Abstract 103 Table 1b Predictors for transitions to the resolved NP State

SLE NP events		
	(n = 270 transitions)	
Variable	**HR (CI)**	**p-value**
Asian race/ethnicity*	1.72 (1.17,2.54)	0.006
Any Peripheral	0.89 (0.65,1.24)	0.500
Any Central-Focal	1.74 (1.33,2.27)	<0.001
All Central-Diffuse	1.00	
Past non-SLE NP events (without headache)	0.93 (0.59,1.47)	0.76
Concurrent non-SLE NP events (without headache)	0.63 (0.44,0.91)	0.12
Previous headache	0.98 (0.67,1.43)	0.93
Current headache	0.80 (0.58,1.09)	0.15
Non-SLE NP events excluding headaches		
	(n = 176 transitions)	
Variable	**HR (CI)**	**p-value**
Hispanic race/ethnicity*	1.43 (0.96,2.13)	0.082
Non-US African race/ethnicity*	2.06 (1.14,3.73)	0.017
Age at SLE diagnosis	0.98 (0.96,0.99)	<0.001
Any Peripheral	0.76 (0.44,1.29)	0.306
Any Central-Focal	1.38 (0.72,2.64)	0.328
All Central-Diffuse	1.00	

*Other race/ethnicities were included in the analysis but the results were not significant.

association with Asian race/ethnicity, post-secondary education, and immunosuppressive or anti-malarial drugs. For non-SLE NP events, excluding headache, there was a positive association with concurrent SLE NP events and negative associations with African and Asian race/ethnicity. NP events attributed to SLE had a higher resolution rate than non-SLE NP events, with the exception of headache that had comparable resolution rates. For SLE NP events, multivariate analysis revealed resolution was more common with Asian race/ethnicity and for central/focal NP events (table 1b). For non-SLE NP events resolution was more common with African race/ethnicity and less common with older age at SLE diagnosis (table 1b).

Model 1 includes time invariant variables or those defined at all time points. Model 2 is restricted to transitions for which there is information as in model 1 and additional time variable explanatory variables available only for events occurring after the initial patient assessment.

Conclusions In a large and long-term study of the occurrence and resolution of NP events in SLE we identified subgroups with better and worse prognosis. The course of NP events differs greatly depending on their nature and attribution.

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104 DISTINCT SPATIAL PROFILE OF INFLAMMATORY GENE EXPRESSION IN THE BRAIN OF A MOUSE MODEL OF NEUROPSYCHIATRIC LUPUS

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Background SLE is an incurable autoimmune disease that results in central nervous system (CNS) involvement with clinical manifestations including anxiety and depression. However, the mechanism/s underlying these neuropsychiatric symptoms (NPSLE) remain unknown. An elevated type 1 interferon (IFNa) signature has been commonly observed in SLE patients, particularly within the CNS of NPSLE patients (Crow et al., 2014, Shiozawa et al., 1992). Given the diversity of clinical CNS manifestations, we hypothesized that type 1 interferon-mediated inflammation occurs in spatially distinct regions within the CNS, resulting in differential behavioral outcomes depending on the impacted brain region.

Methods Spatial distribution of inflammatory gene expression in the brain was performed using MERFISH, a multiplexed spatial transcriptomics platform employing a custom set of RNA probes. Cell source and *in situ* results were validated by RT-PCR, RNA scope and single nucleus sequencing of RNA (sNuc-Seq).

Results Characterization of *Sle 1, yaa* mice in behavior assays, identified anxiety-like, and fatigue-like behaviors consistent with NPSLE. Notably, the behavior changes correlate with distinct patches of interferon stimulated gene (ISG) expression within the subcortical regions of mouse brains. Preliminary single nucleus sequencing (sNuc-Seq) and *in situ* hybridization results implicate astrocytes and oligodendrocytes as the major cell classes enriched in these ISG patches.

Conclusions In summary, our results validate a mouse behavioral model of NPSLE, and show spatially distinct regions of ISG expression within the CNS, opening up a new avenue of investigation into the fundamental mechanisms of NPSLE.

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200 – Cutaneous SLE

201 TYPE I INTERFERON MODULATES LANGERHANS CELL ADAM17 IN LUPUS TO CONTRIBUTE TO PHOTOSENSITIVITY

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Background Photosensitivity is a common feature in systemic lupus erythematosus (SLE), is considered to be a major contributor to SLE skin disease, and can be associated with serious flares of systemic disease, but mechanistic understanding remains limited. Several lines of evidence including the finding of a type I interferon (IFN-I) signature in non-lesional skin, the potentiation of keratinocyte apoptosis by IFN-I, the importance of IFNAR in murine lupus model skin lesion development, and the improved skin scores in the clinical trials of anifrolumab (anti-IFNAR1) point to a pathogenic role for IFN-I in SLE skin disease. We recently showed that Langerhans cells (LCs) limit UVR-induced keratinocyte apoptosis and skin injury via ADAM17-mediated EGFR ligand activation and

that reduced LC ADAM17 activity in two lupus models contributed to their photosensitivity. Non-lesional human SLE skin also showed evidence of a dysfunctional LC-keratinocyte axis; however, what causes LC dysfunction is not known. Here we test the hypothesis that IFN-I in the skin contributes to LC ADAM17 dysfunction and thus photosensitivity.

Methods To assess IFN-I gene signature, microarray of non-lesional skin from human cutaneous LE and RNA sequencing of whole skin from lupus mouse models were performed. To quantify human and murine LC ADAM17 activity and expression, *in vitro* and *ex vivo* flow cytometric-based assays were conducted LCs. To assay photosensitivity, readouts of skin inflammation and cellular infiltrate were measured and characterized.

Results We show that non-lesional skin from human cutaneous LE and photosensitive MRL/lpr and B6.Sle1yaa mice all share IFN-I signatures and that IFN-I is sufficient to reduce human and murine LC ADAM17 activity independently of surface ADAM17 levels. IFN-I induced LC ADAM17 activity defects were abrogated with tofaticinib, a JAK kinase inhibitor approved for rheumatoid arthritis and other rheumatologic diseases. We further show that anti-IFNAR1 treatment prior to UVR exposure in lupus models restores LC ADAM17 activity and limits photosensitivity.

Conclusions Together, our results suggest a model whereby the elevated IFN-I in non-lesional skin contributes to photosensitivity at least in part by causing LC ADAM17 dysfunction. The corollary is that anti-IFNAR has beneficial effects at least in part by correcting LC ADAM17 dysfunction.

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202 CAUSES OF DEATH AMONG POPULATIONS WITH SYSTEMIC LUPUS ERYTHEMATOSUS BY SEX, RACE AND ETHNICITY

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Background Data indicate that minority populations with systemic lupus erythematosus (SLE) are at higher risk of developing disease and have more severe outcomes, including mortality. However, whether specific causes of death vary by race and ethnicity has largely been unexplored, particularly for Asians and Hispanics.

Methods The California Lupus Surveillance Project identified potential SLE cases using community rheumatology and nephrology clinics, community hospitals, and integrated healthcare systems among individuals who were residents of San Francisco County, CA during January 1, 2007 – December 31, 2009. Cases were matched to the 2007-2017 National Death Index (NDI) data, which included the underlying cause of death for each individual. Chi-squared tests were used to examine differences in underlying cause of death by race (white, Black, Asian), ethnicity (Hispanic, non-Hispanic), and sex. Age-standardized mortality ratios (SMRs) between SLE patients and the general San Francisco county population were calculated for the leading cause of death, and estimated observed versus expected deaths by sex, race, and Hispanic/Latino ethnicity.

Abstract 202 Table 1 Standardized mortality ratios of cardiovascular disease (CVD) in SLE patients compared to the general San Francisco county population, age-standardized, 2007–2017

	Total SLE Population	CVD as Underlying Cause of Death		
		Observed CVD Deaths in CLSP	Expected CVD Deaths	SMR (95% CI)
Overall	809	45	12.4	3.63 (2.65, 4.86)
Race				
White	311	13	5.3	2.43 (1.29, 4.16)
Black	164	16	5.5	2.89 (1.65, 4.70)
Asian	294	14	3.7	3.83 (2.09, 6.42)
Ethnicity				
Hispanic	123	7	1.1	6.45 (2.59, 13.29)
Non-Hispanic	604	36	10.6	3.39 (2.37, 4.69)
Sex				
Female	728	40	8.6	4.65 (3.32, 6.34)
Male	81	5	1.4	3.48 (1.13, 8.12)

Results During the study period, 135 deaths related to SLE were identified (n=809). The top underlying cause of death overall (33%) and across all racial and ethnic groups was cardiovascular disease (CVD). Other top causes of death included rheumatic disease (18%) and hematological/oncological conditions (18%) overall, and across all racial groups. Analyses examining any cause of death indicated that rheumatic disease was more commonly indicated among white (50%) and Asian (46%) patients as compared to Black (27%) patients with SLE. In comparison to the general population of San Francisco County, CVD as the underlying cause of death was over three times higher among individuals with SLE (SMR=3.63) (table 1). CVD deaths for those with SLE were nearly three times higher for Black, approximately four times higher for Asian, and over six times higher for Hispanic/Latino individuals. CVD deaths were also elevated for females (SMR=4.7) and males (SMR=3.5) with SLE compared to the general population.

Conclusions Our results show that CVD is the leading underlying cause of death among SLE patients across various racial and ethnic groups, and that rheumatic disease may be less likely to be listed as a cause of death among Black patients with SLE. Further, Asian and Hispanic/Latino SLE patients experience a disproportionate burden of CVD mortality compared with the general population.

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203 NON-LESIONAL AND LESIONAL LUPUS SKIN SHARE INFLAMMATORY PHENOTYPES THAT DRIVE ACTIVATION OF CD16+ DCS

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