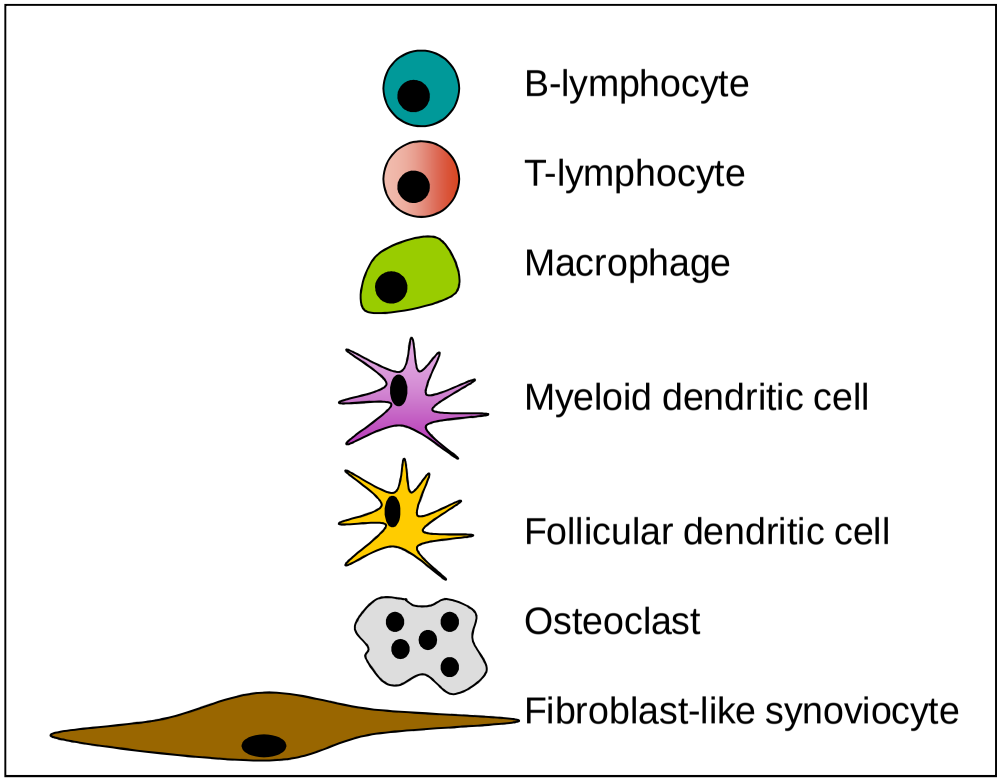
Administered by monthly intravenous infusion

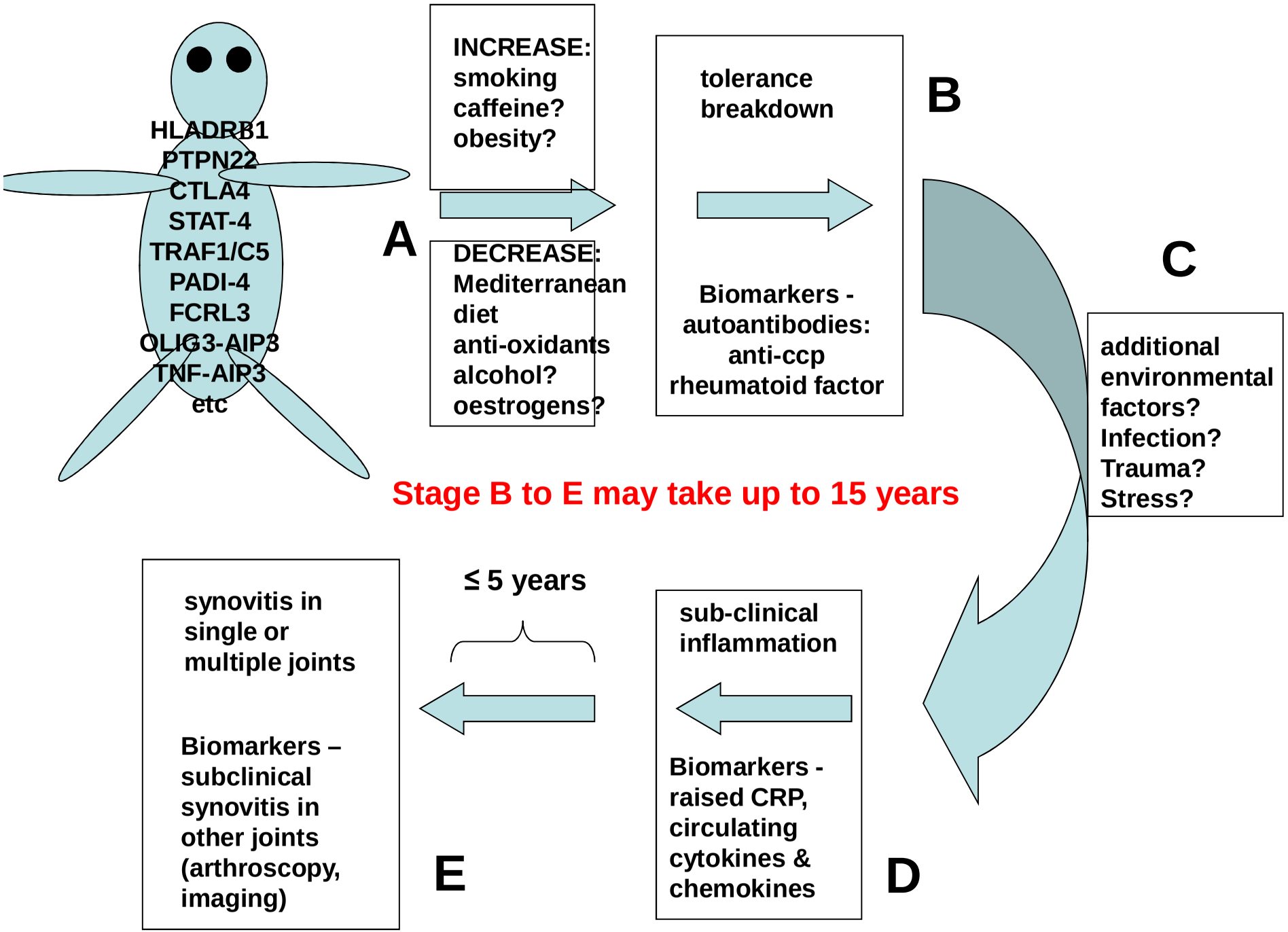
Box 3

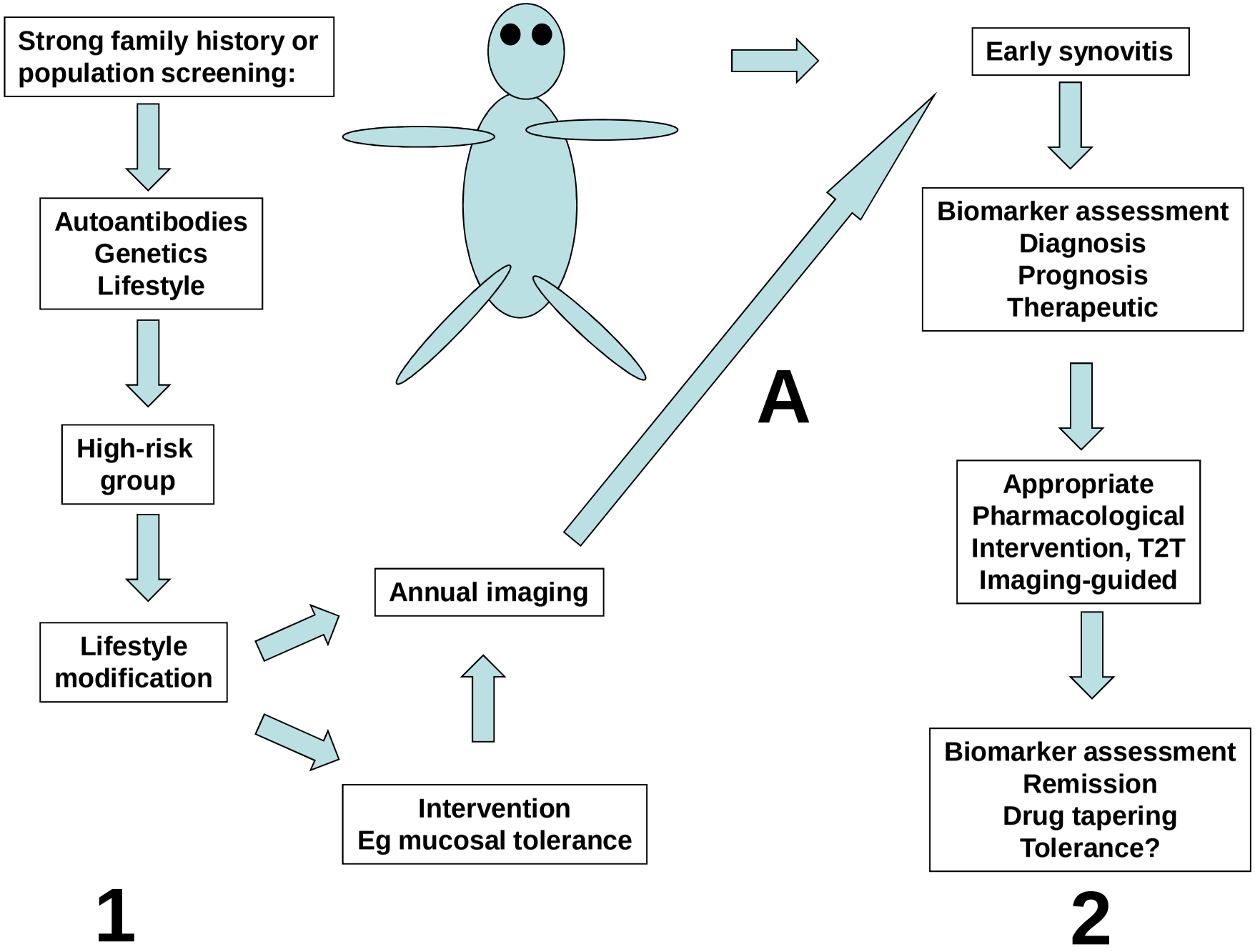
Areas of current and future research with potential therapeutic impact

Improved markers of 'pre-RA' – early identification of 'at risk' individuals, enabling 'preventative' studies
Window of opportunity – what is/are the pathological correlates?
Therapeutic 'escape' – what underlies loss of therapeutic response.
?similar to tumour 'escape' in malignancy
Methotrexate – identification of mode of action and efficacy biomarkers, to optimise therapy with this 'anchor' drug and develop related compounds
Biomarkers of diagnosis to enable rapid diagnosis
Biomarkers of prognosis to assist targeted treatment
Biomarkers of therapeutic response to optimise choice of therapy
Biomarkers of true remission (imaging and blood) to assist with therapy tapering
Biomarkers of tolerance induction to inform withdrawal of therapy


CD40:CD40L
IL-12, IL-6,
TGFβ
CD28:B7
IFN-γ
TNFα
IL-17
IL-15
TNFα
IL-1β
IL-6
Chemokines
Cathepsins
GM-CSF
MMP-1
MMP-3
IL-1β
IL-6
LTβ
APRIL
BlyS
IL-17
IL-6
TNFα
IL1β
RANKL
IL-6
IL-10
TNFα
LT-β
IL-4
IL-5
CD40:CD40L
CD28:B7


B-lymphocyte
T-lymphocyte
Macrophage
Myeloid dendritic cell
Follicular dendritic cell
Osteoclast
Fibroblast-like synoviocyte


HLADRB1
PTPN22
CTLA4
STAT-4
TRAF1/C5
PADI-4
FCRL3
OLIG3-AIP3
TNF-AIP3
etc
A
INCREASE:
smoking
caffeine?
obesity?
DECREASE:
Mediterranean diet
anti-oxidants
alcohol?
oestrogens?
tolerance breakdown
Biomarkers - autoantibodies:
anti-ccp
rheumatoid factor
B
C
additional environmental factors?
Infection?
Trauma?
Stress?
Stage B to E may take up to 15 years
≤ 5 years
synovitis in single or multiple joints
Biomarkers – subclinical synovitis in other joints (arthroscopy, imaging)
E
sub-clinical inflammation
Biomarkers - raised CRP, circulating cytokines & chemokines
D


Strong family history or population screening:
Autoantibodies
Genetics
Lifestyle
High-risk group
Lifestyle modification
Annual imaging
Intervention
Eg mucosal tolerance
1
A
Early synovitis
Biomarker assessment
Diagnosis
Prognosis
Therapeutic
Appropriate
Pharmacological
Intervention, T2T
Imaging-guided
Biomarker assessment
Remission
Drug tapering
Tolerance?
2