(aNR), inactive LN patients (iLN), inactive non-renal SLE patients, chronic kidney disease (CKD) patients, and healthy controls (HC) (all p < 0.0001) (table 1, figure 1A). uL-selectin positively correlated with global and renal disease activities (all p < 0.0001) and was significantly associated with activity index (AI) and chronicity index (CI) (figure 1E-F). It also correlated with conventional metrics (serum C3, anti-dsDNA and 24h proteinuria) and histological characteristics (figure 1G). Univariate and multivariate logistic regression analyses revealed low uL-selectin as an independent risk factor for high CI (CI>3) (figure 1J). Similar results were noted in the US-based cohort consisting of Caucasian, African American and Hispanic subjects (figure 1B-D). In a longitudinal cohort of LN patients, uL-selectin levels decreased at the end of follow up in the remission group (p=0.001), but not in non-remission patients (p=0.58) (figure 1H-I).

Conclusions uL-selectin is a novel biomarker of clinical disease activity and renal histopathology in LN across multiple ethnicities. It also reflects treatment response in LN patients during follow up.

LO-006 CHANGE IN URINARY BIOMARKERS AT THREE MONTHS PREDICTS 1-YEAR TREATMENT RESPONSE OF LUPUS NEPHRITIS BETTER THAN PROTEINURIA

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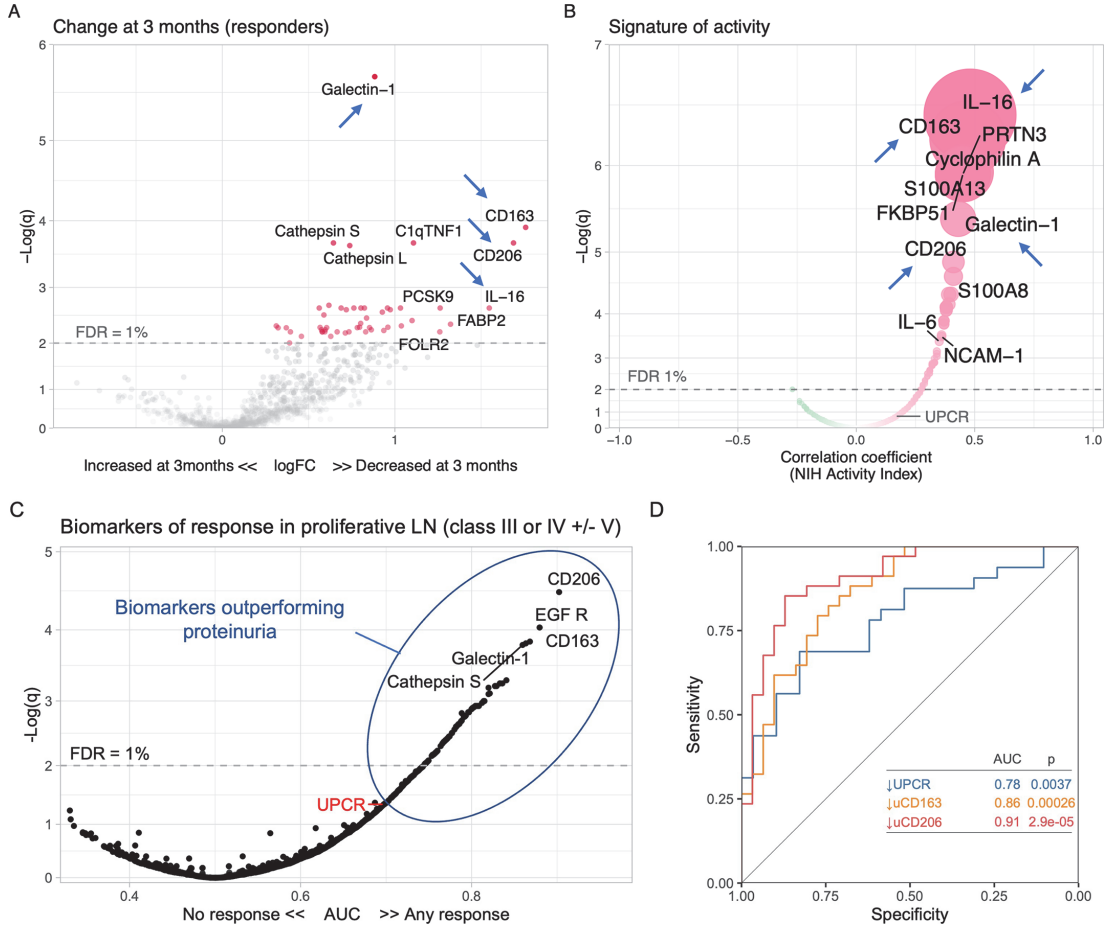

Abstract LO-006 Figure 1 (A) Volcano plot of the changes of the urinary proteomic profile of treatment responders at 3 months after kidney biopsy compared to time of biopsy. (B) Correlation of urinary biomarkers at time of biopsy the NIH Activity Index. (C) Area under the curve (AUC) of the 1yr response prediction of the change of a biomarker at 3 months. (D) ROC curves comparing the performance of 3-months biomarker decline. FDR, false discovery rate. q, adjusted p value, UPCR, urine protein-to-creatinine ratio

Background A decline of urine protein-to-creatinine ratio (UPCR) to < 0.5 is associated with better long-term preservation of kidney function in lupus nephritis (LN). UPCR < 0.5 defines complete response in guidelines and clinical trials when achieved after 1 or 2 years. Biomarkers of early response are needed to guide early treatment changes. We studied longitudinal urine proteomic profiles in LN to identify early predictors of proteinuric response.

Methods We quantified 1200 biomarkers (Kiloplex, RayBiotech) in urine samples collected on the day of (73%) or within 3 weeks (27%) of kidney biopsy and week 12, 24, or 52 in LN patients (ISN class III, IV, V, or mixed) with proteinuria > 1 g/d. Response was defined at one year from renal biopsy: Complete = UPCR < 0.5, serum creatinine (sCr) < 125% of baseline, prednisone ≤ 10mg/d; Partial = UPCR < 50% from baseline but >0.5, sCr < 125% of baseline, but prednisone allowed to 15 mg/d; Non responder = not meeting previous definitions.

Results A total of 127 patients were included: 48 (38%) with pure proliferative LN (class III or IV), 41 (32%) with mixed LN (III or IV +/- V), and 38% (30%) with pure membranous LN. Response was complete in 34 (27%), partial in 29 (23%), and none in 64 (50%). There were no urinary biomarkers at baseline that predicted response. We then analyzed the changes in urinary proteins at 3 months compared to baseline. Patients who responded at 1 year showed an early decline in 51 urinary proteins led by CD163, IL-16, and CD206 (macrophage mannose receptor) (figure 1A) which matched the proteomic signature associated with histological activity (figure 1B). No changes were observed in nonresponders. The decline of several urinary biomarkers at 3 months outperformed a decline in UPCR (clinical standard) in predicting the 1 year response. In particular, a decline of CD163 predicted 1 year response in ROC analysis with an area under the curve (AUC) of 83% compared to an AUC of 75% for UPCR decline. In proliferative LN, urinary biomarkers displayed superior performance with an AUC of 91%, 86%, and 78% for the decline of CD206, CD163, and UPCR, respectively (figure 1C-D). Pathway enrichment analysis identified leukocyte activation, neutrophil degranulation, and matrix degradation as the main pathways reduced at 3 months in responders.

Conclusions An early decline in urinary biomarkers of histological activity is associated with proteinuric response at 1 year. These findings indicate that effective immunosuppression induces by three months an immunological response in the kidney that can be noninvasively monitored in the urine. Biomarkers of immunological response outperformed early decline of UPCR, the standard of care, in predicting 1-year proteinuric response, especially in proliferative LN. Because biomarkers of immunological response parallel intrarenal activity, they could detect early treatment response/failure and allow early treatment changes. They could serve as surrogate endpoints in clinical trials. Longitudinal studies are needed to confirm that this immunological response is a better predictor of long-term kidney function preservation than proteinuric responses.

Plenary session 2: disease mechanism

LO-007 EZH2 DEFICIENCY IN B CELLS IMPAIRS PLASMABLAST DIFFERENTIATION AND AMELIORATES LUPUS-LIKE DISEASE IN MICE

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Background Enhancer of zeste homolog 2 (EZH2) is an epigenetic regulator with a role in B cell development. We have previously demonstrated increased EZH2 expression in peripheral blood mononuclear cells isolated from lupus patients, and that pharmacological inhibition of EZH2 alleviates lupus-like disease in mouse models. The goal of this study was to evaluate the role of B cell EZH2 overexpression in lupus pathogenesis.

Methods Using CRISPR/Cas9 technology, we generated an MRL/lpr mouse with floxed Ezh2, which was crossed with CD19-Cre mice. Autoantibody production, proteinuria, and kidney histology were evaluated. Flow cytometry, single cell RNA sequencing, and single cell B cell receptor sequencing were used to investigate compositional and functional changes of B cell subsets. In vitro B cell culture with/without an XBP1 inhibitor was performed. EZH2 and XBP1 mRNA levels in CD19+ B cells isolated from SLE patients and healthy controls were analyzed.

Results Ezh2 deletion in B cells decreased autoantibody production and improved glomerulonephritis in MRL/lpr mice. B cell development and differentiation were altered in the bone marrow and spleen in EZH2-deficient mice. Differentiation of germinal center (GC) B cells and plasmablasts was impaired. XBP1, a key transcription factor in B cell development, was downregulated in the absence of EZH2, and inhibiting XBP1 in vitro impairs plasmablast differentiation similar to EZH2-deficient mice. Single cell B cell receptor RNA sequencing revealed defective immunoglobulin class switch recombination in EZH2-deficient mice. In human lupus B cells, there was a strong correlation between EZH2 and XBP1 mRNA expression levels.

Conclusions Our results suggest that EZH2 overexpression in B cells contributes to disease pathogenesis in lupus. EZH2 enhances GC B cell development and the differentiation of plasmablasts via upregulating XBP1. Inhibiting B cell EZH2 expression impairs B cell development and immunoglobulin class switch recombination, and might provide a novel therapeutic approach in lupus.