up to this time five eligible RA patients aged 45 years. Mononuclear (as macrophage) and T-cells have important role in RA. Isoyama et al. demonstrated a correlation between IL-6 level and STAT3 activation so it might be suggested a possible role of pSTAT3 as a biomarker of disease activity. However, further studies are needed to explore the important role of JAK-STAT pathway in RA.

**REFERENCES:**


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**AB0135**

**CIRCADIAN RHYTHMS OF IMMUNE CELLS IN HEALTHY INDIVIDUALS AND PATIENTS WITH RHEUMATOID ARTHRITIS**

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**Background:** Clinical symptoms of rheumatoid arthritis (RA), such as stiffness, swelling and pain, manifest in circadian pattern with the highest intensity occurs at dawn. This is known to correlate with the circadian expression of IL-6, which peaks before the onset of the symptom. Despite this finding, the circadian behaviour of immune system in cellular and molecular level in RA patients has not yet been extensively investigated.

**Objectives:** Our previous study suggested that immunological circadian rhythms in patients with RA were altered when compared to the healthy individuals. Currently, we are performing 24 hours study involving RA patients and healthy individuals to further monitor the dynamic occurrence of diverse immune cells in the periphery.

**Methods:** Up to this time five eligible RA patients aged 45–75 years and twelve eligible healthy controls were recruited to join the study. On the study day, the blood was drawn in two hours interval throughout 24 hours. The participants were provided with regular meal, allowed to eat snacks ad libitum and carry passive activities. The absolute number of circulating immune cells was determined using TruCount. RNA were isolated from CD14+ monocytes and analysed by real-time PCR.

**Results:** The major populations of immune cells in the periphery of healthy controls, including CD4+ T cells, CD8+ T cells, regulatory T cells, B cells and monocytes, displayed circadian rhythm that peaks during the rest phase. The rhythms are in general shifted a few hours later in the RA patients. Noteworthy, CD14 monocyte, which is one of the major sources of IL-6 in RA, showed a more pronounced rhythm with higher amplitude in RA patients compared to healthy individuals. Furthermore, the following clock genes are rhythmically expressed in CD14 monocytes of both groups: Rorα, Per1, Per2, Per3 and DBP. The peak of Rorα, Per1, Per3 DBP and CRYY is shifted a few hours later in RA patients. Interestingly, circadian variation is not observed in the expression of RevErba in healthy individuals, while in the RA patients a rhythm is established.

**Conclusions:** In general, circadian rhythm of immune system in cellular and molecular level in RA patients appears to undergo phase shift and peaks a few hours later in comparison to healthy individuals. New established rhythms were also observed in cellular and molecular level. Another round of study involving seven RA patients is planned this spring to complete the project. Considering our data, we will continue to investigate circadian rhythms in expanded immune cell population using mass cytometry, immunosassay and microarray. Identification of immunological circadian rhythms in patients with RA and healthy individuals will help us to expand our knowledge in autoimmunity and provide an outlook on potential future implications.

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**AB0136**

**THE EFFECT OF IL-6 RECEPTOR ANTIBODY FOR THE TREATMENT OF MCH-PLP/PLR-RA1 MICE THAT SPONTANEOUSLY DEVELOPED ANKYLOSING ARTHRITIS**

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**Background:** Mch-PLP/PLR-RA1 (RA1) mice are new strain mice which spontaneously developed arthritis in ankle and finally leads to ankylosis.1 There is no report that drug treatment has been applied to these mice.

**Objectives:** To examine the effect of mouse IL-6 receptor antibody MR16–1 for the treatment of RA-1 mice.

**Methods:** Male RA1 mice were randomly divided into treated and control groups. MR 16–1 was applied from 10 weeks of age for the treatment group. Saline was applied for the control group. The drug was administered every two weeks with the initial dose of 2 mg, then 0.5 mg. The effects were evaluated by histological synovia score, in vivo imaging using ICG-encapsulated liposomes and the expression of serum SAA and IL-6.

**Results:** The tissue evaluation was carried out at 14 weeks, 17 weeks and 20 weeks of age. The histological score of treated groups were significantly improved compared with control group at every age. The interclass correlation coefficient was 0.771. In vivo imaging using ICG-encapsulated liposomes showed that significant signal decrease in treated groups at 14 weeks, but no significant difference was observed after 16 weeks. Blood SAA was significantly improved at 17 weeks of age.

**Conclusions:** IL-6 receptor antibody is effective for the treatment of ankylosing arthritis of RA1 mice. IL-6 might be a new potential target of treatment for ankylosing arthritis.

**REFERENCE:**


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**AB0137**

**ARTHRITIS-ASSOCIATED EGGERTHELLA LENTA MODULATE DISEASE VIA METABOLIC AND MICROBIAL ALTERATIONS**

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**Background:** Role of environmental factors in predisposition to develop rheumatoid arthritis (RA) has gained interest due, in part, to the studies showing an association of gut microbiota with immune homeostasis. Although the etiology of RA is unknown, recent studies on the role of gut microbiota in inflammatory adaptive immune response have led to the concept that interaction between the host microbiome and genetic factors influences autoimmunity. We have shown an association of rare lineage commensals, Eggertella lenta, with RA.

**Objectives:** In this study, we aimed to determine how human gut commensal E. lenta modulates gut epithelial integrity and inflammation via metabolites in humanised mice expressing RA-susceptible HLA-DQ.

**Methods:** DQ8 mice following immunisation with type II collagen develop arthritis and antigen-specific cellular and humoral response. DQ8 mice orally gavaged

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with RA-associated *E. lenta* on alternate days for one week and were induced for arthritis. Gavage with microbes continued for 4 weeks. Mice were monitored for onset and progression of arthritis. Epithelial integrity was done by FITC-Dextran assay and citrulline levels in faecal and plasma samples were measured by liquid chromatography mass spectrometry

**Results:** Mice gavaged with *E. lenta* showed a much higher load of gut microbes compared to controls. Interestingly, *E. lenta* did not augment gut permeability as it was similar to non-gavaged arthritic mice. *Eggerthella lenta* is involved in ornithine pathway leading to generation of citrulline. To test if gavage with *E. lenta* accumulated citrulline in the gut, we tested citrulline levels in faecal samples by liquid chromatography mass spectrometry. Surprisingly, mice gavaged with *E. lenta* had lower levels of citrulline in faecal samples compared to mice naïve mice with no gavage. One can speculate from these observations that there is an expansion of commensals, like *E. lenta* in RA, leading to production of citrulline. To determine if citrulline could be accumulated outside of gut, we measured citrulline in sera of mice in various groups, gavaged with *E. lenta* naïve and mice induced for arthritis but no *E. lenta* gavage. Surprisingly, mice gavaged with *E. lenta* and induced for arthritis had lower levels of citrulline as compared to controls induced for arthritis but no gavage, p<0.05. Naïve mice gavaged with *E. lenta* also showed significantly much lower levels compared to sera of naïve mice.

**Conclusions:** This data suggests that *E. lenta* may be a major player in determining certain metabolic pathways. If Citrulline is being converted to arginine and used in other pathways is currently under investigation. Our studies suggest that gut commensals influence immune response in and away from the gut. Commensals and their products may provide novel targets for therapeutic strategies in arthritis.

**REFERENCE:**

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**AB0139 INVESTIGATION OF PREVOTELLA COPRI FROM RHEUMATOID ARTHRITIS PATIENTS**

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**Background:** We have previously reported some of the rheumatoid arthritis (RA) patients had *Prevotella* copri in the intestine. By using germ-free (GF) SKG mice, we also showed that *Prevotella*-dominated gut microbiota contribute to the development of arthritis. However, *P. copri* itself has not been isolated from RA patients and their molecular biology was unknown.

**Objectives:** Firstly, we planned to evaluate the intestinal microbiota in RA patients before and after the treatment. Second, we isolated *P. copri* strains from RA patients and healthy controls (HCs) and analysed whether RA patients derived *P. copri* expanded in the intestine of GF mice.

**Methods:** We first examined whether RA patients have altered composition of microbiota. All the patients were diagnosed according to the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria for RA. We collected faecal samples from 55 RA patients (61.5±9.5 years, mean ages ±SD) and 33 HCs (56.2±8.2 years) to investigate the microbiota by 16S rRNA-based deep sequence technique. We also analysed bacterial counts of *Prevotella* and *Bacteroides fragilis* by qPCR method. Moreover, we isolated *P. copri* from faecal contents of RA patients and HCs. GF mice were inoculated with *P. copri* from RA patients and HCs for further analysis.

**Results:** We found that 34.5% (19/55) of RA patients and 18.1% (6/33) of healthy controls had *P. copri* in the intestine. By using germ-free (GF) SKG mice, we also showed that *Prevotella*-dominated gut microbiota contribute to the development of arthritis. *P. copri* efficiently expanded in the intestine of GF mice.

**Conclusions:** We found that antibiotic of microbiota composition was observed after the RA treatment. Moreover, we successfully isolated *P. copri* from RA patients and HCs. RA patients-derived *P. copri* efficiently expanded in the intestine of GF mice.

**REFERENCE:**