identified 245 differentially accessible regions (DAR) around peaks unique to treatment-naïve pSLE patients, of which over 50% appear to be more accessible in pSLE than HC, and are located more than 100kb from the nearest transcription start site (nTSS), implying transcription factors (TF) may be acting on distal enhancers to regulate transcription. pSLE DAR were enriched for the enhancer H3K4me3. In DAR encompassing TF binding sites, pSLE samples, but not HC, were enriched for several disease-associated SNPs previously identified in lupus genome-wide association studies. Variant calling within DAR found 3864 genes belonging to 129 different biologic processes, including cellular activation in immune response and responses to external stimuli. In contrast, over 80% of peaks unique to pSLE patients post-induction therapy are located distal to nTSS. Induction therapy for pSLE patients included corticosteroids in all patients, cyclophosphamide in 5, and mycophenolate in 3. DAR from the pSLE patients post-induction therapy were not enriched for enhancers or disease-associated SNPs.

Conclusion We demonstrate an epigenetically-distinct profile in pSLE B cells when compared to HC, indicating pSLE B cells are predisposed for disease development. Pathways of significance analyses identified immunologic pathways important in the pro-inflammatory response in treatment-naïve pSLE patients. These pathways were absent in analyses from the same pSLE patients post-induction therapy. Thus, increased chromatin accessibility in genomic regions controlling activation of inflammatory and immune responses suggest transcriptional dysregulation of key players in immune cell activation plays an important role in pathogenesis of SLE. Treatment with corticosteroids and immunosuppressive medication changes this epigenetic profile, making pathways responsible for inflammation and B cell activation less accessible.

Acknowledgment This work would not have been possible without the expertise of Dr Frank Jenkins. This work was funded by the Rheumatology Research Foundation.

Results Patients with systemic lupus erythematosus who inherit two APOL1 risk variants are more likely to progress to ESKD and often display focal and diffuse proliferative or membranous glomerular lesions. Kidney disease often progresses despite cytotoxic therapy. In contrast, APOL1 is not associated with mild LN. Therefore, APOL1 risk variants are nephropathy progression factors. Not all individuals with two APOL1 risk variants develop CKD; modifying factors are required. HIV infection, SARS-CoV-2 infection, and interferon are powerful second hits that initiate nephropathy in genetically susceptible hosts.

Conclusions Conventional treatments for kidney disease often fail to halt the progression of non-diabetic CKD. Novel small molecule inhibitors of APOL1 protein and APOL1 anti-sense oligonucleotides hold great promise for slowing progression of APOL1-associated nephropathy, including LN. Treatments have the potential to reduce disparities in CKD risk among individuals with African ancestry. In addition, the NIH ‘APOL1 Long-term Kidney Transplant Outcomes’ (APOLLO) Consortium is considering the role of APOL1 genotyping in deceased African kidney donors to improve organ allocation. Discovery of the APOL1 genetic association with nephropathy in the lab has moved to the bedside and will improve patient outcomes.

1600 – Biomarkers in clinical trials

1601 SCORING PERSONALIZED MOLECULAR PORTRAITS OF SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS TO PREDICT TREATMENT RESPONSES, FLARES, AND PROGNOSIS

1Daniel Toro-Dominguez, 1,2Raul Lopez-Dominguez, 1Guillermo Barturen, 1Pedro Camona-Saez, 1,2Marta E Alarcon-Riquelme†, 1GENYO, Granada, Spain; 2University of Granada, Granada, Spain; 3Karolinska Institute, Stockholm, Sweden

Objectives Systemic Lupus Erythematosus is a complex autoimmune disease that leads to important worsening of the quality of life and significant suffering to those affected. Currently, therapies used are partially inefficient, mainly due to the molecular heterogeneity of the disease, being personalized medicine the big promise for the future of autoimmunity. With this work we intend to take a step further in that direction by developing MyPROSLE, a system capable of measuring the molecular portrait of individual patients.

Methods We defined co-expressed and functionally annotated gene-modules conserved across two longitudinal datasets with 158 and 301 patients. The dysregulation magnitude of each gene-module was calculated at the patient level using averaged z-scores. We analyzed the association between gene-modules, clinical manifestations and the evolution of the disease by ANOVA, Student’s t-test and Cox proportional-hazard models. Drug responses to hydroxychloroquine and mycophenolate was analyzed by comparing each individual’s molecular portraits. A third dataset of 1760 patients was used to compare the response to Tabalumab.

Results The system allows to quantify the dysregulation of 30 gene-modules individually with respect to healthy distributions. We show that dysregulation of certain gene-modules is strongly associated with different clinical manifestations and with predicting the time when remissions and relapses of the
disease are to occur in the short term. We also demonstrate how the analyzed drugs act specifically on patients with strong dysregulation of gene-modules related with plasma cells.

Conclusion MyPROSLE allows to extract key information for medical practice and may be a support for more precise therapeutic decisions in the future.

**Abstracts**

**1602 TRANSCRIPTOMIC PROFILES PREDICT RESPONSE TO RITUXIMAB IN SLE**

1Lucy M Carter, 1Adewonuola Alase, 2Zoe Wigston, 3Antony Psarras, 4Agata Burska, 1Yuzahfu Yusof, 1John A Reynolds, 1Paul Emery, 1Miriam Wittmann, 1Ian N Bruce, 1Edward Vital, 1NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds; 2Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham and Sandwell and West Birmingham NHS Trust, Birmingham; 3Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, University of Manchester; 4Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds

10.1136/lupus-2021-lupus21century.95

**Background** B cells are a common therapeutic target in SLE but responses are mixed suggesting that some aspects of disease are less B cell-dependent. Transcriptomic analyses have revealed gene-expression profiles that stratify clinical and demographic aspects of lupus. However, these have not been yet linked to response to targeted therapies. Such linkages can elucidate critical pathogenic mediators that differ between transcriptomic subsets.

**Methods** We developed a 96-gene Taqman assay including scores for: Interferon Score A (M1.2 and M3.4), Interferon Score B (M3.4 and M5.12), neutrophils (M4.9), plasmablasts (M4.11), myeloid (M5.7), inflammation (M4.2) and erythropoiesis (M4.4). Each was the median normalised dCT of transcripts representative of the module. This was assessed in whole blood from 123 active SLE patients starting new immunosuppression. After exploring baseline associations, we then evaluated clinical response to a first cycle of rituximab 2x1000mg, using a BILAG-based endpoint (As reduce to B or better, ≤1 persistent B at 6 months, no new A/B)

**Results** Transcriptomic profiles markedly differed between patients with European Ancestry (EA, n=128) compared to African and Asian Ancestries (n=85). EA had significantly lower expression for IFN Score A (p<0.001), IFN Score B (p=0.039), and plasmablasts (p=0.001). No substantive differences were seen in neutrophil (p=0.26), erythropoiesis (p=0.26) and inflammation (p=0.85) scores. In EA, IFN

| Abstract 1602 Table 1 |
|------------------------|
| **Baseline Characteristics of NEA Clusters 1, 2 and 3** |
| **Characteristic** | **Cluster 1** | **Cluster 2** | **Cluster 3** | **p value** |
| | **n = 9** | **n = 36** | **n = 40** | |
| **Female, (%)** | | | | |
| **Ancestry, n (%)** | | | | |
| **Subcontinental Asian** | 3 (33.3) | 11 (30.6) | 13 (32.5) | 0.78 |
| **Chinese and Other Asian** | 0 (0.0) | 7 (19.4) | 4 (10.0) | 0.78 |
| **African including mixed race** | 4 (44.4) | 13 (36.1) | 17 (42.5) | 0.9 |
| **Other including mixed race not otherwise specified** | 2 (22.2) | 5 (13.9) | 17 (42.5) | 0.9 |
| **Age (years), mean (95% CI)** | 45 (35,54) | 35 (21,41) | 37 (32,41) | 0.9 |
| **Disease duration (years), mean (95% CI)** | 17 (6,16) | 14 (11,17) | 12 (8,15) | 0.9 |
| **BILAG A or B score, n (%)** | | | | |
| **Mucocutaneous** | 1 (11.1) | 12 (33.3) | 18 (45.0) | 0.39 |
| **Musculoskeletal** | 2 (22.2) | 16 (44.5) | 15 (45.5) | 0.70 |
| **Renal** | 4 (44.4) | 15 (41.7) | 18 (48.6) | 0.9 |
| **BILAG numerical score, mean (95% CI)** | 16.5 (12.6, 20.3) | 19.5 (16.2, 22.8) | 19.4 (15.9, 22.9) | 0.9 |
| **SLEDAI-2K, mean (95% CI)** | 5.8 (1.0, 10.7) | 10.6 (8.6, 12.6) | 9.9 (7.4, 12.3) | 0.9 |
| **SLICC damage index, mean (95% CI)** | 1.13 (0.2, 2.3) | 0.8 (0.2, 1.4) | 1.03 (0.5, 1.5) | 0.9 |
| **Full blood count, mean (95% CI)** | | | | |
| **Hb** | 116.1 (98.0, 134.3) | 110.23 (103.1, 117.3) | 120.3 (112.4, 128.4) | 0.9 |
| **Neutrophils** | 9.6 (5.0, 14.2) | 6.0 (4.7, 7.2) | 4.0 (2.7, 5.5) | 0.9 |
| **Lymphocytes** | 1.83 (1.0, 2.6) | 0.79 (0.61, 1.0) | 1.61 (1.1, 2.1) | 0.9 |
| **Total IgG (g/L), mean (95% CI)** | 7.5 (6.1, 8.9) | 17.2 (14.8, 20.0) | 16.9 (14.2, 19.6) | 0.038 |
| **Low C3 or C4, n (%)** | 3 (33.3) | 21 (61.8) | 24 (50.0) | 0.29 |
| **Concurrent Immunosuppressant, n (%)** | | | | |
| **Any agent (MMF, CsA, Tac, MMF, AZA)** | 2 (22.2) | 15 (38.5) | 22 (55.0) | 0.16 |
| **Mycophenolate mofetil** | 1 (11.1) | 13 (36.1) | 18 (45.0) | 0.16 |
| **Azathioprine** | 0 (0.0) | 3 (8.3) | 2 (5.0) | 0.60 |
| **Anti-malarial, m (%)** | 5 (55.6) | 18 (50.0) | 21 (47.7) | 0.95 |
| **Oral prednisolone dose (mg), mean (95% CI)** | 19.9 (13.0, 26.6) | 11.7 (8.3, 15) | 11.3 (8.9, 13.7) | 0.033 |
| **RTX response analysis n = 45** | | | | |
| **BILAG response (6 month), n/N (%)** | 1/7 (14.3) | 16/19 (84.2) | 8/19 (42.1) | 0.002 |