

# Estrogens and interleukin-17 in arthritis and associated osteoporosis

## Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet, kommer att offentligens försvaras i föreläsningssalen våning 3, Guldhedsgatan 10A, Göteborg, fredagen den 9 december 2016 klockan 9.00.

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## Avhandlingen baseras på följande delarbeten

- I. Andersson A, Bernardi AI, Stubelius A, Nurkkala-Karlsson M, Ohlsson C, Carlsten H, Islander U. Selective oestrogen receptor modulators lasofoxifene and bazedoxifene inhibit joint inflammation and osteoporosis in ovariectomised mice with collagen-induced arthritis. *Rheumatology (Oxford)*. 2016; 55(3): 553-63.
- II. Andersson A, Bernardi AI, Nurkkala-Karlsson M, Stubelius A, Grahnmö L, Ohlsson C, Carlsten H, Islander U. Suppression of experimental arthritis and associated bone loss by a tissue-selective estrogen complex. *Endocrinology*. 2016; 157 (3): 1013-20.
- III. Grahnmö L, Andersson A, Nurkkala-Karlsson M, Stubelius A, Lagerquist MK, Svensson MN, Ohlsson C, Carlsten H, Islander U. Trabecular bone loss in collagen antibody-induced arthritis. *Arthritis Res Ther*. 2015; 25; 17:189.
- IV. Andersson A, Stubelius A, Karlsson MN, Engdahl C, Erlandsson M, Grahnmö L, Lagerquist MK, Islander U. Estrogen regulates T helper 17 phenotype and localization in experimental autoimmune arthritis. *Arthritis Res Ther*. 2015; 13; 17:32.
- V. Andersson A, Grahnmö L, Engdahl C, Stubelius A, Lagerquist MK, Carlsten H, Islander U. IL-17-producing  $\gamma\delta$ T cells are regulated by estrogen during development of experimental arthritis. *Clin Immunol*. 2015; 161 (2): 324-32.

**SAHLGRENKA AKADEMIN  
INSTITUTIONEN FÖR MEDICIN**



# **Estrogens and interleukin-17 in arthritis and associated osteoporosis**

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## **Abstract**

Rheumatoid arthritis (RA), a disease characterized by persistent joint inflammation and joint destruction, is frequently associated with generalized osteoporosis. A female preponderance (3:1) is present in RA, and conditions with sex hormone alterations such as pregnancy and menopause influence the disease. Estrogen-containing hormone replacement therapy (HRT) in postmenopausal RA reduces disease activity and prevents osteoporosis; however, use of HRT is restrictive due to risk of adverse effects. Selective estrogen receptor modulators (SERM) utilize positive effects of estrogens – prevent osteoporosis and reduce menopausal symptoms – with minimized side effects. SERM are also combined with estrogens to achieve a tissue-restricted estrogenic response (tissue-selective estrogen complex [TSEC]). Effects of new SERM and TSEC have not been studied in RA. Thus, the first aim of the thesis was to elucidate effects of new SERM and TSEC on arthritis and associated osteoporosis in an experimental arthritis model. The T cell cytokine interleukin-17A (IL-17) mediates both joint inflammation and bone degradation in RA; however, if IL-17-producing T cells can be regulated by sex hormones have been scarcely studied. Thus, the second aim of the thesis was to study influence of estradiol (E2) on IL-17-producing T cells in experimental arthritis.

To address these aims, ovariectomized (“postmenopausal”) female mice were subjected to collagen-induced arthritis (CIA). E2, SERM, and TSEC therapy in CIA mice dramatically reduced joint inflammation and destruction, and prevented osteoporosis, compared with placebo control. Moreover, E2 reduced IL-17-producing Th17 and  $\gamma\delta$ T cell numbers in joints, in contrast to lymph nodes where E2 increased their numbers. In line with modulated cell distribution, the migration-associated phenotype of IL-17-producing T cells was altered by E2. In conclusion, this thesis increases the understanding of sex hormonal influence in arthritis. Furthermore, the experimental evidence obtained herein motivates initiation of clinical trials evaluating addition of SERM or TSEC to postmenopausal women with RA at risk for osteoporosis.

**Keywords:** arthritis (experimental), osteoporosis, interleukin-17, estradiol, estrogens, selective estrogen receptor modulators