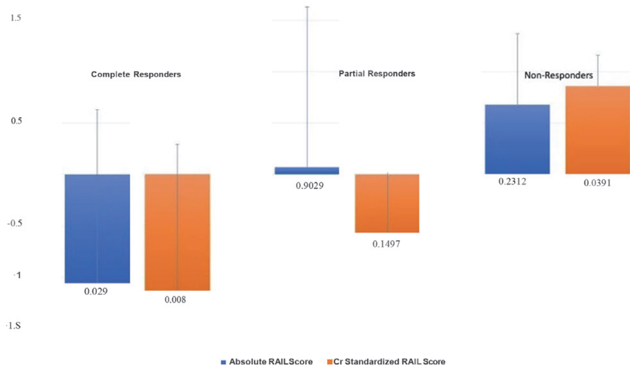

Abstract 1115 Figure 1 Change in pRAIL score by clinical response status

partial responders (0.07 ± 1.56, p= 0.91), as shown in figure 1.

Conclusions This study shows the pRAIL score (both absolute and standardized) distinguishes complete responders versus partial responders during induction therapy. Complete responders pRAIL score decrease by mean of 1 point, whereas partial responders had no change. Notably, standardized pRAIL scores yielded more pronounced differences during induction therapy among both partial and complete responders.

1116 EVIDENCE IN SUPPORT OF THE HYPOTHESIS THAT BOLSTERING ENDOTHELIAL CELL SPHINGOSINE 1-PHOSPHATE RECEPTOR 1 SIGNALING IS A RATIONAL APPROACH FOR THE TREATMENT OF LUPUS NEPHRITIS

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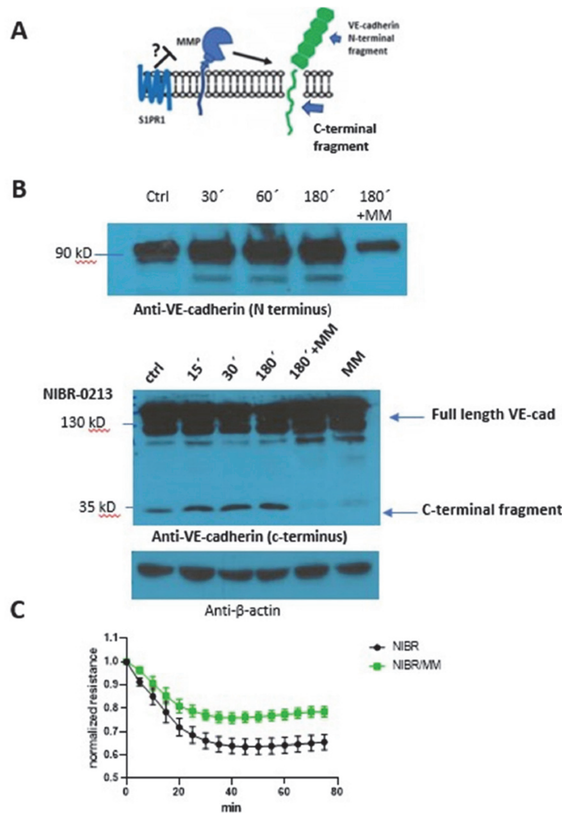
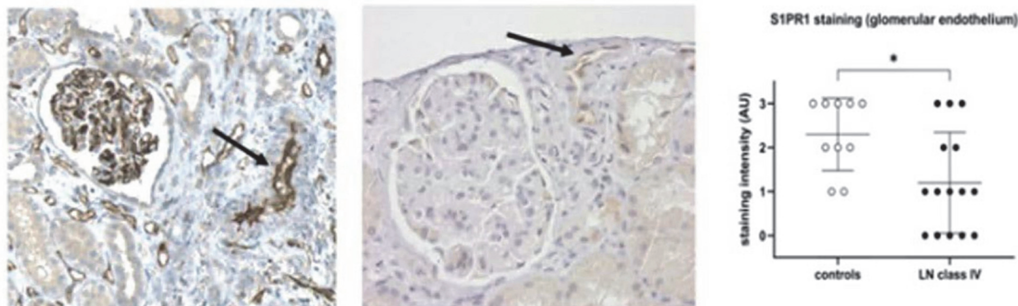
10.1136/lupus-2022-lupus21century.81

Background Proliferative lupus nephritis (LN) is characterized by robust glomerular and tubulo- interstitial inflammation, sub-endothelial deposits of immunoglobulin, and increased endothelial cell permeability. Sphingosine 1- Phosphate Receptor 1 (S1PR1) has multiple protective effects on endothelial cells (ECs): it maintains barrier function thereby protecting against vascular leakage, it limits the number of leukocytes adhering to and transmigrating across ECs, and it protects ECs against apoptosis in response to inflammatory cytokines. Despite these important protective effects, the role of S1PR1 signaling in endothelial cells in lupus nephritis (LN) has yet to be elucidated. In prior work, we showed that S1PR1 modulators attenuated immune complex mediated vascular injury in skin and lung, leading to our hypothesis that EC S1PR1 signaling limits inflammatory injury in lupus nephritis. In current studies, we assessed whether patients with LN have decreased EC S1PR1 expression, and we performed in vitro mechanistic studies to determine whether S1PR1 maintains barrier function, at least in part, by restraining the metalloproteinase



Abstract 1116 Figure 2 Evidence that S1PR1 restrains a metalloproteinase that cleaves VE-cadherin and attenuates barrier function. (A) Proposed model (B) Western blot of supernatants (top panel) or lysates (middle panel) from HUVEC treated with NIBR-0213 collected at 30-180 min +/- the MMP inhibitor MM. Lysates were probed with an antibody to β-actin as a loading control (bottom panel). (C) ECIS study of confluent HUVEC treated with NIBR (black curve) vs NIBR + MM (green curve)



Abstract 1116 Figure 1 Immunohistochemistry images of control (left) and SLE (right) renal biopsies demonstrating glomerular EC loss of S1PR1 in SLE. Arrow denote EC S1PR1 staining. Graph on right showing quantification; Mann-Whitney test p=0.02, controls n=10 and SLE Class IV LN n=15.

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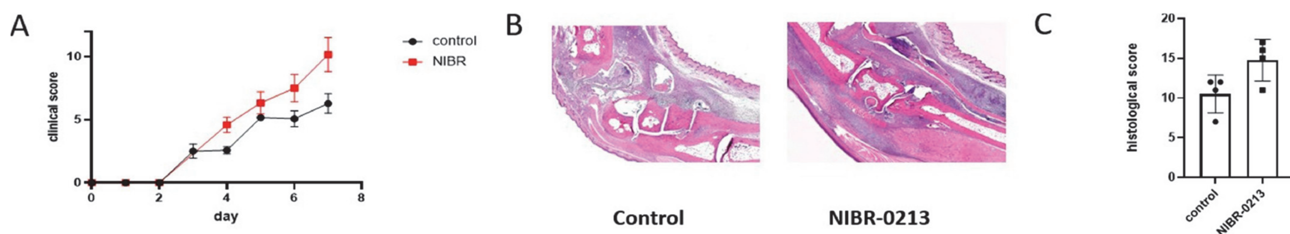

Abstract 1116 Figure 3 S1PR1 antagonist NIBR-0213 exacerbates immune complex mediated arthritis. (A) Clinical scores of mice subjected to serum induced arthritis (SIA) days 0-7. (B) Representative H&E stained sample of ankle obtained on day 7 after SIA. (C) Histological scoring of mice on day 7 after SIA.

cleavage of VE-cadherin, a key protector against vascular permeability that is highly expressed on renal ECs and is shed during inflammatory states. To further support the hypothesis that S1PR1 signaling is protective in immune complex mediated disease, we also examined the effects of a S1PR1 antagonist on serum induced arthritis, a relatively acute model of immune complex mediated arthritis to determine whether it increased disease severity.

Methods (1) Assessment of S1PR1 expression in human LN: renal biopsy samples from 15 SLE patients with class IV LN and kidney samples from age, sex and race matched controls were evaluated by immunohistochemistry and scored for the expression of S1PR1 in a blinded fashion. Staining of S1PR1 was assigned an arbitrary value of 0-4 with 4 corresponding to maximal expression and 0 corresponding to no signal above the isotype control antibody. (2) In vitro studies to test the hypothesis that S1PR1 antagonism induced VE-cadherin shedding: HUVEC were treated with an S1PR1 antagonist NIBR-0213 (1 uM) for 30, 60, or 180 min +/- the presence of a pan-metalloproteinase inhibitor marimastat (MM) and VE-cadherin shedding was assessed by western blotting. (3) EC resistance, a measure of barrier function, was measured in NIBR treated ECs +/- MM by Electric cell- substrate impedance sensing (ECIS). (4) In vivo studies to determine whether NIBR-0213 exacerbated injury in serum induced arthritis, a model of immune complex mediated injury: NIBR 30 mg/kg was administered once daily to WT C57BL/6 mice receiving 75 ul of K/BxN serum on days 0 and 2. Clinical scores were assessed daily and histological scoring was assessed on H&E stained paraffin embedded sections.

Results Assessment of S1PR1 staining in human renal tissues: 5/15 patients with lupus nephritis had EC S1PR1 expression scores of 0 in renal microvasculature compared to 0/10 controls and 10/15 patients had EC S1PR1 expression scores of 0-1 compared to 2/10 controls (figure 1).

In vitro mechanistic studies: acute blockade of S1PR1 signaling with the antagonist NIBR-0213 induced shedding of VE-cadherin in a metalloproteinase - dependent manner in as measured by increased C- terminal (remaining transmembrane fragment) and N-terminal VE-cadherin (cleaved extracellular domain) in HUVEC lysates and supernatants, respectively (Fig. 2). ECIS demonstrated that NIBR induced a drop in resistance (a measure of barrier function), as expected, but that metalloproteinase inhibition attenuated this drop in resistance suggesting that the increase in permeability induced by S1PR1 blockade requires shedding of VE-cadherin and/or other molecules that contribute to functional adherens junctions.

In vivo S1PR1 blockade in serum induced arthritis: NIBR-0213 treatment of mice subjected to serum induced arthritis exacerbated injury - based on clinical and histological assessments (Fig 3), suggesting S1PR1 signaling contributes to maintenance of EC barrier function and inhibition of S1PR1 signaling leads to vascular escape of mediators that contribute to tissue damage.

Conclusion Our studies indicate that EC S1PR1 signaling maintains barrier function, in part by restraining MMP-dependent cleavage of VE-cadherin, and thereby may protect against immune complex mediated injury in experimental models. In some patients with LN, markedly decreased EC S1PR1 expression may result in loss of barrier integrity and increased vulnerability to glomerular injury. We identify a potential new approach to attenuate renal immune complex driven glomerular injury – enhancement of EC barrier function through S1PR1 signaling. Future studies will test the role of EC S1PR1 signaling in a mouse model of lupus nephritis.

Lupus Nephritis

1117 NEUTROPHIL EXTRACELLULAR TRAPS AS A BIOMARKER TO PREDICT OUTCOMES IN LUPUS NEPHRITIS

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10.1136/lupus-2022-lupus21century.82

Background Neutrophil Extracellular Traps (NETs) have been implicated in Lupus Nephritis (LN) pathogenesis. SLE neutrophils release High Mobility Group Box-1 (HMGB1) protein, in turn, HMGB1 in NETs correlates with histologic findings of Active LN (ALN). The aim was to determine if the amount of NET complexes (Elastase-DNA and HMGB1-DNA) in serum at the time of a LN flare predicts renal outcomes in the following 24 months.

Methods The study had a 2-staged approach. In an exploratory cohort composed of active SLE (clinical SLEDAI $\geq$ 1), inactive SLE and healthy controls (HC), we assessed the association between our in-house ELISA assays for Elastase-DNA

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