identified differential expression of approximately 2000 genes between 564 and WT mice. To identify a role for interferon, RNA libraries were prepared from 564 and WT mice treated with a neutralizing antibody to IFNAR. Of the differentially expressed genes in lupus mice, about 20% were IFNa dependent. Notably, the microglia isolated from the lupus strain expressed an interferon gene signature that included IFNbeta but not IFNa. Pathway analysis of the interferon-dependent genes identified increased expression of genes important in phagocytosis and metabolic activity. Finally, reduction in peripheral levels of interferon alpha was protective from synapse loss and altered behavior (Bialas et al Nature 2017).

Conclusions We conclude that elevated blood levels of IFNa can promote neurological symptoms in mice. These findings suggest that therapies that block peripheral autoimmunity and reduce circulating levels of IFNa may protect against the symptoms of CNS lupus.

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TD-07 DISSECTING THE ROLE OF MYELOID CELLS IN LUPUS NEPHRITIS

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Background The NIH- sponsored AMP -PEARL (Accelerating Medicine Partnership lupus network Pathway Exploration and Analysis in RenaL disease) consortium sequenced RNA from ~2900 single cells from lupus nephritis kidney biopsies from 24 patients and discovered 22 immune cell types. While providing unprecedented molecular information, the study lacked *in situ* immune cell spatial context and was underpowered for associations with clinical outcomes. Thus, we aimed to investigate the spatial organization of the immune landscape in lupus nephritis tissue and determine whether *in situ* immune cell organization drives clinical outcomes. We hypothesize that the immune cell infiltrate in lupus nephritis tissue is highly organized and promotes kidney remodeling that drives clinical outcomes.

Methods We assembled a new, larger cohort of 40 lupus nephritis patients who presented with varying disease severity, undergoing their first kidney biopsies (naïve to potent immune-modulators). From these biopsy samples, we are dissecting the organizational landscape, role, and clinical associations of the five newly discovered myeloid subsets in formalin fixed paraffin embedded tissue. To map the *in situ* spatial relationships, we converted single cell RNA-sequencing signatures into molecular stains based on highly expressed myeloid subset-specific discriminatory genes with known biological functions. We then stained clinical samples from our cohort for multiplex fluorescent imaging of newly identified cell subsets.

Results We have validated the five new myeloid subsets (three monocytes, one dendritic cell, and one macrophage) in class IV lupus nephritis tissue and we are working to do the same in other histological classes. In addition, we are deconstructing myeloid subset cellular neighborhoods by mapping each to renal compartments, tissue damage, and quantifying the composition of the neighborhood's immune cell (T, B, NK cells) infiltrate.

Conclusions By converting single cell RNA sequencing information into molecular stains we have developed a novel approach to validate *in situ* five newly identified myeloid subsets in class IV lupus nephritis and we are pursuing other histological classes. We are deconstructing the *in situ* cellular neighborhood by mapping each subset across tissue to determine its relation to histopathological lesions and clinical outcomes. We expect these data to link the new myeloid subsets to distinct cellular neighborhoods, and provide the first-ever connection between well-characterized *in situ* local immune responses, their histopathologic lesions, and clinical outcomes in our clinically annotated cohort. This work will lay the groundwork for disease re-classification based on the immune response and could highlight important cell-types and pathways driving disease for follow up studies.

TD-08 HIGH TYPE I INTERFERON ACTIVITY IS ASSOCIATED WITH ACTIVE CLASS III/IV LUPUS NEPHRITIS IN EUROPEAN-AMERICAN LUPUS PATIENTS INDEPENDENT OF ANTI-DSDNA ANTIBODIES

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Background Lupus nephritis (LN) is one of the most severe types of organ involvement in systemic lupus erythematosus (SLE), despite the recent advances in immunosuppressive therapies. High type I interferon (IFN) is a heritable risk for SLE, and some previous studies have suggested a link between high IFN and lupus nephritis. However, little is known about the relationships between high levels of IFN and the subtypes of LN, and whether IFN is more associated with anti-dsDNA antibodies or with clinical nephritis.

Methods We studied 244 European-American (EA) SLE patients and measured type I IFN in sera by performing WISH IFN bioassay as described previously. Subtypes of LN were confirmed by renal biopsy review. Complements, anti-dsDNA and other auto-antibodies were measured in the clinical laboratory, and standard clinical cut-offs were used to define a positive result. Non-parametric analyses were used to compare IFN data with the clinical data. RNA *in-situ* hybridization was used to assess markers of plasmacytoid dendritic cells (PDCs) and IFN-induced gene expression in renal biopsy samples.

Results IFN level and SLEDAI score was positively correlated ($r=0.26$, $p<0.0001$, Spearman) in our cross-sectional evaluation. EA subjects with a high level of IFN (IFN score ≥ 2) were more likely to have renal manifestations compared to the subjects with a low level of IFN (IFN score <2) ($p<0.001$, OR=3.0, Fisher's exact test). In addition, the incidence rate of class III/IV LN was significantly higher among patients with a high level of IFN compared to the patients with low levels of IFN ($p<0.01$, OR=5.5, Fisher's exact test). Notably, IFN level was significantly higher in active class III/IV LN compared to inactive class III/IV LN ($p<0.05$ Mann-Whitney U) and this was not observed in non-class III/IV LN populations. Positivity of ds-DNA antibody did not show significant difference between inactive class III/IV LN and active

class III/IV LN. Using RNA-*in-situ* hybridization methods, we document infiltration of class III/IV nephrtis biopsy tissue with PDCs with IFN-signature positive cells surrounding them, supporting local production of type I IFNs.

Conclusions Our data support an association between type I IFN and class III/IV nephritis that is independent of overall SLEDAI and anti-dsDNA antibodies, suggesting that IFN is involved in renal pathogenesis. These data also suggest that IFN could predict renal disease activity or the future risk of developing LN, especially class III/IV LN in EA SLE patients.

TD-09 IL-34 PROMOTES MACROPHAGE-MEDIATED LUPUS NEPHRITIS IN MRL-*FAS*^{LPR} MICE

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Background Nephritis is the major cause of mortality and morbidity in patients with lupus. Macrophages (Mø) are central to kidney destruction in lupus-prone mice and patients. CSF-1, and the newly identified IL-34, mediate Mø survival and proliferation. However, IL-34 and CSF-1 differ during development and disease. While CSF-1 and IL-34 share the CSF-1 receptor (cFMS), expressed by Mø, IL-34 binds to a second receptor, Protein-Tyrosine Phosphatase ζ (PTPRZ) in inflamed kidneys. Intra-renal IL-34, cFMS, and PTPRZ are increased during the progression of lupus nephritis in MRL-*Fas*^{lpr} mice. Therefore, we hypothesized that IL-34 is a potential therapeutic target for lupus nephritis.

Methods and Results Using MRL-*Fas*^{lpr} IL-34 knockout (KO) mice, we found that the time-related magnitude of Mø-rich lupus nephritis and systemic illness (skin, salivary glands) were markedly suppressed in IL-34 KO MRL-*Fas*^{lpr} mice compared to wild-type (WT) or IL-34 heterzygous mice. IL-34 fostered intra-renal Mø accumulation via two mechanisms: 1) intra-renal Mø proliferation, and 2) monocyte proliferation in bone marrow that increases circulating monocytes, which are recruited into the kidney. cFMS is expressed on Mø and PTPRZ on tubular epithelial cells (TEC). We found IL-34 increased intra-renal Mø which in turn, released mediators that induced TEC apoptosis. Importantly, CSF-1 did not compensate for the absence of IL-34. These findings are translational as IL-34, *cFMS* and PTPRZ are upregulated on kidney TEC in patients with lupus nephritis compared with healthy controls and IL-34 levels are elevated and track with disease activity in the serum and urine in patients with lupus nephritis. We are currently detailing the distinct mechanistic contribution of each IL-34 receptor to the pathogenesis of lupus nephritis.

Conclusion Our findings suggest that IL-34 is a promising potential therapeutic target for patients with lupus nephritis.