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.

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## 1510 PREDICTING RISK OF SEVERE LUPUS NEPHRITIS IN AFRICAN AMERICANS: THE *APOL1* STORY

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**Background** Compared to European, Asian and Native Americans, African Americans have a 3-fold higher risk of developing end-stage kidney disease (ESKD) and are more likely to develop severe lupus nephritis (LN).

**Methods** Strong genetic association is observed between the apolipoprotein L1 gene (*APOL1*) and a spectrum of non-diabetic chronic kidney diseases (CKD) in African Americans, including LN, focal segmental glomerulosclerosis, solidified glomerulosclerosis (hypertension-attributed nephropathy), HIV-associated nephropathy, sickle cell nephropathy, and premature failure of transplanted kidneys from *APOL1* high-risk donors. *APOL1* risk variants arose in sub-Saharan Africa and are present only in those who possess recent African ancestry. These variants account for much of the excess risk for LN and CKD in African Americans. Studies in transgenic mice prove that *APOL1* risk variants cause CKD. Kidney disease is due to locally produced APOL1 protein in kidney cells, not circulating APOL1 protein in the blood.

**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 American 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

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**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