Disclosure of Interests: Nisha Nair: None declared, Darren Plant: None declared, John Isaacs Speakers bureau: Abbvie, Gilead, Roche, UCB, Grant/ research support from: GSK, Janssen, Pfizer, Ann Morgan Speakers bureau: Roche, Chugai, Consultant of: GSK, Roche, Chugai, AstraZeneca, Regeneron, Sanofi, Vifor, Grant/research support from: Roche, Kiniksa Pharmaceuticals, Kimme Hyrich Consultant of: AbbVie, Grant/research support from: Pfizer, BMS, Anne Barton Grant/research support from: I have received grant funding from Pfizer, Galapagos, Scipher Medicine and Bristol Myers Squibb., Anthony G Wilson: None declared

AB0011 DNA METHYLATION AS A BIOMARKER OF TOCILIZUMAB RESPONSE IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Tocilizumab (TCZ) is a disease-modifying antirheumatic biologic drug, which targets the IL-6 signalling pathway and is effective in ameliorating disease activity in rheumatoid arthritis (RA). However, approximately 50% of patients do not respond adequately to TCZ and some patients report adverse events. Considering there is growing evidence that DNA methylation is implicated in RA susceptibility and response to some biologics (1, 2), we investigated DNA methylation as a candidate biomarker for response to TCZ in RA.

Objectives: To identify differential DNA methylation signatures in whole blood associated with TCZ response in patients with RA.

Methods: Epigenome-wide DNA methylation patterns were measured using the Illumina HumanMethylation EPIC BeadChip (Illumina) in whole-blood derived DNA samples from patients with RA. DNA was extracted from blood samples taken pre-treatment and following 3 months on therapy, and response was determined at 6 months using the Clinical Disease Activity Index (CDAI). Patients who had good response (n=10) or poor response (n=10) to TCZ by 6 months were selected. Samples from secondary poor responders (n=10) (patients who had an improvement of CDAI and were in remission at 3 months, followed by a worsening of CDAI at 6 months) were also analysed. Differentially methylated positions (DMPs) were identified using linear regression, adjusting for gender, age, cell composition, smoking status, and glucocorticoid use.

Results: In the pre-treatment samples, 20 DMPs were significantly associated with response status at 6 months (unadjusted p-value <10^{-6}), whilst in the 3 month samples, 21 DMPs were associated with response. One DMP, cg03121467, was significantly less methylated in good responders compared to poor responders in the pre-treatment samples. This DMP is close to EPB41L4A and may play a role in β-catenin signalling. Interestingly, cg10136146 was significantly less methylated in secondary poor responders compared to both good and poor responders in the 3 month samples. This DMP maps close to CD81, which plays a role in mediating the development and activation of B and T lymphocytes.

Conclusion: These preliminary results provide evidence that DNA methylation patterns may predict response to TCZ. Further regional and pathway analyses are in progress and validation of these findings in other larger data sets is required.

References:

AB0012 IDENTIFICATION OF NEW BIOMARKERS FOR SINOMENINE TREATMENT IN RHEUMATOID ARTHRITIS BASED ON BIOINFORMATICS ANALYSIS

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Background: Sinomenine (SIN) were extracted from Caulis Sinomenii and achieved an remarkable therapeutic effect for Rheumatoid Arthritis (RA). However, the mechanism of SIN acting on RA is not clear yet.

Objectives: To excavate potential targets and mechanisms of SIN for RA through bioinformatics.

Methods: The microarray data were downloaded from the Gene Expression Omnibus (GEO) database. GEO2R was used to identify differentially expressed genes (DEGs) and the unique value was retained. The potential targets of active compounds from various databases were screened. Based on the overlapping genes, Cytoscape 3.7.2 software was used to construct a protein-protein interactions (PPI) network and to visualize the mechanisms of the treatment by Gene Ontology (GO) enrichment analysis of Genes and Genomes (KEGG) analysis by DAVID database. Finally, we used AutoDockTools 1.5.6 for molecular docking.

Results: A total of 5053 DEGs and 1070 intersections were obtained, including 486 up-regulated and 584 down-regulated targets. 298 SIN targets were collected from various databases. 84 potential targets were obtained by intersecting with DEGs. There are 80 nodes and 305 edges were obtained in PPI network. Based on the degree, the top 10 target genes were AKT1, RGRF, MTOR, JAK2, NOS3, IL2, IL6, MMP9, MAPK8, HSP90AA1. The core targets were most relevant to protein phosphorylation, signal transduction though GO analysis. The results of the KEGG enrichment analysis included PI3K-Akt signaling pathway and Neuroactive ligand-receptor interaction. Following analysis found that AKT1, EGFR, MTOR and JAK2 existed in the PI3K-Akt signaling pathway. Molecular docking was used to confirm that the binding energy of AKT1 was -7.86 kJ mol^{-1}, EGFR was -5.33kJ mol^{-1}, and MTOR was -4.77 kJ mol^{-1}.JAK2 was -3.25 kJ mol^{-1}. AKT1 and EGFR was further identified as the core targets.

Conclusion: Present study showed that AKT1 and EGFR may be the key targets of SIN acting on the PI3K-Akt signaling pathway, thereby inhibiting the progression of disease and improving RA.

Keywords: Sinomenine; Rheumatoid Arthritis; bioinformatics; Disclosure of Interests: None declared

Funding: This project was supported by grants from National Natural Science Foundation of China (No. 81703783 and 81503415); Identification of new biomarkers for Sinomenine treatment in Rheumatoid Arthritis based on bioinformatics analysis

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Disclosure of Interests: None declared

AB0013 DNA METHYLATION AS A BIOMARKER FOR TREATMENT RESPONSE TO TOCILIZUMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS

1.05-12.38); p=0.019; LR ↑ =1.30 (Cl↓, 1.03-1.43); LR ↓ =0.36 (Cl↑, 0.12-0.92) and increase of AA genotype frequency in healthy women (p 2-t =0.041). We revealed that minor allele G of PTPN2 rs2542151 is more frequent in SLE women vs healthy controls and has overdominant model of inheritance (OR=138 (Cl↓, 1.09-3.59); p=0.028; LR ↑ =1.57 (Cl↓, 1.07-2.20); LR ↓ =0.79 (Cl↑, 0.62-0.97)). There were no significant differences in genotypes and alleles distribution for PTPN22 rs2476610, RUNX1 rs9979383, SLC7A11 rs13128867 and IL6 rs1800795 in studied population and we noted only non-significant tendency in minor SNP genotypes distribution of IL6 rs4845618 and IL6R rs2228145 between healthy controls and women with SLE.

Conclusion: Our data suggest the susceptibility to SLE in women with TT genotype of STAT4 rs5714865 polymorphism and allele G carriers of both TRAF1/C5 rs3761847 and PTPN2 rs2542151 as well as protective role of AGER rs1035798 A allele carriage against SLE development in women of Belarusian population.

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Acknowledgements: This research was supported by The Research Technical Program “DNA Identification” (2017–2021), project number: 6.4 Disclosure of Interests: None declared