ageing mechanisms, diagnosis/prognosis of age-related disease and even novel treatment targets.

**Objectives:** To quantify relationships between circulating microRNA expression and biological ageing and determine whether microRNAs may be a molecular clock.

**Methods:** This pilot work is a nested sub-study within a prospective, longitudinal birth cohort from May/June 1947 (the Newcastle Thousand Families Study NTFS). Serum samples from 23 subjects taken at ages 50 and 62 years were extracted from the biobank. HTG EdgeSeq microRNA whole transcriptome assay was performed, measuring expression of 2083 human microRNA transcripts using an array followed by next generation sequencing. Global microRNA expression profiles were generated and analysed using this technology, profiling all known microRNAs from a small volume of serum (<15 μL). NIH funding has been secured for whole cohort analysis.

**Results:** Resulting data has shown very strong associations (up to p<10^-17) for biological ageing, with 84 microRNAs meeting p-values<0.05 (see heat map). Analysing the whole cohort will independently validate and extend the findings, in order to identify an ageing signature; the molecular clock.

**Conclusions:** This study suggests very strong changes in microRNAs in individuals between 50 and 62, suggesting microRNA signature is a molecular clock. These observations need to be confirmed and extended to validate serum microRNAs as biomarkers for ageing, for early detection of age-related disease and as tools to monitor ageing trajectory.

**REFERENCES:**


**Acknowledgements:** Whole cohort analysis: funding secured from NHIR Biomedical Research Centre for Ageing, Newcastle-upon-Tyne, UK and benefits from an industrial partnership with HTG Molecular, Inc. USA.

**Disclosure of Interest:** None declared

**DOI:** 10.1136/annrheumdis-2018-eular.2049

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**THU0020 TOCILIZUMAB DECREASES THE PRO-INFLAMMATORY ROLE OF PLATELETS IN RHEUMATOID ARTHRITIS: IDENTIFICATION OF A NEW MECHANISM OF ACTION ASSOCIATED WITH POSITIVE RESPONSE?**

C. Prum Delepine1,2, C. Derambure3, F. Vidal4, A. Pinta5, D. Pau6, E. Conde da Silva Fraga6, O. Boyer7, E. Senbel7, P. Gaudin7,8, O. Vittecoq9, T. Lequerre9,10,11

1rheumatology department, CHU Rouen; 2Inserm U 1234; 3Inserm U 1245, Normandie University, UNIROUEN, Rouen; 4Roche SAS, Boulogne-Billancourt; 5rheumatology department, Hôpital Sainte Marguerite, Marseille; 6rheumatology department, Grenoble hospital, Echirolles; 7GIREP AE7405, Grenoble Alpes University, Grenoble, France

**Background:** Tocilizumab (TCZ), a humanised monoclonal antibody directed against IL-6 receptor, is an efficient treatment for rheumatoid arthritis (RA) but its mechanisms of action are not yet well understood.

**Objectives:** To identify new mechanisms of action of TCZ, by the study of gene expression fluctuations, between baseline (BL) and 3 months of treatment (T3m), in RA patients.

**Methods:** TOSCA study has been realised to evaluate efficiency and tolerance of TCZ administered subcutaneously in active RA patients. Among the 125 patients of TOSCA study, 38 were ranked according to their treatment response after 3 months: 29 good responders (GR), 19 of which were also treated by methotrexate (MTX) and 10 non responders (NR), 7 of which were treated by MTX (GR: DAS 28-ESR..<3.2 and Delta DAS28-ESR(T3m-BL)<3; NR: DAS 28-ESR>3.2 and Delta DAS28-ESR(T3m-BL)<3). A transcriptomic analysis was performed using a 44K whole human genomic DNA microarray (Agilent) on whole blood cells collected at BL and at T3m. We identified genes with statistically significant expression fluctuations between BL and T3m specifically in GR (and not in NR group), treated by TCZ in monotherapy (excluding genes which fluctuated only with the association TCZ-MTX). Functional bio-informatics analysis was applied to this set of transcripts, by interrogation of Gene Ontology database, using Single Experiment Analysis tool and Natural Language Processing algorithms.

**Results:** Overall, 1089 transcripts significantly dysregulated were identified only in GR group at T3m (t test, p<0.05). This first set of transcripts was reduced to 783 by exclusion of transcripts that were fluctuated specifically when MTX was associated with TCZ in GR group. The functional analysis with these 783 genes dysregulated under TCZ in monotherapy enabled the identification of 8 transcripts (CLU, F13A1, ITGA2B, ITGB3, SELP, SNCA, SPARC, TREM1) whose relative abundances were significantly reduced at T3m. These genes were enriched in "platelet alpha granule" GO functional category. Proteins encode by these genes, either released in blood circulation or expressed at the cell membrane in case of platelet activation, have a pro-inflammatory activity through an interaction between platelets and immune cells.

**Conclusions:** This transcriptomic analysis suggests a new mechanism of action of TCZ in RA and the importance of platelets activation in RA pathophysiology. Indeed, genes linked with the pro-inflammatory role of platelets were down regulated. Further functional studies will be necessary to validate the direct effect of TCZ on platelets in RA.

**Acknowledgements:** The authors would like to thank the SFR (Société Française de Rhumatologie) for the attribution of research fellowship and Roche, France, for the support by a grant.

**Disclosure of Interest:** C. Prum Delepine: None declared, C. Derambure: None declared, F. Vidal: None declared, A. Pinta Employee of: Roche Laboratory, D. Pau Employee of: Roche Laboratory, E. Conde da Silva Fraga Employee of: Roche Laboratory, O. Boyer: None declared, E. Senbel: None declared, P. Gaudin: None declared, O. Vittecoq: None declared, T. Lequerre Grant/research support from: Roche Laboratory

**DOI:** 10.1136/annrheumdis-2018-eular.1841
for leukotriene A4 hydrolase, which converts LTA4 to LTB4; microsomal glutathione S-transferase, which converts LTA4 to LTC4; and gamma-glutamyltransferase (LTC4 > LTB4). In contrast, Tr14, but not diclofenac strongly induced Nrf2 mRNA at 12–36 hours.

Conclusions: Tr14 and diclofenac had very different effects on the COX/LOX synthetic pathway after cutaneous wounding. Tr14 allowed normal autoinduction of COX2 mRNA by PGES2, but suppressed mRNA levels for the key enzymes in the leukotriene synthetic pathway. A likely explanation for these effects is that Tr14 strongly induced Nrf2 mRNA, which is known to co-repress the leukotriene enzymes via transcription factor Bach1.

Disclosure of Interest: None declared


THU0022

ANALYSIS OF 47 NON-MHC ANKYLOSING SPONDYLITIS SUSCEPTIBILITY LOCI REVEALS SHARED ASSOCIATED VARIANTS ACROSS CAUCASIANS AND CHINESE HAN

1Department of Rheumatology, Zhejiang University School of Medicine, Hangzhou, China
2Human Genetics, Genome Institute of Singapore, Singapore, Singapore

Objectives: To identify novel patient endotypes using in depth immune phenotyping.

Methods: Peripheral blood was collected from patients with primary Sjögren’s syndrome (pSS) and systemic lupus erythematosus (SLE) have led to attempts to treat pSS and SLE patients with similar biologic therapeutics. However, the results of many clinical trials are disappointing and no effective treatments are available for pSS and few for SLE patients with refractory disease.

Objectives: To identify novel patient endotypes using in depth immune phenotyping that facilitates the selection of biological therapies for patients regardless of diagnostic labels.

Methods: Peripheral blood was collected from patients with pSS and SLE.

Results: Patients with pSS, SLE and SS/SLE had both unique and shared defects in immune cell phenotype. Hierarchical clustering of CD19+ B-cells, CD4+ and CD8+ T-cells across the three disease groups identified five distinct endotypes spanning diagnostic boundaries. Three of the endotypes had distinct immune signatures, characterised by predominantly B-cell, T-cell memory or CD4+CD8- T-cell subset fingerprints respectively, while two clusters had no distinct immune profiles. Notably, clinical and disease features were not significantly different between clusters.

REFERENCES:

Disclosure of Interest: None declared


THU0023

COMPLEX IMMUNOPHENOTYPING STRATIFIES PATIENTS WITH PRIMARY SJÖGREN’S SYNDROME, SYSTEMIC LUPUS ERYTHEMATOSUS AND SECONDARY SJÖGREN’S SYNDROME ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS INTO DISTINCT CLINICALLY RELEVANT GROUPS WITH POTENTIAL THERAPEUTIC IMPLICATIONS

N. Thompson1, A. Gandhi2, R. Radmmore2, V. Gupta3, G. Robinson1, L. Martin-Gutierrez1, D. Isenberg2, E. Jury1, C. Ciuraru1, 1Inflammation, 2Rheumatology, University College London, London, UK

Background: Similarities in the clinical and laboratory features of patients with primary Sjögren’s syndrome (pSS) and systemic lupus erythematosus (SLE) led to attempts to treat pSS and SLE patients with similar biologic therapeutics. However, the results of many clinical trials are disappointing and no effective treatments are available for pSS and few for SLE patients with refractory disease.

Objectives: To identify novel patient endotypes using in depth immune phenotyping that facilitates the selection of biological therapies for patients regardless of diagnostic labels.

Methods: Peripheral blood was collected from patients with pSS (n=38), SLE (n=38), SS/SLE (n=15) and age-sex/matched controls (n=34). In-depth phenotyping of peripheral B and T-cell subsets by flow-cytometry, followed by unsupervised cluster analysis were performed. ROC analysis identified immune signatures characteristic for each cluster.

Results: Patients with pSS, SLE and SS/SLE had been both unique and shared defects in immune cell phenotype. Hierarchical clustering of CD19+ B-cells, CD4+ and CD8+ T-cells across the three disease groups identified five distinct endotypes spanning diagnostic boundaries. Three of the endotypes had distinct immune signatures, characterised by predominantly B-cell, T-cell memory or CD4+CD8- T-cell subset fingerprints respectively, while two clusters had no distinct immune profiles. Notably, clinical and disease features were not significantly different between clusters.