REPORT

Potential new targets in arthritis therapy: interleukin (IL)-17 and its relation to tumour necrosis factor and IL-1 in experimental arthritis

M I Koenders, L A B Joosten, W B van den Berg

Ann Rheum Dis 2006;**65**(Suppl III):iii29–iii33. doi: 10.1136/ard.2006.058529

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterised by chronic joint inflammation and destruction. Interleukin (IL)-17 is a T cell cytokine expressed in the synovium and synovial fluid of patients with RA. IL-17 is a potent inducer of various cytokines such as tumour necrosis factor (TNF) and IL-1. IL-17 has been shown to have additive or even synergistic effects with TNF and IL-1 during the induction of cytokine expression and joint damage in vitro and in vivo. TNF α and IL-1 are considered powerful targets in the treatment of RA because of their leading role in driving the enhanced production of cytokines, chemokines, and degradative enzymes. Besides anti-TNF and anti-IL-1 therapies, whose clinical efficacy is now established, new targets have been proposed for RA which is not responding to conventional treatments. This paper discusses the role of IL-17 in experimental arthritis and its interrelationship with TNF and IL-1, currently the most targeted cytokines in the treatment of RA. IL-17 is involved in both initiation and progression of murine experimental arthritis. Studies have shown that IL-17 not only synergises with TNF, but also enhances inflammation and destruction independent of IL-1 and TNF. On the basis of these studies, the authors propose IL-17 as an interesting additional target in the treatment of RA.

Interleukin (IL)-17 is a proinflammatory cytokine produced by activated memory T cells. IL-17 producing T cells were thought to differentiate from T helper (Th) 1 cells, but recently they have been considered a separate Th lineage (Th 17) promoted by IL-23 (fig 1).^{1,2}

IL-17 AS A PATHOGENIC FACTOR IN RA

Despite the beneficial role of IL-17 in host defense against some infectious pathogens, this T cell factor has been associated with autoimmune diseases such as Crohn's disease, multiple sclerosis, systemic sclerosis, systemic lupus erythematosus, and rheumatoid arthritis (RA). IL-17 is spontaneously produced by RA synovial membrane cultures,³ and elevated levels have been detected in the synovial fluid of patients with RA.^{3–7} In vitro studies have shown that IL-17, via activation of nuclear factor (NF)- κ B, stimulates production of proinflammatory cytokines and chemokines such as IL-1, tumour necrosis factor (TNF), IL-6, IL-8, and macrophage inflammatory protein (MIP)-1 α .^{8–10} Furthermore, IL-17 stimulates the expression of matrix metalloproteinases (MMPs) and receptor activator of NF- κ B ligand (RANKL).^{5,11–13} Interestingly, IL-17 has been shown to act in synergy with IL-1 and TNF during cytokine and chemokine production by cultured synovial fibroblasts,^{14–16} and IL-17

synergises with TNF to induce cartilage destruction in vitro.¹⁷ These observations suggest an important role for IL-17 in the pathogenesis of RA (fig 2).

INVOLVEMENT OF IL-17 IN EXPERIMENTAL ARTHRITIS

IL-17 in initiation of experimental arthritis

IL-17 is an important cytokine for antigen specific T cell responses and T cell dependent antibody production.¹⁸ A marked suppression of the incidence of collagen induced arthritis (CIA) has been found in IL-17-deficient mice, with IL-17-deficiency resulting in reduced arthritis severity, accompanied by impairment of responses of collagen specific T and B cells.¹⁹ In addition, an important role for IL-17 in the initiation of experimental arthritis was shown in IL-1 receptor antagonist (IL-1Ra) deficient mice, which spontaneously develop arthritis due to excessive IL-1 signalling. In IL-1Ra^{-/-} mice, IL-17 expression is greatly enhanced in the arthritic joints and in supernatants of stimulated lymphocytes, and spontaneous arthritis no longer develops in IL-1Ra deficient mice which also lack IL-17.²⁰ Blockage of endogenous IL-17 in collagen type II immunised DBA-1 mice before onset of CIA has also been shown to reduce the incidence of arthritis significantly.²¹ Interestingly, T cell responses and production of anticollagen antibody were not affected by this anti-IL-17 treatment,²¹ indicating that in this phase of CIA, IL-17 no longer acts on the T and B cell compartment contributing to the arthritic process. These data suggest that during the early initiation phase of experimental arthritis, IL-17 is required for normal T and B cell function, and in the late phase of initiation (just before onset of disease) IL-17 contributes to the development of arthritis directly or through the induction of other proinflammatory and destructive mediators.

IL-17 in progression of experimental arthritis

Apart from its role in initiation of experimental arthritis, IL-17 has been shown to contribute to the progression of arthritis in animal models. In experiments to study the effects of anti-IL-17 treatment in CIA after the onset of disease, neutralisation of IL-17 after onset of CIA reduced joint inflammation, cartilage destruction, and bone erosion.²² Systemic IL-6 was reduced and fewer synovial IL-1 positive and RANKL positive cells were detected after blockage of endogenous IL-17.²² Interestingly, even late after onset, neutralisation of IL-17 had clinical effects.²² In comparison with its contribution to CIA, IL-17 plays a more prominent

Abbreviations: AIA, antigen induced arthritis; CIA, collagen induced arthritis; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; MMP, matrix metalloproteinase; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor κ B ligand; SCW, streptococcal cell wall; TNF, tumour necrosis factor; Th, T helper

Figure 1 T helper (Th) cell differentiation: the interleukin (IL)-17 producing Th 17 cells form a distinct Th lineage that is promoted by IL-23. IFN, interferon; TNF, tumour necrosis factor.

role in arthritis models that are mainly driven by T cells, such as the IL-1Ra^{-/-} model and especially the antigen induced arthritis (AIA) flare reaction. In IL-1Ra^{-/-} mice, arthritis can be transferred by T cells²³ and is abrogated when mice are also deficient for IL-17.²⁰ We have found that blocking IL-17 after onset of arthritis halts further progression of this T cell driven arthritis model (Koenders *et al.*, publication in progress). We also blocked IL-17 in experimental flare reactions during AIA. This arthritis model is unique for its antigen specific arthritic flare reaction, mainly driven by (memory) T cells, and a major role for IL-17 has been demonstrated using anti-IL-17 antibodies.²⁴ Blockage of IL-17 during reactivation of experimental arthritis completely prevented joint influx of inflammatory cells and also suppressed expression of IL-1, TNF, and RANKL.²⁴

Overexpression of IL-17 in a naive murine knee joint using an adenoviral vector results in joint inflammation, cartilage proteoglycan depletion, and bone erosion.²¹ Adenoviral IL-17 injected in the knee joint of type II collagen immunised mice was shown to accelerate the onset of CIA and aggravate the synovial inflammation and joint destruction.²¹ Furthermore, overexpression of this T cell cytokine turned acute arthritis models in more severe and chronic models.²⁵⁻²⁶ To study the role of IL-17 in the progression of an acute joint inflammation into a chronic, destructive synovitis, IL-17 receptor deficient mice were given repeated injections of streptococcal cell wall (SCW) fragments directly into the knee joint at weekly intervals. Whereas the arthritis in wild-type mice became more severe after each injection, joint inflammation was significantly suppressed in IL-17R^{-/-} mice.²⁷ In addition, IL-17 receptor deficiency prevented cartilage destruction and resulted in impaired synovial expression of IL-1 and MMPs during chronic reactivated SCW induced arthritis.²⁷

These findings indicate that IL-17, in addition to its role in initiation of arthritis, plays an important role in the progression of experimental arthritis. IL-17 plays a critical role in turning an acute, macrophage driven joint inflammation into a chronic, cartilage destructive synovitis, and the role of IL-17 in the arthritic process becomes clearly more prominent when T cells play a more dominant role.

IL-17 IN RELATION TO TNF AND IL-1

Comparison of the role of IL-17 with TNF and IL-1 in experimental arthritis

Where should IL-17 be positioned in the initiation and progression of experimental arthritis in comparison with TNF and IL-1?

Collagen arthritis experiments in TNFR1^{-/-} and TNF^{-/-} mice have shown that in the absence of TNF signalling, CIA develops with decreased incidence and severity. However, once arthritis in a joint is initiated, progression and destruction is independent of TNF.²⁸⁻²⁹ Comparable results were obtained with anti-TNF treatment during CIA. Blockage of TNF was effective shortly after onset of collagen arthritis, but it was hardly effective in later phases of CIA.³⁰ Blockage of IL-17 before onset of CIA results in suppressed incidence and severity of arthritis,²¹ and neutralisation of IL-17 after onset of arthritis significantly slows progression of CIA.²² In contrast with anti-TNF, anti-IL-17 treatment is effective even when started late after onset (table 1).²² Like IL-17, and in contrast with TNF, IL-1 has been shown to contribute to both initiation and progression of CIA. Incidence of CIA is completely blocked in IL-1αβ^{-/-} mice,³¹ and anti-IL-1 treatment results in an impressive reduction of both inflammation and destruction even in fully established CIA (table 1).³²

Figure 2 Schematic overview of the actions of interleukin (IL)-17 that contribute to the arthritic process: IL-17 stimulates various cell types to produce cytokines, chemokines, and destructive mediators, thereby contributing to joint inflammation and destruction of cartilage and bone. COX2, cyclo-oxygenase-2; GM-CSF, granulocyte macrophage-colony stimulating factor; GRO, growth related oncogene; LIF, leucocyte inhibitory factor; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; RANKL, receptor activator of nuclear factor κB ligand; Th, T helper; TNF, tumour necrosis factor.

Table 1 Comparison of the effects of blocking IL-17, IL-1, and TNF in different arthritis models

	Anti-IL-17	Anti-IL-1	Anti-TNF
CIA*			
Before onset	+ Incidence and severity ↓	++ Complete prevention of CIA ^{29, 31}	+ Incidence and severity ↓
After onset	+ Severity ↓, treated early and late after onset	++ Severity ↓ ↓, treated early and late after onset ²⁹	+/- Severity ↓, when treated early but not late after onset ²⁹
IL-1Ra^{-/-} model‡			
Before onset	++ IL-1Ra ^{-/-} xIL-17 ^{-/-} mice have no onset of disease ²⁰	Not studied	+ IL-1Ra ^{-/-} xTNF ^{-/-} mice have reduced incidence and severity ²²
After onset	+ Prevents increase in severity; no suppressive effect	++ Very effective suppression of disease	- Not effective; increase in severity comparable to control group
AIA-flare§			
Before onset	++ Effective blocking of flare reaction and destruction	++ Effective blocking of flare reaction and destruction	Not studied

*CIA; collagen induced arthritis in DBA-1J mice, treated before onset of disease or in established arthritis

‡IL-1Ra^{-/-} model; spontaneous arthritis in mice deficient for the IL-1 receptor antagonist (IL-1Ra^{-/-})

§AIA-flare; antigen induced arthritis in C57Bl/6 mice, reactivated by intra-articular injection of 2 µg mBSA

-, not effective; +, effective; ++, very effective.

IL-1 is also the driving factor in spontaneous arthritis in IL-1Ra^{-/-} mice. Since both IL-17 and TNF have been shown to play an important role in the spontaneous development of arthritis in IL-1Ra^{-/-} mice,^{20, 23} we investigated the role of these cytokines in the progression of this arthritis model. In contrast with its role at the onset of disease, TNF was not important during further progression of arthritis in IL-1Ra^{-/-} mice, as was shown by blocking TNF after onset of arthritis (Koenders *et al*, publication in progress) (table 1). Although this arthritis model can be transferred to naive wild-type mice by T cells and IL-17 is greatly enhanced in IL-1Ra^{-/-} mice,^{20, 23} anti-IL-17 treatment prevented further disease progression but did not completely abrogate disease (Koenders *et al*, publication in progress). Blockage of IL-1 completely blocked arthritis and reduced production of IL-17 by splenic lymphocytes, showing that even after onset of disease IL-1 controls this spontaneous arthritis model.

Despite the distinct roles for IL-1 and IL-17 in the progression of CIA and IL-1Ra^{-/-} arthritis, with a major role for IL-1 and a supportive function for IL-17, IL-17 becomes clearly more important when T cells play a more prominent role in the arthritis process. Flare reactions during AIA mediated by antigen specific T cells have been effectively blocked by both anti-IL-17 and anti-IL-1 treatment (table 1).²⁴ Anti-IL-17 was more effective in suppressing joint swelling and more potently reduced the expression of IL-1, TNF, and RANKL than anti-IL-1 treatment.²⁴ These data suggest a role for IL-17 upstream of IL-1 and TNF, driving the local expression of these proinflammatory cytokines.

The blockage studies show that IL-17 does not have a superior role than IL-1 and TNF in CIA but it plays a more prominent role in arthritis models which are more driven by T cells, such as the IL-1Ra^{-/-} model and especially the AIA flare reaction. An increase in IL-17 producing T cells in the arthritic joint seems to make the local arthritic process less dependent on IL-1 and more driven by IL-17.

Position of IL-17 and TNF in the cytokine network

To speculate on the potential of IL-17 as a therapeutic target in the treatment of RA, we should position this T cell cytokine in the network and cascades of proinflammatory cytokines that drive the arthritic process. In vitro studies have shown that IL-17 can induce other proinflammatory cytokines and

chemokines such as IL-1, TNF, IL-6, and IL-8.³⁻⁷ Adenoviral overexpression of IL-17 in various cytokine deficient mice showed that IL-17 is not dependent on IL-1, but strongly depends on TNF (fig 3).²⁶ TNF deficient mice were completely protected against IL-17 induced joint inflammation and cartilage proteoglycan depletion, in contrast with IL-1^{-/-} mice and wild-type controls.²⁶ The strong dependency of IL-17 on TNF would suggest that anti-TNF treatment during RA would be sufficient to block both the effects of TNF and IL-17. However, this TNF dependency changes when IL-17 is overexpressed in combination with arthritic stimuli. IL-17 aggravated KxB/N serum transfer arthritis to a similar degree in TNF deficient mice and their wild-types, and also enhanced SCW arthritis independent of TNF.²⁶ Additional IL-1 blockage showed that this loss of TNF dependency under arthritic conditions is not the result of synergistic effects of IL-17 with IL-1 (fig 3).²⁶ This indicates that despite the strong dependency of IL-17 on TNF in a naive joint, it acts independent of TNF under arthritic conditions.

Figure 3 IL-17 mediated joint pathology loses its dependency on tumour necrosis factor (TNF) under arthritic conditions. Joint inflammation after adenoviral overexpression of interleukin (IL-17) (AdIL-17) is blocked in naive TNF deficient mice. In contrast, IL-17-aggravated streptococcal cell wall (SCW) arthritis is not suppressed in the absence of TNF, and additional IL-1 blocking is not effective. WT, wild-type.

As IL-17 is not the only inducer of TNF, and because IL-17 can act both dependent and independent of TNF, IL-17 should not be simply regarded as an upstream mediator of TNF. On the contrary, these findings and the fact that these two cytokines can have additive or even synergistic effects⁸⁻¹¹ indicate that neutralisation of both IL-17 and TNF might be more effective than blocking one of these cytokines alone. Overexpression studies have shown that IL-17 significantly enhanced the joint inflammatory and destructive capacity of TNF, with strong synergistic effects on chondrocyte death and cartilage surface erosions (Lubberts, Koenders, *et al*, publication in progress). Furthermore, in collagen arthritis, we have observed that neutralisation of IL-17 in addition to TNF further improves protection against joint damage and is still effective during late stage CIA (Lubberts, Koenders, *et al*, publication in progress). This indicates that blockage of IL-17 should perhaps not be considered as a replacement for anti-TNF treatment, but could be a powerful additional therapy in cases where blockage of TNF alone is not sufficient for suppression of arthritis.

IL-17 and IL-1 in the cytokine cascade

IL-1 is considered an important catabolic cytokine in experimental murine arthritis. TNF mediated joint pathology runs partly through IL-1, as has been shown with anti-IL-1 treatment in TNF transgenic mice.³³ IL-1 deficiency during local TNF overexpression in murine knee joints also resulted in markedly reduced joint inflammation and destruction (Koenders, 2004, personal observation). In addition to its catabolic properties, IL-1 is essential for proper T cell activation. IL-1 produced by antigen presenting cells enhances the expression of CD40L and OX40, crucial for T cell priming and antigen specific B cell responses.³⁴ Because of this role in T cell development, IL-1 acts as an upstream mediator of IL-17 in experimental arthritis. This is elegantly demonstrated by the IL-1Ra^{-/-} mice, which spontaneously develop arthritis driven by T cells producing IL-17.²⁰⁻²³ In response to the production of IL-17, local IL-1 expression in the inflamed joint is enhanced, which can be downregulated by anti-IL-17 treatment.²²⁻²⁴ This suggests another role for IL-1 downstream of IL-17. Since IL-1 acts both upstream and downstream of IL-17, we speculate that IL-1 is essential for the formation/activation of Th 17 cells, and that during reactivation of local memory cells IL-17 becomes the most important cytokine, not only driving (part of) the local IL-1 and TNF production but also having effects independent of IL-1 and TNF (fig 4).

As IL-1 is a crucial catabolic cytokine in our arthritis models, we investigated whether IL-17 mediates cartilage damage through the induction of IL-1, or independent of IL-1. IL-17 was overexpressed by intra-articular injection of an adenovirus in IL-1 deficient mice with SCW induced arthritis. In the presence of IL-17, depletion of cartilage proteoglycan in experimental arthritis was not suppressed by deficiency of IL-1, and the expression of MMPs was also no longer dependent on IL-1 (fig 5).²⁵ This loss of IL-1-dependency was confirmed in CIA, in which anti-IL-1 treatment did not decrease cartilage destruction during IL-17 overexpression.²⁵ In this study we showed that IL-17 not only acts up/downstream of IL-1, but can also have identical effects on cartilage destruction in the absence of IL-1.

FUTURE PERSPECTIVES: IL-17 AS CLINICAL TARGET IN RA

The recent animal studies using knockout mice, adenoviruses, and neutralising antibodies have helped us to understand the role of IL-17 in experimental arthritis, and to position IL-17 in relation to TNF and IL-1. IL-17 is a T cell factor, contributing to the initiation and progression of

Figure 4 The position of interleukin (IL)-17 in the arthritic process in relation to IL-1 and tumour necrosis factor (TNF). Note that IL-1 acts upstream of IL-17 in its function of activating T cells, but that IL-17 induces the local expression of IL-1 in the arthritic joint. In addition, IL-17 induces TNF and can synergise with this cytokine, but IL-17 also acts independent of IL-1 and TNF. MHC, major histocompatibility complex; TCR, T cell receptor.

arthritis. IL-17 enhances joint inflammation and destruction of cartilage and bone, and can act both synergistically with and independent of TNF and IL-1.

The most important question, however, remains unanswered: Is IL-17 also relevant in patients with RA? This T cell cytokine has been shown to be expressed in the inflamed joints, and correlations have been found with radiographic damage. However, these are only minor indications for a role of IL-17 in RA. Although the development and use of

Figure 5 Overexpression of interleukin (IL)-17 in streptococcal cell wall (SCW) arthritis replaces the catabolic function of IL-1 in this arthritis model. In SCW arthritis, IL-1 is the main catabolic cytokine driving the depletion of proteoglycan (PG) and matrix metalloproteinase (MMP)13 expression. However, IL-17 can enhance cartilage damage and MMP expression in SCW arthritis independent of IL-1. WT, wild-type.

advanced humanised arthritis models can help us predict the clinical outcome of anti-IL-17 therapies, this question can only be answered by clinical trials. Anti-IL-17 therapy as monotherapy in clinical trials could have disappointing effects, and hopefully it will also be tested in combination with TNF and IL-1 blockers. IL-17 might not be the key regulator in the arthritic process, but this T cell cytokine is an important contributor because of its close relationship with TNF and IL-1.

Authors' affiliations

M I Koenders, L A B Joosten, W B van den Berg, Radboud University Nijmegen Medical Center, Department of Rheumatology, Rheumatology Research and Advanced Therapeutics, Nijmegen, the Netherlands

This work was supported by the Dutch Arthritis Association (grant NR 00-1-302), and by a grant of Novartis Pharma AG, Basel, Switzerland.

Competing interests: none declared

Correspondence to: M I Koenders, Radboud University Nijmegen Medical Center, Department of Rheumatology, Rheumatology Research and Advanced Therapeutics, 272, Geert Grooteplein 26, PO Box 9101, 6500 HB Nijmegen, the Netherlands; m.koenders@reuma.umcn.nl

REFERENCES

- Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol* 2005;6:1123-32.
- Park H, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, et al. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nat Immunol* 2005;6:1133-41.
- Chabaud M, Durand JM, Buchs N, Fossiez F, Page G, Frappart L, et al. Human interleukin-17: a T cell-derived proinflammatory cytokine produced by the rheumatoid synovium. *Arthritis Rheum* 1999;42:963-70.
- Ziolkowska M, Koc A, Luszczkiewicz G, Ksiezopolska-Pietrzak K, Klimczak E, Chwalinska-Sadowska H, et al. High levels of IL-17 in rheumatoid arthritis patients: IL-15 triggers in vitro IL-17 production via cyclosporin A-sensitive mechanism. *J Immunol* 2000;164:2832-8.
- Kotake S, Udagawa N, Takahashi N, Matsuzaki K, Itoh K, Ishiyama S, et al. IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. *J Clin Invest* 1999;103:1345-52.
- Hwang SY, Kim HY. Expression of IL-17 homologs and their receptors in the synovial cells of rheumatoid arthritis patients. *Mol Cells* 2005;19:180-4.
- Raza K, Falciani F, Curnow SJ, Ross EJ, Lee CY, Akbar AN, et al. Early rheumatoid arthritis is characterized by a distinct and transient synovial fluid cytokine profile of T cell and stromal cell origin. *Arthritis Res Ther* 2005;7:R784-R795.
- Fossiez F, Djossou O, Chomarat P, Flores-Romo L, AitYahia S, Maat C, et al. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. *J Exp Med* 1996;183:2593-603.
- Yao Z, Fanslow WC, Seldin MF, Rousseau AM, Painter SL, Comeau MR, et al. Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. *Immunity* 1995;3:811-21.
- Jovanovic DV, Di Battista JA, Martel-Pelletier J, Jolicoeur FC, He Y, Zhang M, et al. IL-17 stimulates the production and expression of proinflammatory cytokines, IL-beta and TNF-alpha, by human macrophages. *J Immunol* 1998;160:3513-21.
- Chabaud M, Garnerio P, Dayer JM, Guerne PA, Fossiez F, Miossec P. Contribution of interleukin 17 to synovium matrix destruction in rheumatoid arthritis. *Cytokine* 2000;12:1092-9.
- Benderdour M, Tardif G, Pelletier JP, Di Battista JA, Rebour P, Ranger P, et al. Interleukin 17 (IL-17) induces collagenase-3 production in human osteoarthritic chondrocytes via AP-1 dependent activation: differential activation of AP-1 members by IL-17 and IL-1beta. *J Rheumatol* 2002;29:1262-72.
- Koshy PJ, Henderson N, Logan C, Life PF, Cawston TE, Rowan AD. Interleukin 17 induces cartilage collagen breakdown: novel synergistic effects in combination with proinflammatory cytokines. *Ann Rheum Dis* 2002;61:704-13.
- Chabaud M, Page G, Miossec P. Enhancing effect of IL-1, IL-17, and TNF-alpha on macrophage inflammatory protein-3alpha production in rheumatoid arthritis: regulation by soluble receptors and Th2 cytokines. *J Immunol* 2001;167:6015-20.
- Katz Y, Nativ O, Beer Y. Interleukin-17 enhances tumor necrosis factor alpha-induced synthesis of interleukins 1, 6, and 8 in skin and synovial fibroblasts: a possible role as a "fine-tuning cytokine" in inflammation processes. *Arthritis Rheum* 2001;44:2176-84.
- Chabaud M, Miossec P. The combination of tumor necrosis factor alpha blockade with interleukin-1 and interleukin-17 blockade is more effective for controlling synovial inflammation and bone resorption in an ex vivo model. *Arthritis Rheum* 2001;44:1293-303.
- Van Bezooijen RL, Wee-Pals L, Papapoulos SE, Lowik CW. Interleukin 17 synergises with tumour necrosis factor alpha to induce cartilage destruction in vitro. *Ann Rheum Dis* 2002;61:870-6.
- Nakae S, Komiyama Y, Nambu A, Sudo K, Iwase M, Homma I, et al. Antigen-specific T cell sensitization is impaired in IL-17-deficient mice, causing suppression of allergic cellular and humoral responses. *Immunity* 2002;17:375.
- Nakae S, Nambu A, Sudo K, Iwakura Y. Suppression of immune induction of collagen-induced arthritis in IL-17-deficient mice. *J Immunol* 2003;171:6173-7.
- Nakae S, Saijo S, Horai R, Sudo K, Mori S, Iwakura Y. IL-17 production from activated T cells is required for the spontaneous development of destructive arthritis in mice deficient in IL-1 receptor antagonist. *Proc Natl Acad Sci U S A* 2003;100:5986-90.
- Lubberts E, Joosten LA, Oppers B, van den Bersselaar L, Coenen-de Roo CJ, Kolls JK, et al. IL-1-independent role of IL-17 in synovial inflammation and joint destruction during collagen-induced arthritis. *J Immunol* 2001;167:1004-13.
- Lubberts E, Koenders MI, Oppers-Walgreen B, van den Bersselaar L, Coenen-de Roo CJ, Joosten LAB, et al. Treatment with a neutralizing anti-murine interleukin-17 antibody after the onset of collagen-induced arthritis reduces joint inflammation, cartilage destruction, and bone erosion. *Arthritis Rheum* 2004;50:650-9.
- Koenders MI, Lubberts E, Oppers-Walgreen B, van den BL, Helsen MM, Di Padova FE, et al. Blocking of interleukin-17 during reactivation of experimental arthritis prevents joint inflammation and bone erosion by decreasing RANKL and interleukin-1. *Am J Pathol* 2005;167:141-9.
- Koenders MI, Lubberts E, Oppers-Walgreen B, van den BL, Helsen MM, Kolls JK, et al. Induction of cartilage damage by overexpression of T cell interleukin-17A in experimental arthritis in mice deficient in interleukin-1. *Arthritis Rheum* 2005;52:975-83.
- Koenders MI, Lubberts E, van de Loo FA, Oppers-Walgreen B, van den BL, Helsen MM, et al. Interleukin-17 acts independently of TNF-alpha under arthritic conditions. *J Immunol* 2006;176:6262-9.
- Koenders MI, Kolls JK, Oppers-Walgreen B, van den Bersselaar L, Joosten L, Schurr J, et al. Interleukin-17 receptor deficiency results in impaired synovial expression of interleukin-1 and matrix metalloproteinases 3, 9, and 13 and prevents cartilage destruction during chronic reactivated Streptococcal Cell Wall-induced arthritis. *Arthritis Rheum* 2005;52:3239-47.
- Mori L, Iselin S, De LG, Lesslauer W. Attenuation of collagen-induced arthritis in 55-kDa TNF receptor type 1 (TNFR1)-IgG1-treated and TNFR1-deficient mice. *J Immunol* 1996;157:3178-82.
- Campbell IK, O'Donnell K, Lawlor KE, Wicks IP. Severe inflammatory arthritis and lymphadenopathy in the absence of TNF. *J Clin Invest* 2001;107:1519-27.
- Joosten LAB, Helsen MMA, Vandeloo FAJ, Vandenberg WB. Anticytokine treatment of established type II collagen-induced arthritis in DBA/1 mice - a comparative study using anti-TNF alpha, anti-IL-1 alpha/beta, and IL-1Ra. *Arthritis Rheum* 1996;39:797-809.
- Saijo S, Asano M, Horai R, Yamamoto H, Iwakura Y. Suppression of autoimmune arthritis in interleukin-1-deficient mice in which T cell activation is impaired due to low levels of CD40 ligand and OX40 expression on T cells. *Arthritis Rheum* 2002;46:533-44.
- van den Berg WB, Joosten LAB, Helsen M, Vandeloo FAJ. Amelioration of established murine collagen-induced arthritis with anti-IL-1 treatment. *Clin Exp Immunol* 1994;95:237-43.
- Horai R, Nakajima A, Habiro K, Kotani M, Nakae S, Matsuki T, et al. TNF-alpha is crucial for the development of autoimmune arthritis in IL-1 receptor antagonist-deficient mice. *J Clin Invest* 2004;114:1603-11.
- Probert L, Plows D, Kontogeorgos G, Kollias G. The type I interleukin-1 receptor acts in series with tumor necrosis factor (TNF) to induce arthritis in TNF-transgenic mice. *Eur J Immunol* 1995;25:1794-7.
- Nakae S, Asano M, Horai R, Sakaguchi N, Iwakura Y. IL-1 enhances T cell-dependent antibody production through induction of CD40 ligand and OX40 on T cells. *J Immunol* 2001;167:90-7.