

Interleukin 10 treatment for rheumatoid arthritis

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Interleukin (IL) 10 looms as a highly promising treatment for rheumatoid arthritis (RA) because of its capacity to inhibit cellular immunity and deactivate macrophages. In RA, activated CD4 T helper cells and macrophages are believed to be the primary driving force behind joint inflammation. Synovial macrophages play a critical part in stimulating synovial inflammation. They produce abundant quantities of pro-inflammatory cytokines such as IL1 and tumour necrosis factor (TNF) α . The body attempts to keep the inflammatory response in check by upregulating the synthesis of endogenous inhibitors such as IL1 receptor antagonist (ra), soluble TNF receptors (TNFR), and IL10. These inhibitors act in concert to dampen the inflammatory response. IL10 is relatively unique in its ability to downregulate the production of multiple pro-inflammatory cytokines, leading to the notion that IL10 would be an effective treatment for RA.

Biology of IL10

Monocytes and macrophages produce IL10 when they are activated with the bacterial endotoxin lipopolysaccharide (LPS). There is an initial burst of pro-inflammatory cytokines (TNF α , IL1, IL6, and GM-CSF) followed later by a rise in IL10 synthesis.¹ LPS stimulated IL10 production requires both the synthesis of TNF α and IL1 as well as cognate interactions between monocytes and T cells.^{2,3} IL10 release from LPS stimulated monocytes may be increased by transforming growth factor (TGF) β , interferon (IFN) α , IFN β ,⁴⁻⁶ histamine⁷ and ligation of the Fc γ receptor I.⁸ On the other hand, LPS stimulated IL10 production may be inhibited by IL4, IFN γ ,^{9,10} and ligation of CD23, the low affinity IgE receptor.¹¹ IL10 and IL12 appear to be coordinately regulated in many of these experimental systems such that IL12 upregulates the synthesis of IL10 that controls the extent of the response.^{7,8}

T cells also produce IL10. This cytokine is a component of the overall T helper (Th) cell cytokine profile that has used to define specific Th cell subsets: Th0, Th1, and Th2. These subsets are readily distinguishable in mice in which Th1 cells secrete IL2, IFN γ , and TNF β and Th2 cells synthesise IL4, IL5, IL6, IL10, and IL13.¹² Precursor Th0 cells produce IL2, IFN γ , IL4, and IL10.¹² In mice, the differentiation of the immune response depends on the relative amounts of IL12 and IL4. Monocyte derived IL12 polarises the immune system towards a Th1 cellular response, while IL4 preferentially activates Th2 cells to stimulate B cell mediated humoral immunity.¹² Human Th cells overlap in their patterns of cytokine production and are termed Th1-like and Th2-

like. In humans, a Th cell phenotype in which high levels of IL10 are produced relative to IFN γ or IL2 appears to favour deactivation of an inflammatory response.¹³

IL10 exerts both stimulatory and inhibitory effects on a variety of cell types. The therapeutic potential of IL10 as an anti-inflammatory agent derives from its capacity to inhibit the monocyte/macrophage. IL10 has been shown in vitro to potently downregulate LPS induced production of TNF α , IL1, IL6, IL8, G-CSF, and GM-CSF.¹ It also inhibits LPS induced and hyaluronan induced synthesis of macrophage inflammatory protein (MIP) 1 α and MIP1 β , two members of the C-C family of chemokines.^{14,15} IL10 also suppresses macrophage synthesis of reactive oxygen intermediates¹⁶ and nitric oxide¹⁷ and blocks cyclooxygenase-2 dependent synthesis of interstitial collagenase and gelatinase B.¹⁸ Moreover, in monocyte cultures, IL10 has been shown to diminish cell surface expression of p75 TNF receptors and promote release of soluble p75 TNF receptors¹⁹ and soluble IL1ra.²⁰ Taken together, IL10 produces diverse anti-inflammatory effects.

T cell function is also regulated by IL10. The net effects of IL10 are to weaken a Th1 cellular response and strengthen a Th2 humoral response. IL10 inhibits Th1 cell production of IFN γ . This inhibitory effect is indirect and probably results from several mechanisms. Firstly, IL10 reduces the expression of HLA-DR on the surface of antigen presenting cells (APCs), interfering with antigen mediated T cell activation.^{1,21} IL10 also downregulates the expression of ICAM-1, CD80, and CD86 on the surface of APCs, which decreases co-stimulatory activity.²² Finally, IL10 abrogates IL12 driven Th1 cellular responses by decreasing the transcription of the p40 subunit of the IL12 receptor.²³

On the other hand, IL10 increases Th2 cell mediated humoral immunity by stimulating the growth and differentiation of B cells.²⁴⁻²⁶ B cells activated in culture by IL10 and anti-CD40 monoclonal antibody proliferate, differentiate into antibody secreting cells, and switch to IgA, IgG1, and IgE isotypes.²⁷ IL10 also augments IgG4 production.²⁷ The life of a B cell can be extended by IL10 through induction of bcl-2 protein.²⁸

IL10 mechanisms in animal models

Investigations in animal models have provided key insights into the biology of IL10. As IL10 inhibits Th1 cellular immunity, its presence in excessive amounts could theoretically pose an increased risk for infection. In mice, IL10 treatment inhibits the delayed type hypersensitivity reaction to *Leishmania major* antigen.²⁹

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and exacerbates *Candida albicans*³⁰ and *Listeria monocytogenes*³¹ infections. IL10 functions have also been examined in transgenic mice. Transgenic T cells that overproduce IL10 can lose their ability to mediate a Th1 dependent pathological response.²⁹ Mice bearing transgenic T cells with a high output of IL10 still mount a competent Th1 response to *L. major* infection,³² but show impaired control of mycobacterial infection.³³ Transgenic mice whose APCs are engineered to overproduce IL10 also show certain defects in cellular and humoral immunity and greater susceptibility to infection with *L. monocytogenes* and *L. major*.³⁴ Overall, these data suggest that IL10 plays an important part in host defence against intracellular pathogens.

The mechanisms of IL10 have been studied in several different animal models of autoimmunity, including experimental allergic encephalomyelitis (EAE) in rodents, non-obese diabetic (NOD) mice, murine type II collagen induced arthritis (CIA), and IL10 transgenic mice. IL10 can both inhibit and promote autoimmune disease in these models. In EAE, IL10 seems to exert a predominately inhibitory effect on disease. Clinical recovery from EAE is accompanied by increased CNS synthesis of IL10.³⁵ Treatment with IL10 abrogates the subsequent development of EAE during the initiation phase of disease, but has no therapeutic benefit on established EAE.³⁶ The functions of IL10 are more obscure in the NOD mouse. Whereas systemic IL10 administration in the NOD mouse prevents the development of diabetes,³⁷ transgenic mice whose pancreatic cells are engineered to overproduce IL10 are characterised by accelerated disease.^{38, 39} These contrasting effects illustrate the potential importance of environment (for example, systemic versus tissue) on the clinical outcome of cytokine therapy.

IL10 is a mediator of murine CIA. The development of murine CIA is associated with increasing IL10 expression by synovial cells and chondrocytes.⁴⁰ IL10 treatment suppresses the clinical manifestations of both early and established CIA and reduces the histological signs of joint inflammation, synovial tissue expression of TNF α and IL1 mRNA, and the destruction of articular cartilage and bone.^{41, 42} Treatment of murine CIA with high doses of IL12 augments IL10 synthesis and decreases joint inflammation,⁴³ exemplifying the coordinated regulation of these two cytokines. These animal studies have provided further basis for the clinical development of IL10 as a possible treatment for RA.

IL10 in RA

The cellular sources of IL10 in the rheumatoid synovium are macrophages and, to a lesser extent, T cells.⁴⁴ IL10 properties have been extensively investigated in ex vivo cultures of synovial tissue containing a mixture of synovial cells (fibroblast-like and macrophage-like) and lymphocytes. These cultures have been shown to produce IL10 as well as the pro-inflammatory cytokines TNF α , IL1, IL6, IL8, and GM-CSF.^{44, 45} Most of the IL10 in these

cultures derives from the macrophage-like cells. The pro-inflammatory cytokines themselves appear to trigger the synthesis of IL10 as evidenced by experiments in which adding TNF α or IL1 has been shown to augment IL10 production.⁴⁴ IL10 acts to curb the inflammatory response. Neutralisation of endogenous IL10 with anti-IL10 antibodies has been shown to increase the production of TNF α and IL1.⁴⁴ IL10 also inhibits the production of IL8, G-CSF, and GM-CSF in culture and IFN γ induced expression of HLA-DR, ICAM-1, and VCAM-1.⁴⁶ These results provide evidence for a tightly regulated cytokine network in which IL10 serves to inhibit synovial inflammation.

IL10 is also the product of synovial T cells. Most cloned T cells isolated from the rheumatoid joint display a T helper (Th) 1-like phenotype, and may produce IL10.⁴⁷ In fact, when stimulated with mitogens or growth factors, the majority of synovial T cell clones have been shown to produce both IL10 and IFN γ .⁴⁸ This pattern of cytokine production is compatible with the view that RA is a Th1 mediated pathological response.

IL10 may be immunostimulatory in the synovial microenvironment by promoting antibody production. In synoviocyte cultures, IL10 has been shown to upregulate the production of IgM rheumatoid factor (RF),⁴⁹ which may explain why IgM RF secreting B cells accumulate in the rheumatoid synovium.

Synovial fluid from patients with RA contains detectable levels of IL10 mRNA and protein.^{50, 51} The predominant source of IL10 in the synovial fluid is the mononuclear cell (MNC).^{51, 52} The addition of IL10 to synovial fluid cultures suppresses MNC production of TNF α , IL1, and GM-CSF, reduces MNC surface expression of HLA-DR, increases MNC surface expression of CD16 and CD64, and decreases spontaneous MNC proliferation.^{51, 52} IL10 also stimulates MNC expression of the surface p75 TNF receptor and the release of its soluble counterpart into the culture supernatant.⁵³

IL10 may be an important enhancer of cartilage growth. Conditioned media from antigen stimulated synovial fluid MNCs have been shown to inhibit proteoglycan synthesis by cultured cartilage explants, an effect largely dependent on TNF α and IL1.⁵² This inhibitory effect on proteoglycan synthesis is reversed by IL10.⁵²

The median serum level of IL10 is increased in patients with RA compared with that of healthy controls.⁵⁰ Blood MNCs from patients with RA spontaneously produce IL10 in culture⁵⁴ and represent the main source of circulatory IL10. Serum IL10 levels do not correlate with clinical measures of disease activity, but they are positively correlated with serum RF titres.⁵⁰ In culture, IL10 inhibits blood MNC production of TNF α , IL1, and IL6⁴⁵ as well as stimulates MNC release of soluble p75 TNF receptor.⁵³

Clinical applications of IL10 in RA

The first clinical studies of IL10 were undertaken to examine the safety and immunomodulatory

latory properties of this cytokine in 17 healthy persons. Single intravenous infusions of 1, 10 and 25 µg/kg of IL10 were observed to produce transient neutrophilia, monocytosis, and lymphopenia.⁵⁵ IL10 infusions also inhibited mitogen induced proliferation of peripheral blood MNCs and, in whole blood cultures, decreased LPS stimulated production of TNF α and IL1.⁵⁵ These single doses of IL10 did not cause significant toxicity.

A phase I dose escalating, double blind, placebo controlled phase I trial has been performed in 72 patients with active RA.⁵⁶ In this study, eligible subjects were treated with 0.5, 1.0, 5, 10, or 20 µg/kg of recombinant human IL10 or placebo, which was administered daily by subcutaneous injection. The only significant toxicity observed was thrombocytopenia in subjects receiving the highest IL10 doses. Four subjects in the 20 µg/kg dose group developed an asymptomatic, transient drop in platelet count below 100 000/mm³. The platelet counts rapidly normalised in each case after stopping the IL10 injections. In addition, IL10 treatment was associated with an increase in serum levels of soluble p55 and p75 TNFRs and IL1ra. Although the small sample sizes precluded any conclusions about clinical efficacy, a trend towards clinical improvement was noted in the 5 µg/kg dose group. Further trials are in progress to evaluate the clinical efficacy and safety of IL10 treatment for RA.

Concluding remarks

Advances in our understanding of the pathogenesis of RA have illuminated new therapeutic strategies that target cytokines involved in the inflammatory response. IL10 is a central participant in this inflammatory process. It functions primarily as an inhibitory cytokine to suppress Th1 mediated cellular responses and deactivate macrophages. Importantly, IL10 acts to diminish the production of pro-inflammatory cytokines such as TNF α and IL1, which are important mediators of joint inflammation in RA. The results from animal studies provide further support to the concept that IL10 administration could ameliorate the signs and symptoms of arthritis. Recombinant IL10 treatment is now being investigated in patients with RA. Its ultimate niche in the therapeutic armamentarium for RA remains to be seen, but cytokine modulation beyond the simple antagonism of TNF α and IL1 may be necessary to most effectively treat this diseased population.

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- 1 de Waal Malefyt R, Abrams J, Bennett B, Figdor CG, de Vries JE. Interleukin 10 (IL-10) inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes. *J Exp Med* 1991;174:1209-20.
- 2 Wanidworanun C, Strober W. Predominant role of tumor necrosis factor- α in human monocyte IL-10 synthesis. *J Immunol* 1993;151:6853-61.
- 3 Parry SL, Sebbag M, Feldmann M, Brennan FM. Contact with T cells modulates monocyte IL-10 production. Role of T cell membrane TNF- α . *J Immunol* 1997;158:3673-81.
- 4 Maeda H, Kuwahara H, Ichimura Y, Ohtsuki M, Kurakata S, Shiraiishi A. TGF- β enhances macrophage ability to produce IL-10 in normal and tumor-bearing mice. *J Immunol* 1995;155:4926-32.

- 5 Aman MJ, Tretter T, Eisenbeis I, Bug G, *et al.* Interferon- α stimulates production of IL-10 in activated CD4⁺T cells and monocytes. *Blood* 1996;87:4731-6.
- 6 Porriani AM, Gambi D, Reder AT. Interferon effects on interleukin-10 secretion. Mononuclear cell response to interleukin-10 is normal in multiple sclerosis patients. *J Neuroimmunol* 1995;61:27-34.
- 7 Elenkov IJ, Webster E, Papanicolaou DA, Fleisher TA, Chrousos GP, Wilder RL. Histamine potently suppresses human IL-12 and stimulates IL-10 production via H2 receptors. *J Immunol* 1998;161:2586-93.
- 8 Sutterwala FS, Noel GJ, Salgame P, Mosser DM. Reversal of proinflammatory responses by ligating the macrophage Fc γ receptor type I. *J Exp Med* 1998;188:217-22.
- 9 Chomarat P, Risoan M, Banchereau J, Miossec P. Interferon γ inhibits interleukin 10 production by monocytes. *J Exp Med* 1993;177:523-7.
- 10 Bonder CS, Finlay-Jones JJ, Hart PH. Interleukin-4 regulation of human monocyte and macrophage interleukin-10 and interleukin-12 production. Role of a functional interleukin-2 γ -chain. *Immunology* 1999;96:529-36.
- 11 Dugas N, Vouldoukis I, Becherel P, *et al.* Triggering of CD23b antigen by anti-CD23 monoclonal antibodies induces interleukin 10 production by human macrophages. *Eur J Immunol* 1996;26:1394-8.
- 12 Miossec P, van den Berg W. Th1/Th2 cytokine balance in arthritis. *Arthritis Rheum* 1997;40:2105-15.
- 13 Katsikis PD, Cohen SBA, Londei M, Feldmann M. Are CD4⁺ T_H1 cells pro-inflammatory or anti-inflammatory? The ratio of IL-10 to IFN- γ or IL-2 determines their function. *Int Immunol* 1995;7:1287-94.
- 14 Horton MR, Burdick MD, Strieter RM, Bao C, Noble PW. Regulation of hyaluronan induced chemokine gene expression by IL-10 and IFN- γ in mouse macrophages. *J Immunol* 1998;160:3023-30.
- 15 Sherry B, Espinoza M, Manogue KR, Cerami A. Induction of the chemokine β peptides, MIP-1 α and MIP-1 β , by lipopolysaccharide is differentially regulated by immunomodulatory cytokines γ IFN, IL-10, IL-4, and TGF- β . *Mol Med* 1998;4:648-57.
- 16 Bogdan C, Vodovotz Y, Nathan C. Macrophage deactivation by interleukin 10. *J Exp Med* 1991;174:1549-55.
- 17 Cenci E, Romani L, Mencacci A, *et al.* Interleukin-4 and interleukin-10 inhibit nitric oxide-dependent macrophage killing of *Candida albicans*. *Eur J Immunol* 1993;23:1034-8.
- 18 Mertz PM, DeWitt DL, Stetler-Stevenson WG, Wahl LM. Interleukin-10 suppression of monocyte prostaglandin H synthase-2. *J Biol Chem* 1994;269:21322-9.
- 19 Joyce DA, Gibbons DP, Green P, Steer JH, Feldmann M, Brennan FM. Two inhibitors of pro-inflammatory cytokine release, interleukin-10 and interleukin-4, have contrasting effects on release of soluble p75 tumor necrosis factor receptor by cultured monocytes. *Eur J Immunol* 1994;24:2699-705.
- 20 Jenkins JK, Malyak M, Arend WP. The effects of interleukin-10 on interleukin-1 receptor antagonist and interleukin-1 β production in human monocytes and neutrophils. *Lymphokine and Cytokine Research* 1994;13:47-54.
- 21 Fiorentino DF, Zlotnik A, Vicira P, *et al.* IL-10 acts on the antigen-presenting cell to inhibit cytokine production by Th1 cells. *J Immunol* 1991;146:3444-51.
- 22 Willems F, Marchant A, Delville J, *et al.* Interleukin-10 inhibits B7 and intercellular adhesion molecule-1 expression on human monocytes. *Eur J Immunol* 1994;24:1007-9.
- 23 Aste-Amezaga M, Ma X, Sartori A, Trinchieri G. Molecular mechanisms of the induction of IL-12 and its inhibition by IL-10. *J Immunol* 1998;160:5936-44.
- 24 Rousset F, Garcia E, Defrance T, *et al.* Interleukin 10 is a potent growth and differentiation factor for activated human B lymphocytes. *Proc Natl Acad Sci USA* 1992;89:1890-3.
- 25 Thompson-Snipes L, Dhar V, Bond MW, Mosmann TR, Moore KW, Rennick DM. Interleukin 10: a novel immunostimulatory factor for mast cells and their progenitors. *J Exp Med* 1991;173:507-10.
- 26 MacNeil IA, Suda T, Moore KW, Mosmann TR, Zlotnick A. IL-10, a novel growth factor for mature and immature T cells. *J Immunol* 1990;145:4167-73.
- 27 Jeannin P, Lecoanet S, Delneste Y, Gauchat J, Bonnefoy J. IgE versus IgG4 production can be differentially regulated by IL-10. *J Immunol* 1998;160:3555-61.
- 28 Levy Y, Brouet J. Interleukin-10 prevents spontaneous death of germinal center B cells by induction of the bc1-2 protein. *J Clin Invest* 1994;93:424-8.
- 29 Powrie F, Menon S, Coffman RL. Interleukin-4 and interleukin-10 synergize to inhibit cell-mediated immunity in vivo. *Eur J Immunol* 1993;23:2223-9.
- 30 Tonnetti L, Spaccapelo R, Cenci E, *et al.* Interleukin-4 and interleukin-10 exacerbate candidiasis in mice. *Eur J Immunol* 1995;25:1559-65.
- 31 Kelly JP, Bancroft GJ. Administration of interleukin-10 abolishes innate resistance to *Listeria monocytogenes*. *Eur J Immunol* 1996;26:356-64.
- 32 Hagenbaugh A, Sharma S, Dubinett SM, *et al.* Altered immune responses in interleukin 10 transgenic mice. *J Exp Med* 1997;185:2101-10.
- 33 Murray PJ, Wang L, Onufryk C, Tepper RI, Young RA. T cell-derived IL-10 antagonizes macrophage function in mycobacterial infection. *J Immunol* 1997;158:315-21.

- 34 Groux H, Cottrez F, Rouleau M, *et al.* A transgenic model to analyze the immunoregulatory role of IL-10 secreted by antigen-presenting cells. *J Immunol* 1999;162:1723-9.
- 35 Kennedy MK, Torrance DS, Picha KS, Mohler KM. Analysis of cytokine mRNA expression in the central nervous system of mice with experimental autoimmune encephalomyelitis reveals that IL-10 mRNA expression correlates with recovery. *J Immunol* 1992;149:2496-505.
- 36 Rott O, Fleischer B, Cash E. Interleukin-10 prevents experimental allergic encephalomyelitis in rats. *Eur J Immunol* 1994;24:1434-40.
- 37 Pennline KJ, Roque-Gaffney E, Monahan M. Recombinant human IL-10 prevents the onset of diabetes in the nonobese diabetic mouse. *Clin Immunol Immunopathol* 1994;71:169-75.
- 38 Wogensens L, Lee M, Sarvetnik N. Production of interleukin 10 by islet cells accelerates immune-mediated destruction of β cells in nonobese diabetic mice. *J Exp Med* 1994;179:1379-84.
- 39 Lee M, Wogensens L, Shizuru J, Oldstone MBA, Sarvetnik N. Pancreatic islet production of murine interleukin-10 does not inhibit immune-mediated tissue destruction. *J Clin Invest* 1994;93:1332-8.
- 40 Kasama T, Strieter RM, Lukacs NW, Lincoln PM, Burdick MD, Kunkel SL. Interleukin 10 expression and chemokine regulation during the evolution of murine type II collagen induced arthritis. *J Clin Invest* 1995;95:2868-76.
- 41 Walmsley M, Katsikis PD, Abney E, *et al.* Interleukin-10 inhibition of the progression of established collagen-induced arthritis. *Arthritis Rheum* 1996;39:495-503.
- 42 Joosten LAB, Lubberts E, Durez P, *et al.* Role of interleukin-4 and interleukin-10 in murine collagen-induced arthritis. Protective effect of interleukin-4 and interleukin-10 treatment on cartilage destruction. *Arthritis Rheum* 1997;40:249-60.
- 43 Kasama T, Yamazaki J, Hanaoka R, *et al.* Biphasic regulation of the development of murine type II collagen-induced arthritis by interleukin-12. Possible involvement of endogenous interleukin-10 and tumor necrosis factor alpha. *Arthritis Rheum* 1999;42:100-9.
- 44 Katsikis PD, Chu C-Q, Brennan FM, Maini RN, Feldmann M. Immunoregulatory role of interleukin 10 in rheumatoid arthritis. *J Exp Med* 1994;179:1517-27.
- 45 Chomarat P, Banchereau J, Miossec P. Differential effects of interleukins 10 and 4 on the production of interleukin-6 by blood and synovium monocytes in rheumatoid arthritis. *Arthritis Rheum* 1995;38:1046-54.
- 46 Kawakami A, Eguchi K, Matsuoka N, *et al.* Inhibitory effects of interleukin-10 on synovial cells of rheumatoid arthritis. *Immunology* 1997;91:252-9.
- 47 Cohen SBA, Katsikis PD, Chu C, *et al.* High level of interleukin-10 production by the activated T cell population within the rheumatoid synovial membrane. *Arthritis Rheum* 1995;38:946-52.
- 48 Morita Y, Yamamura M, Kawashima M, *et al.* Flow cytometric single-cell analysis of cytokine production by CD4+ T cells in synovial tissue and peripheral blood from patients with rheumatoid arthritis. *Arthritis Rheum* 1998;41:1669-76.
- 49 Reparon-Schuijt CC, van Esch WJE, van Kooten C, Levarht EWN, Breedveld FC, Verweij CL. Functional analysis of rheumatoid factor-producing B cells from the synovial fluid of rheumatoid arthritis patients. *Arthritis Rheum* 1998;41:2211-20.
- 50 Cush JJ, Splawski JB, Thomas R, *et al.* Elevated interleukin-10 levels in patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:96-104.
- 51 Isomäki P, Luukkainen R, Saario R, Toivanen P, Punnonen J. Interleukin-10 functions as an antiinflammatory cytokine in rheumatoid synovium. *Arthritis Rheum* 1996;39:386-95.
- 52 van Roon JAG, van Roy JLAM, Gmelig-Meyling FHJ, Lafaber FPJG, Bijlsma JWJ. Prevention and reversal of cartilage degradation in rheumatoid arthritis by interleukin-10 and interleukin-4. *Arthritis Rheum* 1996;39:829-35.
- 53 Hart PH, Hunt EK, Bonder CS, Watson CJ, Finlay-Jones JJ. Regulation of surface and soluble TNF receptor expression on human monocytes and synovial fluid macrophages by IL-4 and IL-10. *J Immunol* 1996;157:3672-80.
- 54 Llorente L, Richaud-Patin Y, Fior R, *et al.* In vivo production of interleukin-10 by non-T cells in rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus. A potential mechanism of B lymphocyte hyperactivity and autoimmunity. *Arthritis Rheum* 1994;37:1647-55.
- 55 Chernoff AK, Granowitz EV, Shapiro L, *et al.* A randomized, controlled trial of IL-10 in humans. Inhibition of inflammatory cytokine production and immune responses. *J Immunol* 1995;154:5492-9.
- 56 Maini RN, Paulus H, Breedveld FC, *et al.* rHuIL-10 in subjects with active rheumatoid arthritis (RA): A phase I and cytokine response study. *Arthritis Rheum* 1997;40(suppl):S224.