thrombotic and atherogenic processes contributing to cardiovascular disease.(2) However, the role of NETs in cardiovascular disease in human gout is not known.

Objectives: Our objective is to investigate the association between neutrophil activation and cardiovascular risk in gout patients. We hypothesize that neutrophil activation mediates inflammation, as well as activation and damage to endothelial cells, partaking in atherosclerosis development.

Methods: Plasma samples from 75 gout patients participating in the 'Reade gout cohort Amsterdam' were analyzed. Patient data was collected on disease activity, demographics, gout history, comorbidities, medication use and cardiovascular risk assessments. Measurements included anthropometry, vital parameters (RR, HF), ECG and lab variables. Levels of NETs, and NET-derived markers (cell-free DNA and peroxidase activity) were analyzed using a MPO-DNA ELISA, as well as fluorimetry. Levels of calprotectin (S100A8/A9) were analyzed by ELISA. Markers of NETosis were related to clinical markers of cardiovascular risk, including BMI, smoking, blood pressure, lipid profile and 10 year risk of cardiovascular mortality (SCORE EU).

Results: No associations were found between markers of cell death (cfDNA and NETs) and cardiovascular risk. However, markers of neutrophil activation, including peroxidase activity correlated with BMI ($r=0.31$, $p=0.008$), waist-hip ratio ($r=0.52$, $p<0.001$), cholesterol ratio ($r=0.51$, $p<0.001$), and triglycerides ($r=0.42$, $p<0.001$). These associations were even stronger in patients with chronic, polyarticular gout. Peroxidase activity was associated with the 10 year risk of cardiovascular comorbidity ($r=0.47$, $p<0.001$, Figure 1A). Calprotectin levels were elevated in hypertension ($p=0.005$) and diabetes ($p=0.02$), with calprotectin levels associating with diabetes independently on BMI (OR=6.2, $p=0.04$). Finally, we constructed a neutrophil risk score ranging from 0-2 based on positivity for peroxidase and/or calprotectin to identify patients with a 'neutrophil activation signature'. The neutrophil risk score strongly associated with CVD risk (Figure 1B). Patients with neutrophil activation signature (risk score 1-2) had markedly elevated cardiovascular risk score ($p=0.001$), with 67.7% of the patients having high cardiovascular risk, versus 32.3% of the patients without a neutrophil activation signature (OR=2.9, $p=0.03$).

Conclusion: We have demonstrated, for the first time, that neutrophil activation markers are associated with several risk factors of cardiovascular disease, including hyperlipidemia, hypertension and diabetes in a large cohort of gout patients. Furthermore, the presence of a neutrophil activation signature is strongly associated with a 10-year risk of cardiovascular comorbidity.

Figure 1A

Figure 1B

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OP0301

C-X-C MOTIF CHEMOKINE 10 (CXCL10) IS A POTENTIAL BIOMARKER OF DISEASE ACTIVITY IN PSORIATIC ARTHRITIS (PSA)

Rohan Machhar¹, Sofia Oke¹, Justine Ye¹, Fatima Abji¹, Vinod Chandran^{1,2,3,4}.

¹Krembil Research Institute, University Health Network, Psoriatic Arthritis Program, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto, Canada;

²Faculty of Medicine, University of Toronto, Division of Rheumatology, Toronto, Canada;

³University of Toronto, Department of Laboratory Medicine and

Pathobiology, Toronto, Canada; ⁴Memorial University of Newfoundland, Faculty of Medicine, Newfoundland, Canada

Background: Assessment of Psoriatic Arthritis (PsA) disease activity requires detailed clinical evaluation complemented by imaging. Current laboratory markers such as CRP do not accurately reflect PsA disease activity. Identifying soluble biomarkers of PsA disease activity is an important perceived clinical need.

Objectives: We aimed to identify markers that correlates with PsA disease activity and change with treatment.

Methods: Serum samples were obtained from a cohort of patients with PsA not on DMARD treatment assessed clinically every 6 months according to a standard protocol including several measures of disease activity: physician and patient global assessment, tender and swollen joint counts, skin scores (BSA, PASI) and the composite measures- Disease Activity Score for PsA (DAPSA) and PsA Disease Activity Score (PASDAS). In the *discovery phase*, we mined our clinical and biomarker database that has linked biomarker and disease activity measures and identified markers that potentially reflect PsA disease activity. In *verification phase 1* we measured the selected 17 markers in 80 PsA samples. 8 Markers that significantly correlated with disease activity were identified based on Spearman correlation coefficients. In the *verification phase 2* these 8 markers were further assayed in an inception cohort of 80 patients. In this phase, physician global assessment of disease activity (including skin and joints-MDGA) was used as the primary measure of disease activity; other skin, MSK and patient reported measures were considered secondary measures. In *verification phase 3* with the hypothesis that markers associated with disease activity would decrease with treatment, the markers that correlated with MDGA were further assayed in 40 patients before and after 6 months of treatment (26 biologics and methotrexate, 14 methotrexate). All assays were done using commercially available ELISA.

Results: In *verification phase 1* 8 markers of 17 tested were found to be associated with measures of disease activity in 80 PsA patients (mean age 47, males 58%, swollen joint count [SJC] 2, tender joint count [TJC] 3.6, PASI 2.9). In *verification phase 2* 2 markers [CXCL10 ($\rho=0.25$, $p=0.03$) and CRP ($\rho=0.26$, $p=0.02$)] tested in 80 patients (mean age 49, males 54%, SJC 1.5, TJC 3.3, PASI 5.6) correlated with MDGA, and did not correlate with each other. Three other markers correlated with secondary measures; COMP correlated with PASDAS ($\rho=0.22$, $p=0.04$), MMP3 correlated with PASI ($\rho=0.27$, $p=0.01$) and CPIL-C2C ratio correlated with active joints ($\rho=-0.27$, $p=0.02$). In *verification phase 3* CXCL10 (baseline mean =246.7(standard deviation 190.79) - 6 month 177.7 (163.8)); ($p=0.0008$) and CRP (18.5 (19.1) - 9.5 (8.9)); ($p=0.002$)] significantly decreased 6 months post treatment.

Conclusion: CXCL10, a marker previously associated with PsA, may also be a marker of PsA disease activity. Identifying a robust outcome measure for disease activity to conduct biomarker studies in a heterogeneous disease like PsA remains a significant challenge.

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OP0302

MUCOSAL-ASSOCIATED INVARIANT T (MAIT)-CELL-DERIVED IL-17A AND IL-17F PRODUCTION IS IL-23-INDEPENDENT AND BIASED TOWARDS IL-17F

Suzanne Cole, Catherine Simpson, Remi Okoye, Meryn Griffiths, Dominique Baeten, Stevan Shaw, Ash Maroof. UCB Pharma, Slough, United Kingdom

Background: The requirement for IL-23 in driving IL-17A and IL-17F production in humans is incompletely understood. Preclinical data support IL-17F, together with IL-17A, as a key driver of chronic tissue inflammation.¹ MAIT cells, an innate-like T cell population, uniformly express ROR γ t but only a minority have been shown to produce IL-17A.² Dysregulation in frequency and function of MAIT cells

has been associated with IL-17A-mediated inflammatory diseases, including PsA and AS.^{3,4} IL-17F production in MAIT cells remains largely unexplored.

Objectives: To explore the importance of IL-23 signalling in MAIT cell-derived IL-17A and IL-17F production, examine the presence of MAIT cells in psoriatic lesional skin and assess the contribution of MAIT cell-derived IL-17A and IL-17F using *in vitro* models of skin inflammation.

Methods: IL-17A and IL-17F production by MAIT cells was assessed by flow cytometry, ELISA, qPCR and CyTOF upon activation by anti-CD3/CD28 or fixed *E. coli* via MR1-presented riboflavin metabolites, with or without disease-relevant recombinant cytokines or an IL-23-neutralising antibody. RNAscope was utilised to observe MAIT cells in psoriatic lesional skin. MAIT cell supernatant, generated from FACS sorted activated MAIT cells, was cultured with normal human dermal fibroblasts (NHDFs) in the presence of IL-17-isoform-specific antibodies, including bimekizumab, a monoclonal antibody that potently and selectively neutralises both IL-17A and IL-17F.

Results: Optimal MAIT cell IL-17A and IL-17F production occurred upon T cell receptor triggering with IL-12 and IL-18, independently of IL-23. IL-17F expression was greater at both gene and protein levels than IL-17A. The kinetics and threshold of activation for IL-17A and IL-17F suggest tighter regulation compared with other inflammatory cytokines, including IFN γ and TNF. Optimal MAIT cell IL-17A and IL-17F production requires monocytes, which contribute to IL-12 production upon IL-18 stimulation. MAIT cells were abundant in psoriatic lesional skin. NHDFs cultured with supernatant generated from activated MAIT cells produced inflammatory mediators IL-6, IL-8 and CCL2, which were reduced upon inhibition of either IL-17A or IL-17F, with optimal suppression achieved following dual neutralisation with bimekizumab.

Conclusion: IL-17A and IL-17F can be produced from MAIT cells independently of IL-23, and contribute to inflammatory responses in NHDFs. These results support dual neutralisation of IL-17A and IL-17F as a complete and targeted approach to suppress IL-17-driven inflammatory responses.

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OP0303

MONOSODIUM URATE AND CALCIUM PYROPHOSPHATE CRYSTAL-INDUCED INTERLEUKIN 1 PRODUCTION DEPENDS ON GLUCOSE UPTAKE THROUGH GLUT1 TRANSPORTER

Félix Renaudin^{1,2}, Laure Campillo-Gimenez^{1,2}, Florence Castelli³, François Fenaille³, Aurélie Prignon⁴, Christèle Combes⁵, Martine Cohen Solal^{1,6}, Frédéric Lioté^{1,6}, Hang Kong Ea^{1,6}. ¹Inserm, UMR1132, Bioscar, Paris, France; ²Université Paris Diderot, Paris, France; ³CEA Paris-Saclay, Laboratoire d'Etudes du Métabolisme des Médicaments, Saclay, France; ⁴UMS28 Phénotypage du petit animal, Hôpital Tenon, Paris, France; ⁵CIRIMAT, Université de Toulouse, INPT, UPS, CNRS, ENSIACET, Toulouse, France; ⁶Hôpital Lariboisière Ap-Hp, service de rhumatologie, centre Viggo Petersen, Paris, France

Background: Monosodium urate (MSU) and monocalcium pyrophosphate dihydrate (mCPPD) crystals are responsible for relapsing acute arthritis which is driven by interleukin 1 β (IL-1 β). IL-1 β production relies on NLRP3 inflammasome activation leading to ASC and caspase-1 recruitment. In tumor cells and in LPS-stimulated macrophages a switch of cell metabolisms toward glycolysis favors IL-1 β production.

Objectives: The aims of this study were to assess 1/whether crystal-induced NLRP3 activation and IL-1 β production involved glucose metabolism and 2/how MSU and mCPPD crystals induced glucose uptake focusing on the role of glucose transporter Glut1.

Methods: Synthetic and pyrogen-free MSU and mCPPD crystals were used to stimulate THP-1 cells and mouse bone marrow-derived macrophages (BMDM). Cells were stimulated in presence or absence of glucose (2g/L) and pyruvate (10mM). Glycolysis was inhibited by 2-deoxy-glucose (2DG) and the role of

glucose transporter 1 (Glut1) was assessed by pharmacological inhibitor (STF-31) and siRNA. IL-1 β production was quantified by ELISA. Metabolomic analysis was performed by mass spectrometry. Glucose uptake was determined using ¹⁸F-DG (Fluor18 labeled-2DG) and positron emission tomography (PET). Glut1 membrane localization was assessed by flux cytometry and confocal microscopy. ASC speck formation by confocal microscopy. *In vivo*, we used murine air pouch model to assess the effects of 2DG and Glut1 inhibition in crystal-mediated inflammation. Glut1 membrane localization of circulating neutrophils was compared to synovial fluid neutrophils harvested during gout flare.

Results: *In vitro*, both MSU and mCPPD crystal-induced IL-1 β secretion and ASC speck formation were inhibited when cells were cultured in glucose-free medium or in presence of 2DG. Similarly, MSU and mCPPD crystal-induced inflammation was abrogated in mice treated with 2DG. In THP-1 cells stimulated by MSU and mCPPD crystals, metabolomic analysis displayed alteration of glycolysis pathway and Krebs cycle and decrease of intracellular ATP production. Interestingly, MSU and mCPPD crystals increased glucose uptake *in vitro*, *ex vivo* and *in vivo*. Crystal-induced IL-1 β secretion was decreased by STF-31 and in THP-1 cells transfected with Glut1 siRNA. Next, we observed that MSU and mCPPD crystals increased membrane localization of Glut1 in THP-1, BMDM and neutrophils infiltrated in air pouch lavages and membranes. Glut1 membrane localization was positively correlated with IL-1 β production. Moreover, during gout flare, the proportion of Glut1 positive neutrophils was higher in synovial fluid neutrophils than in circulating neutrophils. Finally, STF-31 treatment decreased, *in vitro*, glucose uptake induced by MSU and mCPPD crystals, and *in vivo* MSU and mCPPD crystal-induced inflammation.

Conclusion: Glucose uptake through Glut1 transporter enhanced IL-1 β production induced by MSU and mCPPD crystals. Studies to decipher how these crystals induced Glut1 membrane localization are ongoing. Similarly, we investigate how glycolysis regulates NLRP3 and ASC activation. Decreasing Glut1 membrane localization might be a potential target to dampen crystal-induced inflammation.

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OP0304

GENETIC AND FUNCTIONAL STUDY OF OMENTIN REGARDING CARDIOVASCULAR RISK IN AXIAL SPONDYLOARTHRITIS

Fernanda Genre¹, Javier Rueda-Gotor¹, Sara Remuzgo-Martínez¹, Verónica Pulito-Cueto¹, Alfonso Corrales¹, Verónica Mijares¹, Leticia Lera-Gómez¹, Virginia Portilla¹, Rosa Expósito², Cristina Mata², Iván Ferraz-Amaro³, Vanessa Hernández-Hernández³, Santos Castañeda⁴, Esther Vicente⁴, Cristina Fernández-Carballido⁵, María Paz Martínez-Vidal⁶, David Castro-Corredor⁷, Joaquín Anino-Fernández⁷, Juan Carlos Quevedo-Abeledo⁸, Carlos Rodríguez-Lozano⁸, Ricardo Blanco¹, Oreste Gualillo⁹, Javier Martín Ibanez¹⁰, Javier Llorca¹¹, Raquel López-Mejías¹, Miguel A González-Gay^{1,12}. ¹Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, IDIVAL, Santander, Spain; ²Rheum. Div., Hosp. Comarcal de Laredo, Laredo, Spain; ³Rheum. Div., Hosp. Univ. de Canarias, Santa Cruz de Tenerife, Spain; ⁴Rheum. Div., Hosp. Univ. de La Princesa, IIS-Princesa, Madrid, Spain; ⁵Rheum. Div., Hosp. Univ. de San Juan, Alicante, Spain; ⁶Rheum. Div., Hosp. Gral. Univ. de Alicante, Alicante, Spain; ⁷Rheum. Div., Hosp. Gral. Univ. de Ciudad Real, Ciudad Real, Spain; ⁸Rheum. Div., Hosp. Univ. de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain; ⁹SERGAS and IDIS, The NEIRID Group, Santiago University Clinical Hospital, Santiago de Compostela, Spain; ¹⁰Inst. de Parasitol. y Biomed. 'López-Neyra', CSIC, PTS Granada, Granada, Spain; ¹¹Dept. of Epidemiology and Computational Biology, School of Medicine, Univ. of Cantabria, and CIBERESP, IDIVAL, Santander, Spain; ¹²School of Medicine, University of Cantabria, Santander, Spain

Background: Cardiovascular (CV) disease is one of the main causes of mortality in axial spondyloarthritis (axSpA). The higher incidence of CV risk factors and systemic chronic inflammation increase CV risk in axSpA.¹ This is enhanced by a dysregulation of adipokines. Low levels of omentin, an anti-inflammatory adipokine, have been associated with metabolic dysfunction and CV disease in general population and conditions different from axSpA.^{2,3}

Objectives: To evaluate the implication of omentin in CV risk and subclinical atherosclerosis in axSpA at the genetic and functional (mRNA and protein) level.

Methods: 382 patients fulfilling the ASAS classification criteria for axSpA⁴ and 84 controls were included. Carotid ultrasound was performed to evaluate the presence of subclinical atherosclerosis. Serum omentin levels were assessed by ELISA. mRNA expression of *ITLN1*, coding omentin, was evaluated by RT-qPCR. *ITLN1* rs12409609 (C/T), in complete linkage disequilibrium with a polymorphism