spondylitis (SA) are associated with an increased cardiovascular (CV) mortality. Quantitative abnormalities in lipid profiles are insufficient to explain this excess of CV risk and a qualitative approach of HDL composition is required to identify loss of atheroprotective functions and to correctly identify patients at risk. Atheroprotective functions of HDL are directly linked to the structure of HDL mainly composed of phospholipids (PL).

**Objectives:** The main objective of this study is to analyze the PL composition of HDL in patients with chronic inflammatory rheumatic diseases and to compare to matched healthy controls.

**Methods:** HDL structure was assessed in patients with active RA (ACR criteria), PsA (CASPAR criteria) and SA (ASAS criteria) patients before initiating first biologic and in healthy controls matched for age, sex and body mass index. Dyslipidemia treatment or pathology which could interfere with lipid profile were excluded. Demographics data, disease activity, cardiometabolic profile and plasma samples were collected. HDL particle were isolated from plasma after two step ultracentrifugation using gradient of density. Lipidomics analysis were performed using liquid chromatography coupled with mass spectrometry. Phospholipid composition between patients and controls was compared using multivariate analyses to take into account possible confounding variables determined according to univariate results and clinical relevance (age, tobacco consumption, steroids use). Multidimensional analyses as factorial mixed data analysis (FMDA) were performed to complete these analyses.

**Results:** 19 RA, 19 PsA and 12 SA were analyzed (table 1). 220 phospholipids species were identified among which 2 major classes were modified in rheumatic diseases. Phosphatidylcholine (PC) decreased in RA and PsA ($p<0.01$ and $<0.05$ respectively) while lysophosphatidylcholine (LPC) increased significantly ($p<0.01$, and $<0.05$ respectively). Some phospholipids species as PC 40: 8 ($p<0.001$), LPC 16:0 ($p<0.001$), LPC 18:0 ($p<0.001$) were identified as discriminant marker of HDL composition in rheumatic disease as compared to controls.

| | RA (mean±SD) | Controls (mean±sd) | PsA (mean± sd) | Controls (mean±sd) | SA (mean±sd) | Controls (mean±sd) |
|---|---|---|---|---|---|---|
| Number of patients | 19 | 18 | 19 | 17 | 12 | 12 |
| Age | 55.32 ±10,91 | 58.78 ±4,61 | 49.63± 8.04 ** | 57.65±4.77 ** | 45.33±6.56 *** | 57.17±5.69*** |
| Sexe (W/M) (%M) | 1/18 (5,3%) | 1/17 (5,5%) | 10/9 (53%) | 10/7 (58%) | 8/4 (67%) | 8/4 (67%) |
| BMI (kg/m²) | 24.22 ±4,81 | 22.13 ±2,92 | 27.78± 7.60 | 24.55±3.63 | 25.49±4.16 | 23.69±2.92 |
| ApoB/ApoA1 | 0.67 ±0,15 | 0.63 ±0,15 | 0.77± 0.21 | 0.75±0.14 | 0.74±0.12 | 0.75±0.17 |
| CRP (mg/L) | 31.16 ±43,98 *** | 0.80 ±0,72 *** | 19.74±17.33 *** | 1.40±1.83 *** | 2.88±1.97 * | 1.91±2.17 * |
| CV family history Y/N (%) | 1/18 (5,3%) | 0/18 (0%) | 1/18 (5,2%) | 0/17 (0%) | 0/12 (0%) | 0/12 (0%) |
| CV personal history Y/N (%) | 0/19 (0%) | 0/18 (0%) | 0/19 (0%) | 0/17 (0%) | 0/12 (0%) | 0/12 (0%) |
| High blood pressure Y/N (%) | 4/15 (21%) * | 0/18 (0%) * | 2/17 (11%) | 0/17 (0%) | 4/8 (33%) * | 0/12 (0%) * |
| Diabetes mellitus Y/N (%) | 1/18 (5,3%) | 0/18 (0%) | 1/18 (5,2%) | 0/17 (0%) | 0/12 (0%) | 0/12 (0%) |
| Current tabacco use Y/N (%) | 5/14 (26%) * | 0/18 (0%) * | 5/14 (26%) | 0/17 (0%) | 6/6 (50%) ** | 0/12 (0%) ** |
| Disease duration (years) | 6,68±6,33 | | | | | |
| DAS 28 CRP score | 4.56 ±1,45 | | 4.00± 0.99 | | | |
| BASDAI | | | 55.67±18.58 | | 61.14±14.09 | |
| Corticosteroid treatment Y/N (%) | 10/9 (53%) | | 2/17 (11%) | | 1/11 (8,3%) | |
| NSAI treatment Y/N (%) | 9/10 (47%) | | 6/13 (32%) | | 6/6 (50%) | |
| Methotrexate treatment Y/N (%) | 15/4 (79%) | | 9/10 (47%) | | 1/11 (8,3%) | |

Table 1 : Demographics data, cardiometabolic profile and diseases caracteristics

* p<0.05, **p<0.01, ***p<0.0001 using T test or Chi-squared

**Conclusions:** Phospholipids composition of HDL is altered in RA and PsA. These alterations could explain a loss of atheroprotective functions and the excess of CV risk observed in RA and PsA patients. Chronic inflammation, through the activation of phospholipase A2 type II which hydrolyze PC into LPC, could modify the structure of HDL phospholipids and thus could impact HDL functionality such as cholesterol efflux, LDL oxidation modulation, anti-inflammatory and vasculoprotective properties. These preliminary data suggest the major role of inflammation in these alterations.

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## THU0040 NOVEL AKT ACTIVATOR SC-79 IS A POTENTIAL TREATMENT FOR ALCOHOL-INDUCED OSTEONECROSIS OF THE FEMORAL HEAD

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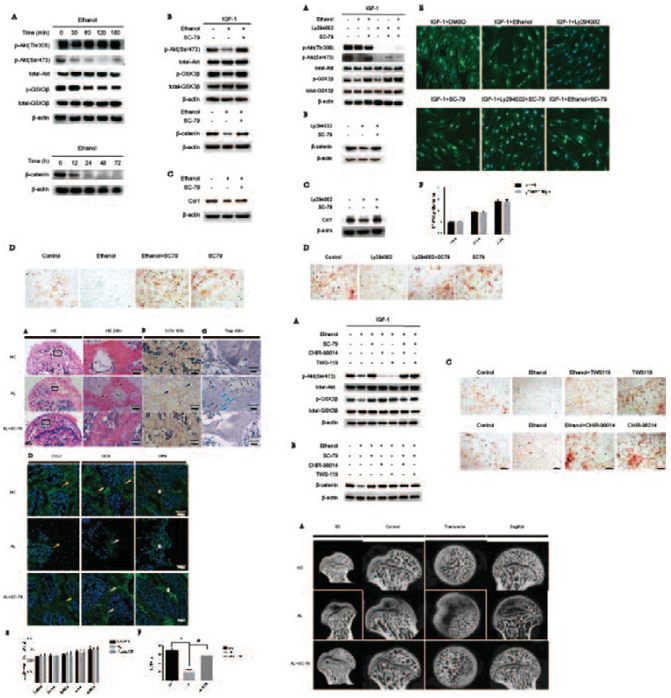
**Background:** Alcohol is known to be one ofthe leading risk factors for osteonecrosis of the femoral head. However, the underlying etiology and protective strategiesof alcohol-induced osteonecrosis of the femoral headhavenot been clarified.

**Objectives:** The aim of this study was to explore the molecular mechanism of alcohol-induced osteonecrosis of the femoral head, and to investigate the protective effect of SC-79 on the disease.

**Methods:** In vitro, we employed RT-PCR, alizarin red staining, alkaline phosphatase activity testing, western blot, immunofluorescence staining to investigate the effect of ethanol on hBMSCs. In vivo experiments, immunofluorescence staining, TRAP, TUNEL and micro-CT were performed to investigate the development of ONFH.

**Results:** In vitro, we found that ethanol could significantly impair the expression of osteogenic genes of RUNX2 and OCN, downregulate osteogenic differentiation, impair IGF-1 induced membrane recruitment of the Akt, suppress the Akt-Ser473 phosphorylationand the subsequent activation of Akt/GSK3β/β-catenin signaling in bone mesenchymal stem cells. Functional studies further confirmed this signaling was the critical mediator during the ethanol-induced inhibitory effects on osteogenesis of BMSCs.Thus, the dephosphorylation of Akt-Ser473 in Akt/GSK3β/β-catenin signaling pathway might be a potential mechanism in the pathogenesis of alcohol-induced osteonecrosis of the femoral head.SC-79, a novel Akt activator was introduced in this study to block the dephosphorylation effect of ethanol on Akt-Ser473 both in vitro and in vivo. In the rat model of alcohol-induced osteonecrosis of the femoral head, micro-CT and histopathological analyses revealed obvious osteonecrosis changes in alcohol-administrated rats while significantly less developed in SC-79 injected rats. OPN, OCN and COL1 immunofluorescence staining revealed that osteogenic response of femoral heads was markedly reduced after alcohol administration, but significantly reversed by SC-79 treatment.



**Conclusions:** Hence, we discovered alcohol-induced osteonecrosis of the femoral headwas associated with the suppression of the Akt-Ser473 in Akt/GSK3β/β-catenin pathway in BMSCs. The administration of SC-79, to elevate Akt activation, might be a clinical strategy to prevent the development of alcohol-inducedosteonecrosis of the femoral head.

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**Disclosure of Interest:** None declared

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## THU0041 PROGRANULIN AND DERIVATIVES CAN BE EMPLOYED AS LATENT DUAL-FUNCTION CHONDROGENIC AND ANTI-INFLAMMATORY THERAPEUTICS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

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**Background:** Rheumatoid Arthritis (RA) is a debilitating inflammatory disease of the joints afflicting around 1% of Western populations. Some of the best treatments are anti-TNF agents, but these only achieve remission in 60% of patients and cause deleterious side effects. Progranulin (PGRN), a cysteine-rich, multi-domain growth factor was reported to bind TNF-receptors (TNFR) blocking pro-inflammatory signalling[2], as well as stimulating chondrogenesis[3]. PGRN is cleavable and its peptides have pleiotropic effects, some of which may be beneficial and others refractory to ameliorating RA. Granulin A (GRN A) was shown to interact with cartilage ECM protein COMP[4]. Atsttrin – comprising 3 fused PGRN regions, was shown to ameliorate arthritic disease[2]. The latency associated peptide (LAP) of TGFβ1 can be fused to short peptides and cytokines via a MMP cleavage site to facilitate targeting to inflamed sites such as RA joints, reducing side effects and enhancing *in vivo* half-life[1]. We hypothesised that a peptide based on PGRN could be fused to LAP and used to both block TNF and stimulate cartilage regeneration in RA joints in a targeted way.

**Objectives:** To produce a panel of PGRN derivatives fused to LAP. To determine the chondrogenic and anti-TNF capacities of the fragments in the presence and absence of MMP activation. To evaluate their efficacy in the CIA model of RA.

**Methods:** Micromass cultures of C28/I2 chondrocytes and C3H10T1/2 mesenchymal cells were employed to determine the ability of PGRN fragments to stimulate chondrogenesis. HT-29 and WEHI-164 TNF sensitive cells were used to evaluate the anti-TNF capacity of LAP-PGRN fragments. Co-immunoprecipitation was used to characterise interactions between PGRN fragments and TNFRII. DBA/1 fibroblasts transduced with lentivirus encoding LAP-PGRN fusions were delivered to DBA/1 mice with CIA to assess anti-arthritic effects.
**Results:** PGRN, LAP-PGRN, LAP-GRN A and LAP-Atsttrin were cloned and expressed in mammalian expression systems. PGRN elevated sulphated proteoglycan production in micromass cultures of C28/I2 human chondrocytes, and also stimulated proliferation of C3H10T1/2 cells. Furthermore, PGRN reduced TNF-mediated catabolism of extracellular matrix in established chondrogenic C3H10T1/2 micromass cultures. LAP-PGRN, LAP-GRN A and LAP-Atsttrin potentiated BMP2 mediated chondrogenesis in C3H10T1/2 micromasses. PGRN failed to protect WEHI-164 fibroblasts or HT-29 colorectal carcinoma cells from TNF-mediated cytotoxicity despite interacting with TNF receptor *in vitro* by co-immunoprecipitation. LAP-PGRN, LAP-GRN A and LAP-Atsttrin all failed to protect WEHI-164 cells from TNF-mediated cytotoxicity, even after MMP1 cleavage and release. CIA disease progression was reduced in DBA/1 mice treated with autologous fibroblasts overexpressing murine Etanercept or PGRN relative to control treatment. LAP-Atsttrin was more effective than LAP-PGRN and LAP-GRN A at reducing arthritic symptoms relative to LAP-Empty controls.
**Conclusions:** These findings suggest that PGRN could be used as a targeted dual-function chondrogenic and anti-inflammatory treatment for RA, but these effects are not elicited directly through the TNF pathway.
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**Disclosure of Interest:** None declared
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## THU0042 LONGITUDINAL IP-10 SERUM LEVELS ASSOCIATE WITH THE COURSE OF DISEASE ACTIVITY AND ACHIEVING DMARD-FREE SUSTAINED REMISSION IN RHEUMATOID ARTHRITIS

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**Background:** Although rheumatoid arthritis (RA) is a chronic autoimmune disease that is persistent in the majority of patients, 10–15% of the RA patients achieve disease modifying anti-rheumatic drugs (DMARD)-free sustained remission over time. Biological mechanisms underlying the persistence of inflammation in RA are yet unidentified. It is well established that increased serum levels of IFN-γ-induced protein 10 (IP-10) are associated with (acute) increased inflammatory responses against mycobacterial pathogens causing leprosy and tuberculosis, thereby providing useful diagnostic tools in these infectious diseases. Based on previous genetic susceptibility studies, we hypothesize that there is an overlap between inflammatory responses observed in these mycobacterial diseases and those observed in RA. Therefore, we determined the association between serial IP-10 serum levels and achieving DMARD-free sustained remission as well as disease activity scores (DAS)-remission.
**Objectives:** To 1) assess the association between IP-10 levels over time in patients that have persistent RA versus patients that achieve DMARD-free sustained remission, and 2) determine the association between IP-10 levels and DAS.
**Methods:** 139 serum samples of 34 RA-patients (1987-criteria), obtained at the time of diagnoses and at yearly intervals thereafter, were studied. 15 patients had persistent RA and 19 patients achieved DMARD-free sustained remission after a median follow up of 2.7 years. IP-10 serum levels were measured using a previously developed, user-friendly lateral flow assay. Baseline and change in IP-10 levels over time were compared between patients with persistent RA and those achieving DMARD-free sustained remission. The association between the change in IP-10 level and the change in DAS was studied; in addition the course of the absolute IP-10 levels and the DAS over time was plotted for individual patients.
**Results:** IP-10 serum levels varied from 316 – 53,685 pg/ml between RA-patients. Patients that had persistent arthritis or achieved DMARD-free sustained remission over time did not differ in baseline IP-10 levels (median persistent RA 1991 pg/ml and median DMARD-free sustained remission 3292 pg/ml, p=0.19). However, a significant decrease in IP-10 levels over time was observed in patients achieving DMARD-free sustained remission (p=0.003), whereas IP-10 levels remained stable in patients with persistent RA. Changes in IP-10 levels correlated well with changes in DAS scores (p=0.05). Also at the level of individual patients, a strong correlation between IP-10 levels and DAS over time was observed.
**Conclusions:** These longitudinal data indicate that IP-10 levels are associated with perseverance of RA as well as with disease activity. Rapid diagnostic tests measuring IP-10 levels can therefore be helpful in monitoring of RA patients.
**Disclosure of Interest:** None declared
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## THU0043 TARGETED MEDICINE: THERAPEUTIC USE OF FUNCTIONAL CYTOKINE ASSAYS IN COMPLEX INFLAMMATORY ARTHRITIS

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**Background:** Functional cytokine assays have been limited to experimental models of inflammatory arthritis without translation into clinical therapy.
**Objectives:** To illustrate the successful use of functional cytokine assays in providing targeted treatment for complex inflammatory arthritis.
**Methods:** A 24 year old male presented in 2014 with a florid asymmetrical polyarthritis associated with an elevated acute phase response (ESR 50, CRP 42, ALP 132). He had no history of psoriasis, inflammatory bowel or eye disease and no family history.
Vasculitis and viral arthritis screen, ACE, ANA, Anti dsDNA, RF and CCP were negative. He was positive for HLA B27 without evidence of spondyloarthropathy on imaging. He was noted to have a monoclonal gammopathy of uncertain significance with normal bone profile, unremarkable urinary BJP and whole body CT scan. His joint symptoms responded to corticosteroid therapy with the addition of hydroxychloroquine and methotrexate. In 2015, his clinical condition had significantly deteriorated with worsening joint inflammation, 3 kg weight loss with a sudden rise in acute phase response, without proven infection. His functionality declined with long term sickness from work.
Biochemical tests revealed: Hb 123, MCV 87.2, Plt 393, Neutrophil 7.76, ESR 86, Alb 31, Calcium 2.68, ALP 387 (noted to be of bony origin), CRP 286, Ferritin 1161, PT 13, and APTT 39. Renal function, protein electrophoresis, blood film, haemolytic screen, viral and autoimmune liver screens were unremarkable. Hydroxychloroquine and methotrexate were temporarily with-held at this stage, although he was maintained on prednisolone 20 mg, with a partial response in his joint symptoms. An infiltrative pathology was a concern and was subsequently excluded.
The next therapeutic step would have been an anti-TNF agent. Nevertheless, due to his atypical and complex disease course, cytokine assays were performed to further characterise his disease profile and provide targeted treatment. Results showed an elevated IL6 production; IV Tocilizumab was selected for the treatment of his inflammatory arthritis. He has had a remarkable response in terms of his systemic and joint symptoms as well as considerable biochemical improvement. He was able to de-escalate his corticosteroid regime and return to work.
**Results:** TNF alpha, IL1 beta, and IL-6 are important inflammatory mediators and targets of intervention in the treatment of Rheumatoid arthritis. They may be induced *in vivo* and *in vitro* using Toll like receptor mediated innate activation. Active Whole Blood Cytokine Profiling was performed for the patient and compared to healthy controls. Innate activation of whole blood with various TLR agonists including LPS (TLR4), PAM3 (TLR1/2), Imiquimod (TLR7) revealed low induction of TNF alpha and IL1 beta in the patient when compared to controls. In contrast, the patient showed an elevated IL-6 production. Patient's cytokine levels in serum and in non-activated whole blood were normal.
**Conclusions:** Our case highlights the potential progression to personalised medicine in achieving optimal patient outcome delivered in a cost-effective way. Functional cytokine assays in the appropriate context and within selected patient groups can help to achieve disease remission by allowing targeted treatment.
**Disclosure of Interest:** None declared
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## THU0044 CHONDROITIN SULPHATE INHIBITS MONOCYTE CHEMOATTRACTANT PROTEIN-1 RELEASE FROM 3T3L1 ADIPOCYTES: A NEW TREATMENT OPPORTUNITY FOR OBESITY-RELATED METABOLIC SYNDROMES?

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**Background:** Monocyte chemoattractant protein-1 (MCP-1) overproduction from inflamed adipose tissue is a major contributor to obesity-related metabolic syndromes. We have recently published that chondroitin sulphate (CS) can attenuate the monosodium urate (MSU) crystal mediated THP-1 macrophage inflammatory response reflected by reduced release of pro-inflammatory cytokines IL-1β and TNFα. We have also recently determined that the CS inhibitory effect is not acting at the inflammasome but upstream, most likely by inhibiting activation of NF-κB.
**Objectives:** We sought to determine whether CS had a similar inhibitory effect on MCP-1 release from lipopolysaccharide (LPS) stimulated adipocytes.
**Methods:** We cultured 3T3-L1 embryonic fibroblasts and induced their differentiation into adipocytes using an established protocol. We then treated the adipocytes with LPS to induce inflammation and thus MCP-1 release. At the same time we added varying concentrations of CS (Bioibérica, Spain) in a physiologically relevant range (10–200 μg/ml) and 24h after we measured MCP-1 release (R&D Systems, Minneapolis, MN, USA). We also cultured THP-1 monocytes and tested whether CS (200 μg/ml) could inhibit cell migration induced by human recombinant MCP-1. Monocyte chemotaxis in response to 24h exposure to