11 Summary

Interferon gamma (IFNγ) produced by T-helper (Th) cells is key to the defense against intracellular pathogens. Circumstantial evidence, however, suggests that IFNγ secreting Th1 cells are also driving autoimmune inflammation such as in Rheumatoid Arthritis (RA). Still, identification of the corresponding IFNγ-inducing stimuli in the joints of RA patients was not successful so far.

In this study, a T-cell receptor (TCR) independent pathway for induction of IFNγ synthesis in human Th cells was identified; IFNγ production was induced by proinflammatory cytokines known to be overexpressed in arthritic joints.
Interleukin-2 (IL-2) receptor gamma chain (γ_c) signalling cytokines (IL-2, IL-7 or IL-15) in combination with IL-12 and IL-18 were identified as essential factors promoting IFNγ secretion in a peripheral blood derived Th cell subpopulation characterised by IL-18 receptor α chain expression and equipped with functional IL-12 receptors.
Analysis of the signalling components involved identified p38 MAPKinase, JanusKinase (JAK) 3 and STAT4 as key molecules mediating cytokine-dependent IFNγ-production. Besides pharmacological inhibition by p38 or JAK3 blockade, cytokine-driven IFNγ-synthesis could be efficiently suppressed by $CD25^+$ regulatory T-cells. Differential expression of 4-1BB (CD137), a member of the Tumor Necrosis Factor Receptor superfamily, allowed discrimination of cytokine- from TCR-induced IFNγ producers, being only detectable after TCR ligation.

4-1BB expression was then analysed on live IFNγ-secreting Th cells isolated directly *ex vivo* from synovial infiltrates of active RA patients. As spontaneous IFNγ production was not associated with 4-1BB expression, secretion of the Th1 cytokine must have been induced by the proinflammatory environment rather that by joint-derived (auto-) antigens.

This study allows deduction of new therapeutic options for controlling inflammation in RA: Pharmacological inhibition of p38 MAPKinase could efficiently block cytokine-induced IFNγ synthesis in synovial Th cells, thereby eliminating a central mediator within an inflammatory cytokine network in the joint. As IFNγ-responses after TCR-

ligation are not dependent on p38 signalling, blockade is not expected to result in general immune suppression, as is the case in patients receiving e.g. anti-TNFα therapy. p38 blockade in rodent arthritis models resulted in significant reduction of joint destruction, arguing in favour of future applications in man.