technique was standardized with the arterial input function centered in the cavernous ICA segment for all subjects.

Analyses: Regions-of-interest (ROI) from previously identified hypermetabolic regions (hippocampus, orbitofrontal cortex, posterior putamen/globus pallidus/thalamus) were selected. Mirror ROIs were placed in bilateral MRI cerebral hemispheres for sampling at same brain levels. Regional DCE curves were generated to compare permeability phases. T-tests were used to evaluate demographic and NP testing differences.

Results SLE subjects performed significantly worse than HCs on 3 ANAM tests (matching grids, match to sample and continuous processing). Mean DCE curves (figure 1) show perfusion (initial spike) and permeability phases of contrast in the sampled tissues. Compared to HCs, SLE subjects demonstrate significantly increased signal in the permeability phase in the hippocampus, indicating leakage into the extravascular space.

Conclusion This is the first report of increased BBBP in SLE subjects that is specific to the hippocampus; a region previously reported to have abnormally increased resting metabolism in SLE subjects. These data, including the abnormal NP testing, support the murine model of autoantibody-mediated cognitive impairment following disruption of the BBB. The results also suggest that DCE-MRI is an effective tool to measure BBBP and its role in NPSLE pending confirmatory studies with increased sample size.

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TD-06

BLOCKADE OF INTERFERON ALPHA RECEPTOR IN LUPUS MICE PROTECTS AGAINST NEUROLOGICAL SYMPTOMS

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Background Systemic lupus erythematosus (SLE) is an incurable autoimmune disease characterized by autoantibody deposition in tissues such as kidney, skin and lungs. Although less well understood, many patients with SLE experience neuropsychiatric symptoms that range from anxiety, depression and cognitive impairment to seizures and, in rare cases, psychosis. Collectively, these symptoms are referred to as central nervous system (CNS) lupus. In some cases, autoantibodies, such as anti-NMDAR or anti-phospholipid antibodies, promote CNS lupus. However, in many patients, CNS symptoms appear prior to serum autoantibody.

Methods Lupus strains of mice used in the project: 564Igi, NZB/W, and MRL/lpr. Behavior testing was performed at the Harvard Behavior core. RNA sequencing of microglia was performed at the MIT sequencing core.

Results We found that lupus-prone mice develop a distinct behavioral phenotype such as impaired learning and memory, anxiety and altered social behavior in which onset is age dependent. Examination of the brains of the lupus mice identified excess microglia engulfment of synapse material and a reduction in synapse density in the frontal cortex and hippocampus that correlates with the behavior phenotype. Comparison of RNA sequences of bulk sorted frontal cortex microglia

Abstract TD-05 Figure 1 Dynamic contrast enhanced MRI curves show increased hippocampus permeability in SLE

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 IFN α dependent. Notably, the microglia isolated from the lupus strain expressed an interferon gene signature that included IFN β but not IFN α . 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 IFN α can promote neurological symptoms in mice. These findings suggest that therapies that block peripheral autoimmunity and reduce circulating levels of IFN α 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