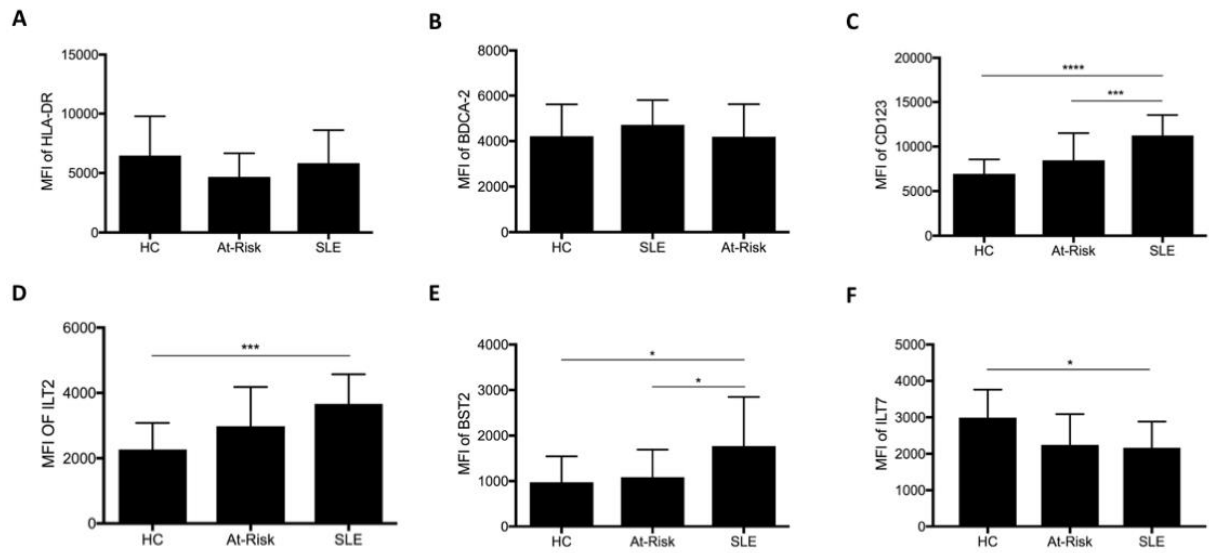
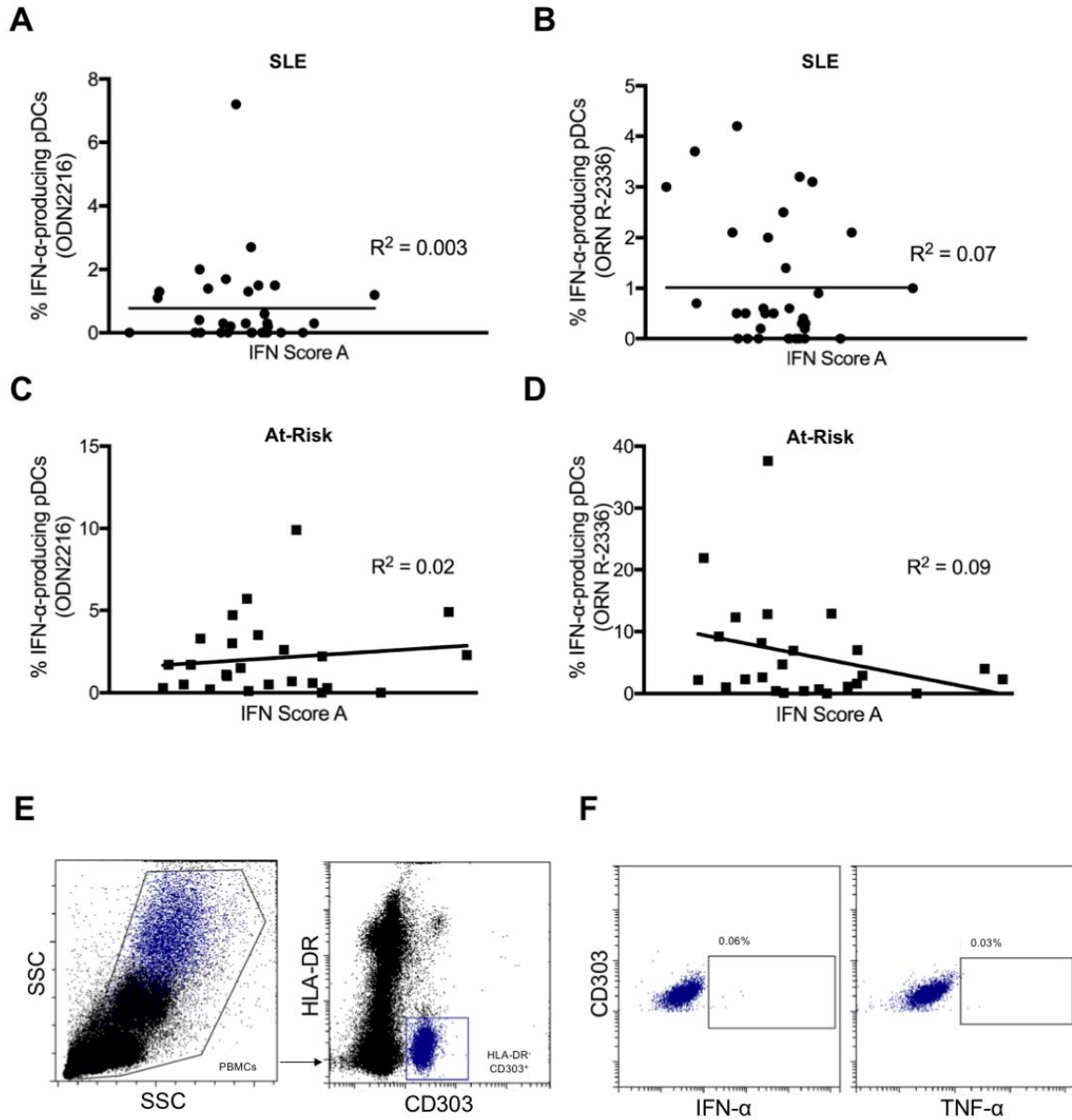


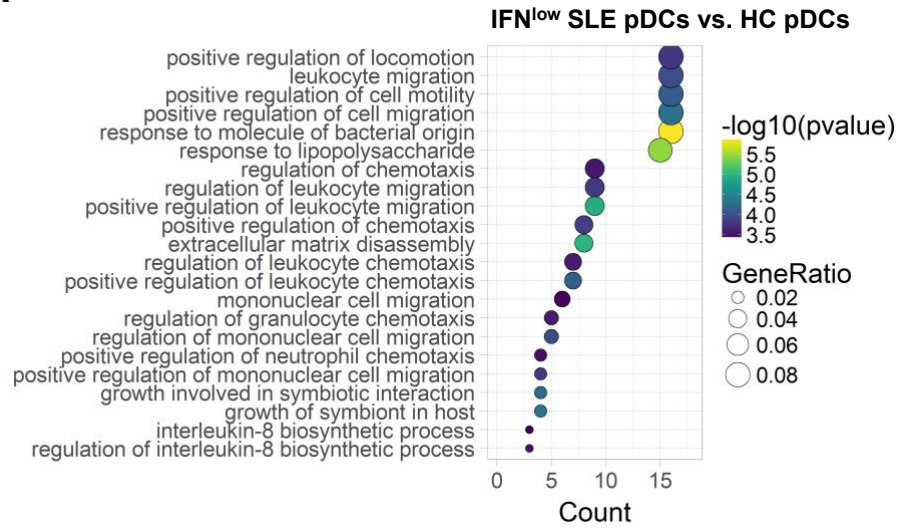
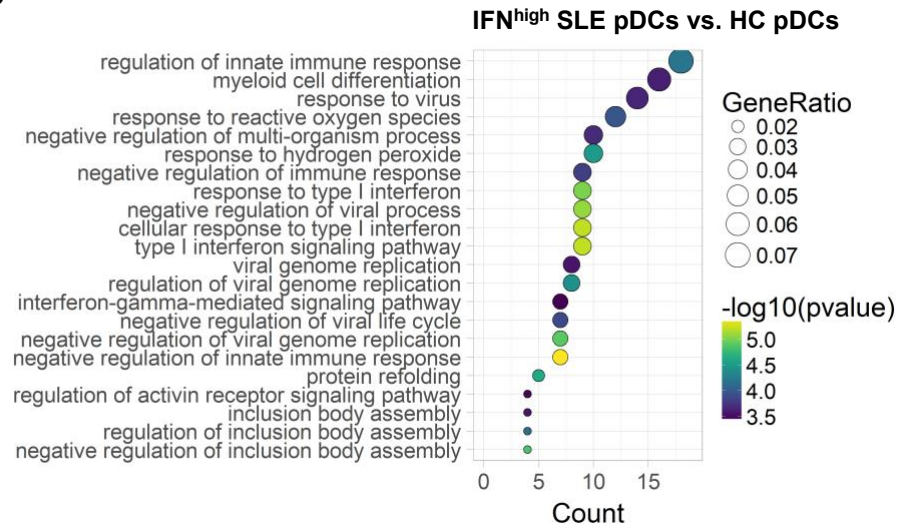
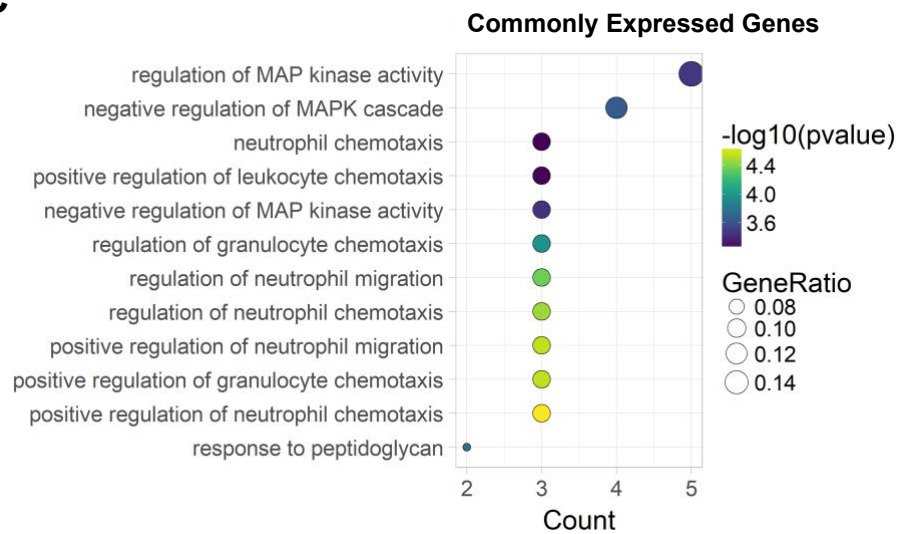
**Supplemental Figure 1.** Association of peripheral pDCs with other immunological parameters. **(A)** Higher IFN Score A was correlated to a higher ENA count. **(B)** The percentage of pDCs in peripheral blood showed no correlation with ENA count. **(C)** Association of percentage of pDCs in peripheral blood and lymphocyte count in At-Risk individuals. **(D)** Association of percentage of pDCs in peripheral blood and lymphocyte count in patients with SLE. **(E)** Association of percentage of pDCs in peripheral blood and lymphocyte count in patients with pSS. Data are represented as mean  $\pm$  SEM. Nonlinear regression **(C-E)**.



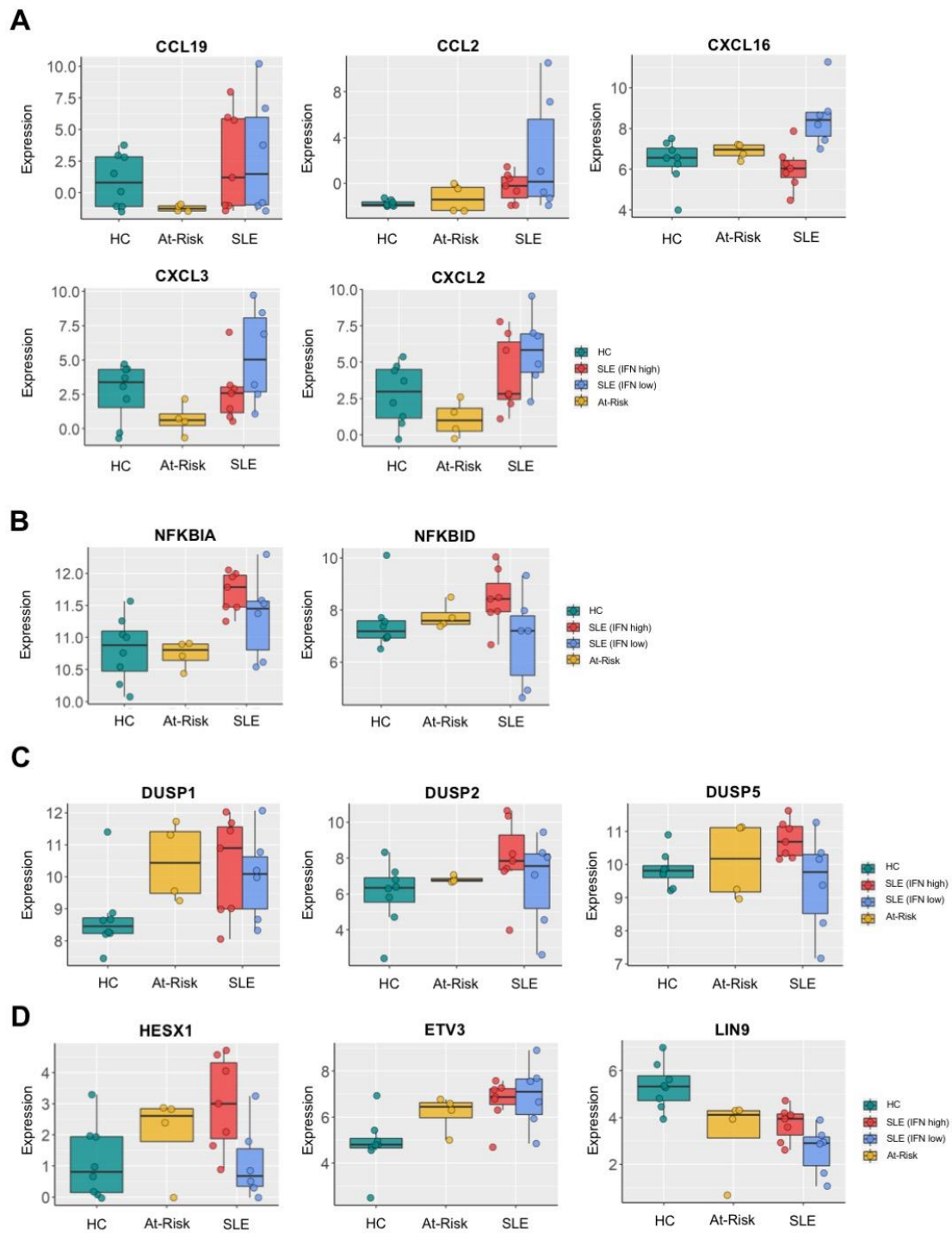
**Supplemental Figure 2.** Phenotyping peripheral pDCs in At-Risk individuals and patients with SLE in comparison with healthy controls (HC) for the expression of HLA-DR (**A**), BDCA-2 (**B**), CD123 (**C**), ILT2 (**D**), BST2 (**E**), and ILT7 (**F**). Data are represented as mean  $\pm$  SEM. \* $P < 0.05$ ; \*\*\* $P < 0.001$ . 2-way ANOVA (**A-F**).



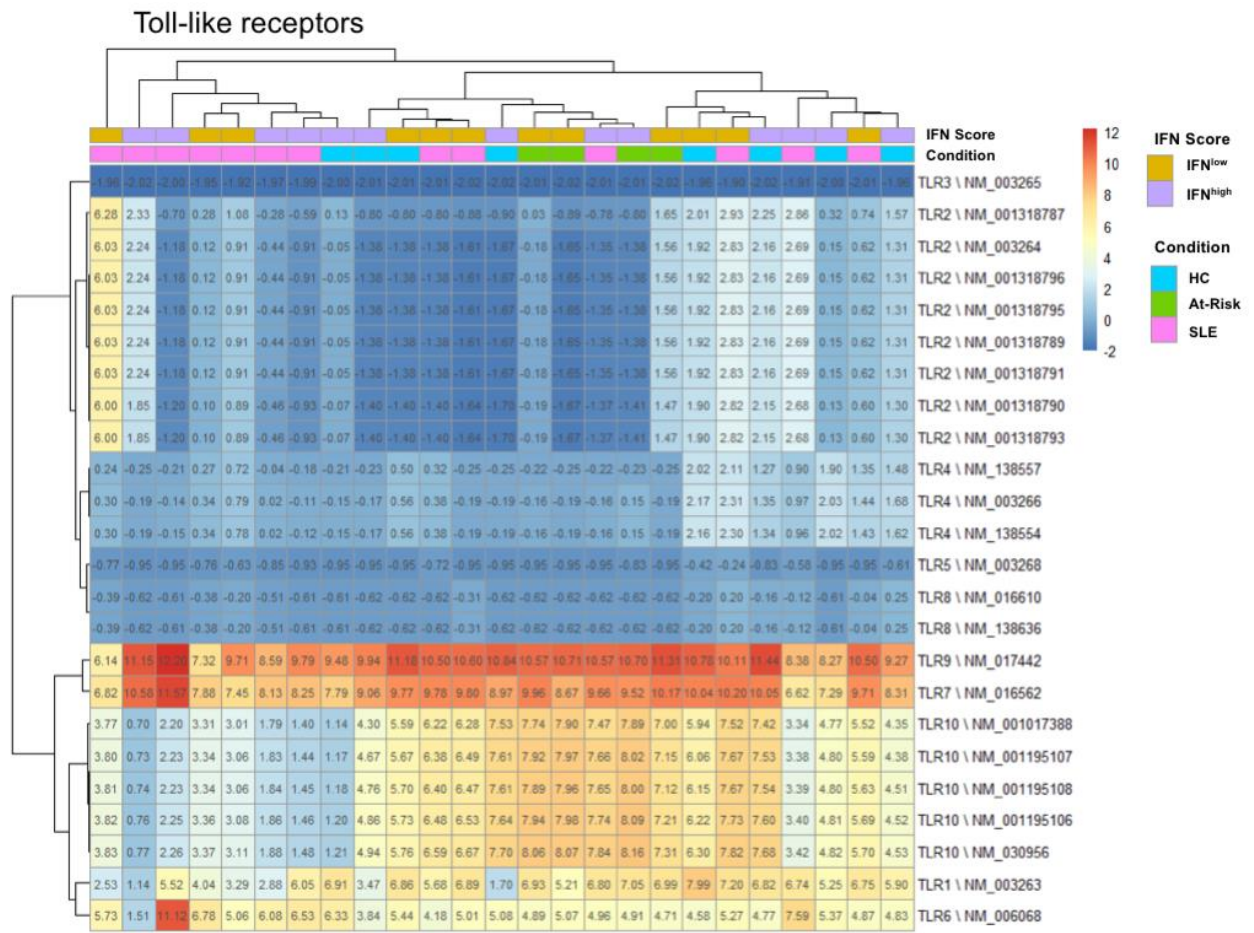
**Supplemental Figure 3.** (A-D) No association between TLR-mediated IFN- $\alpha$  production and IFN Score A in SLE patients and at-risk individuals. (E) Gating of HLA-DR<sup>+</sup>CD303<sup>+</sup> cells from cultured PBMCs. (F) No production of IFN- $\alpha$  or TNF- $\alpha$  was detected by HLA-DR<sup>+</sup>CD303<sup>+</sup> cells after TLR9 stimulation (ODN 2216). Data are represented as mean  $\pm$  SEM. Nonlinear regression (A-D).

**A****B****C**

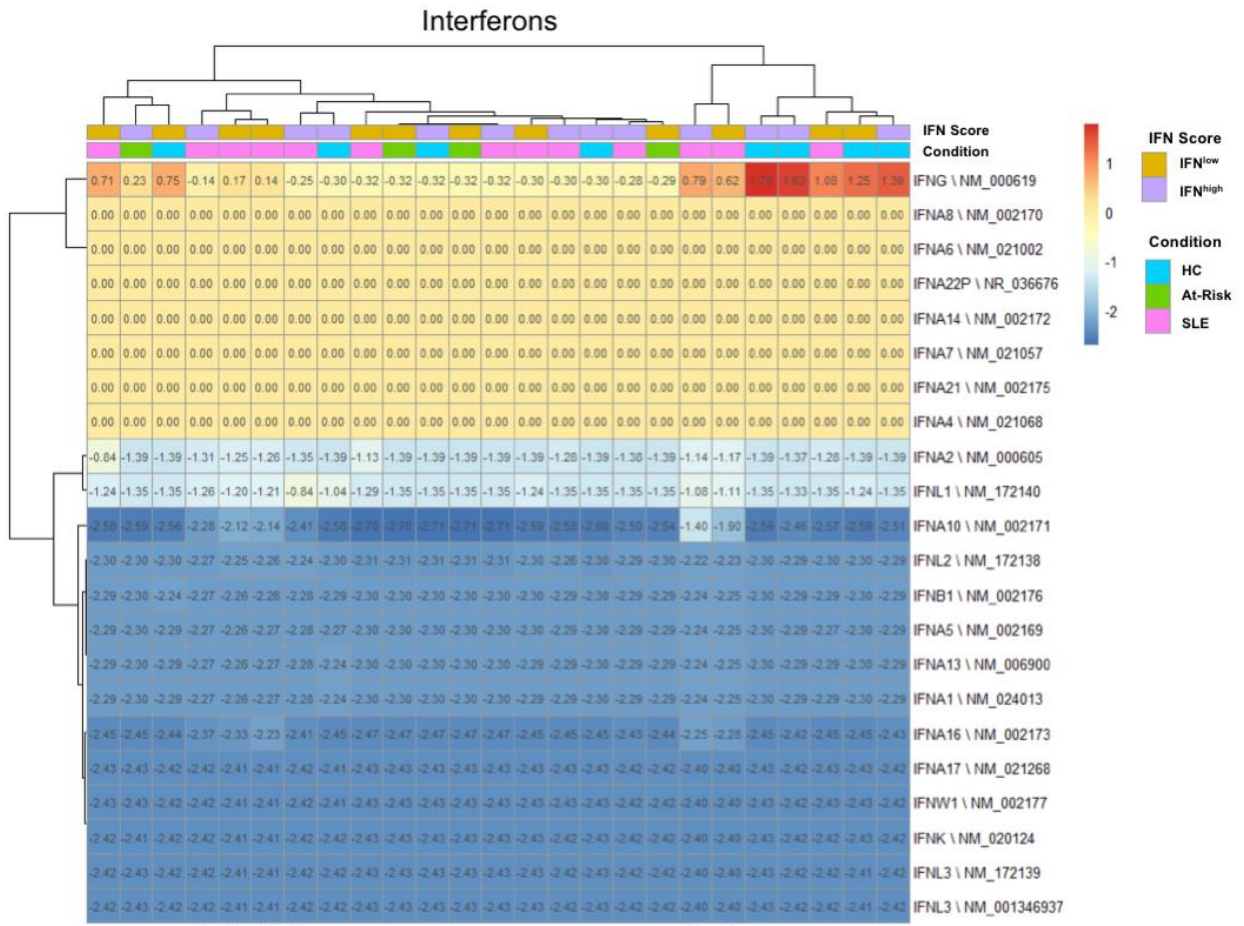
**Supplemental Figure 4.** Gene Ontology Biological Process Term Enrichment in differentially expressed genes in pDCs of IFN<sup>low</sup> SLE patients (A), IFN<sup>high</sup> SLE patients (B) and genes commonly expressed to both (C) in comparison with pDCs from healthy controls.



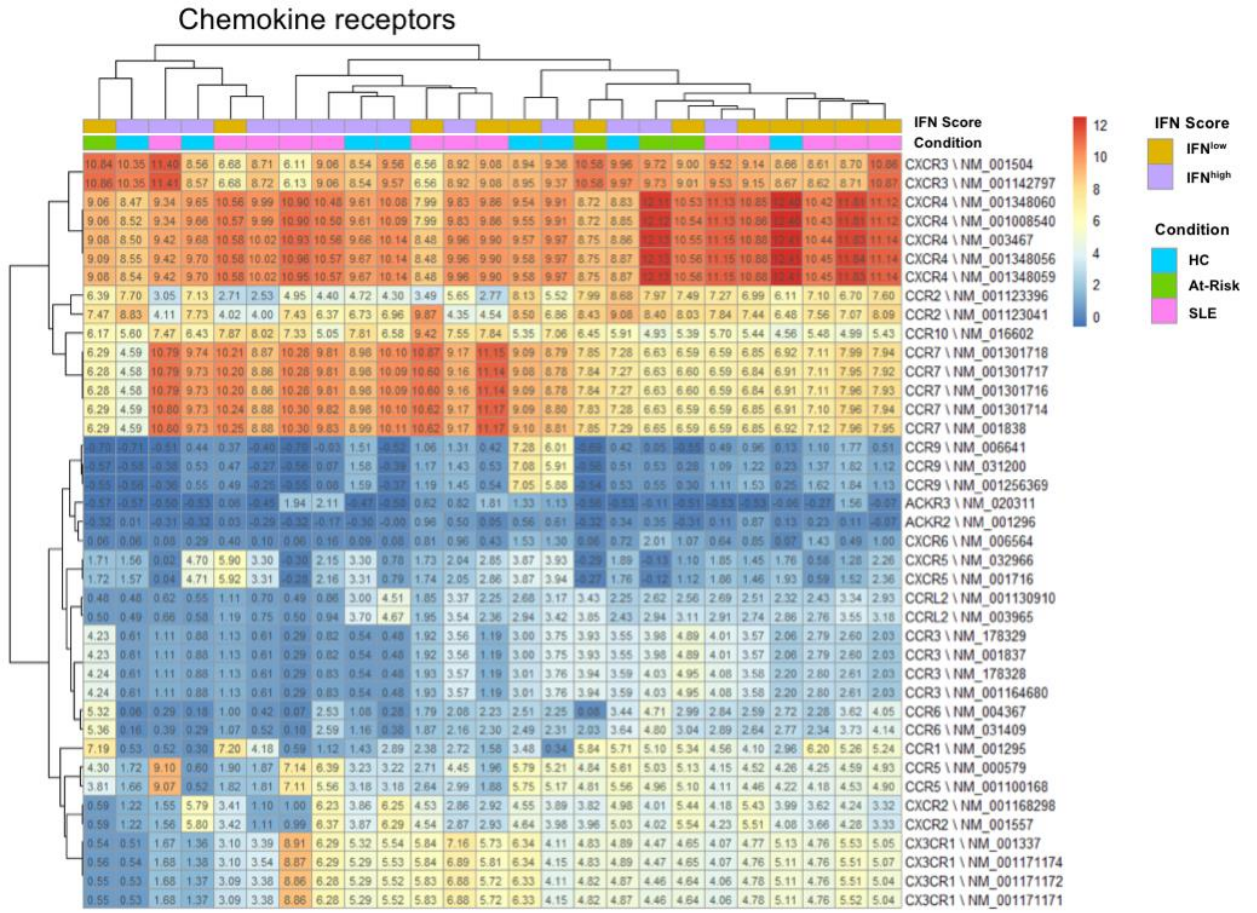
**Supplemental Figure 5.** Differentially expressed genes in pDCs of healthy controls (HC), at-risk individuals (At-Risk), IFN<sup>low</sup> SLE and IFN<sup>high</sup> SLE patients: **(A)** Chemokines; **(B)** NF-κB inhibitors; **(C)** Phosphatases; **(D)** Transcriptional repressors.



**Supplemental Figure 6.** Differential expression of Toll-like receptors (TLRs) in pDCs of healthy controls (HC), at-risk individuals (At-Risk), and SLE patients.

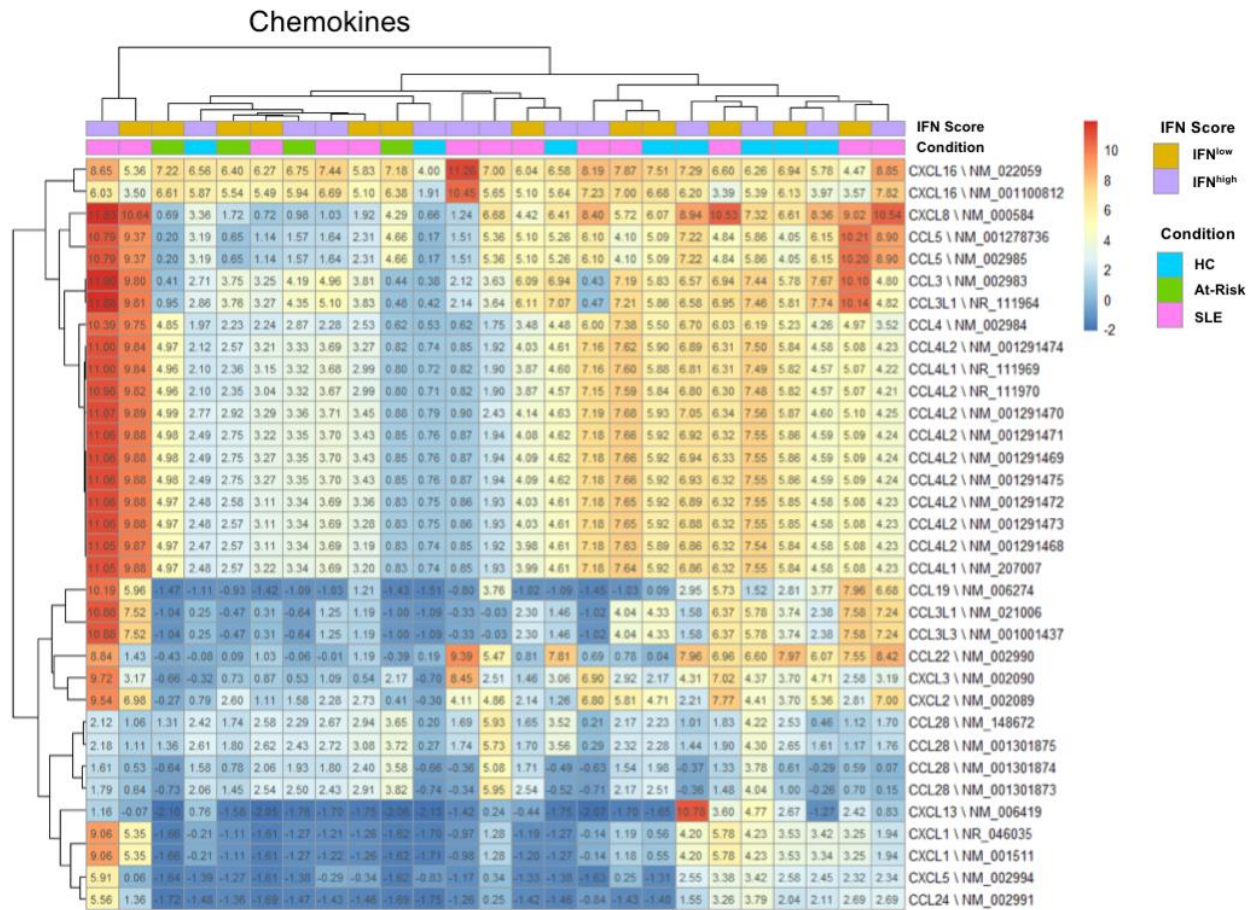


**Supplemental Figure 7.** Differential expression of type I, II, and III IFNs in pDCs of healthy controls (HC), at-risk individuals (At-Risk), and SLE patients.

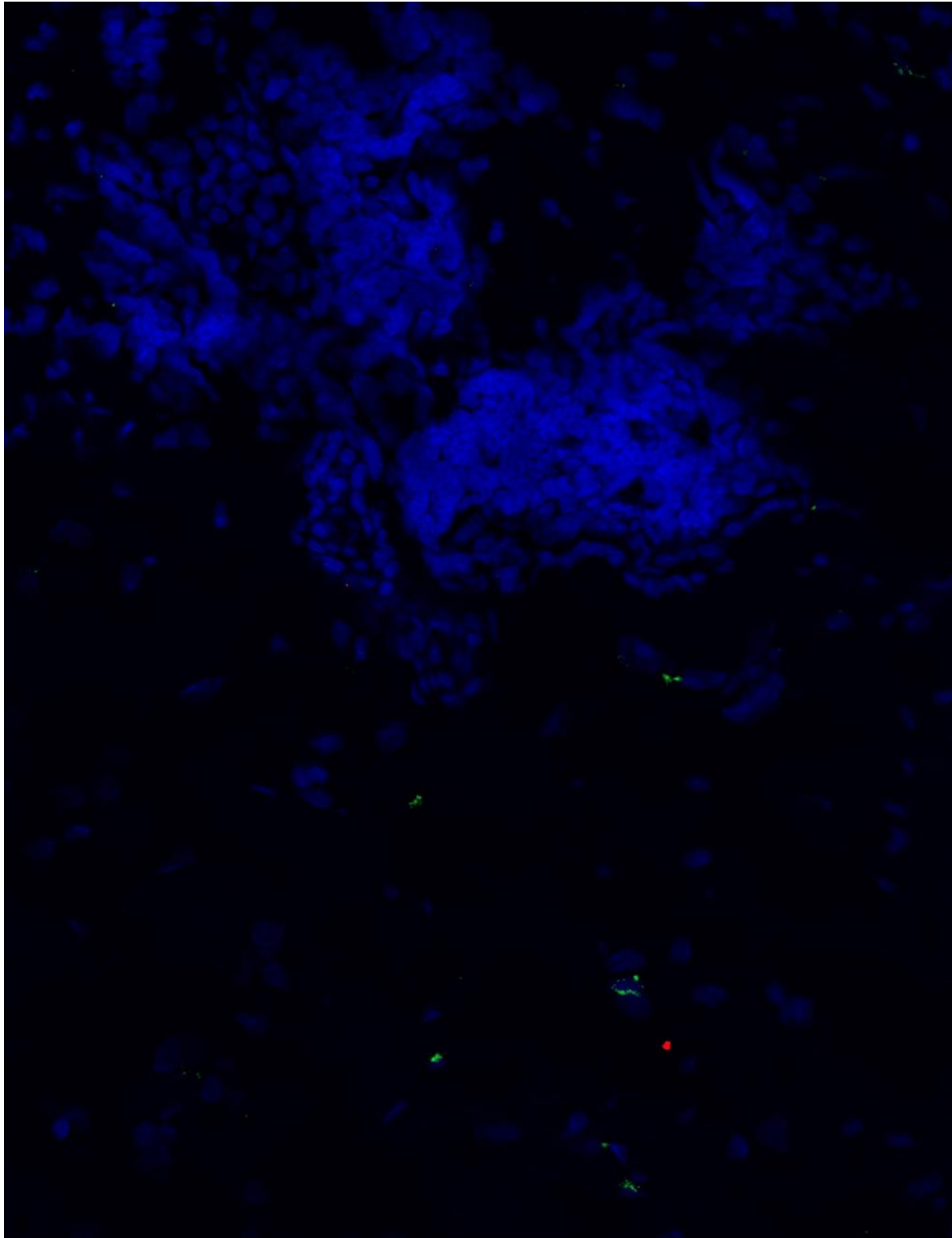


**Supplemental Figure 8.** Differential expression of chemokine receptors in pDCs of healthy controls (HC), at-risk individuals (At-Risk), and SLE patients.





**Supplemental Figure 9.** Differential expression of chemokines in pDCs of healthy controls (HC), at-risk individuals (At-Risk), and SLE patients.



DAPI IFNK (Cy3) IFNA2 (FITC)

**Supplemental Figure 10.** Area of leucocyte infiltration and connective tissue of a patient with SLE with active skin lesion. Skin biopsies were hybridized using RNAscope *in situ* hybridization technology with custom-designed target probes for *IFNA2* and *IFNK*. Hybridization signals were amplified and detected using TSA Plus fluorescein (FITC) for *IFNA2* and TSA Plus Cyanine 3 (Cy3) for *IFNK*. Nuclei were highlighted using DAPI. *IFNA2* expression was detected in cells within the connective tissue but not in infiltrating leucocytes.

Age, median (range) years	44 (18 -76)
Female patients (%)	94
Ethnicity (%)	
Caucasian	74
South Asian	16
East Asian	5
African/Caribbean	5
Clinical symptoms: BILAG Score A/B (%)	
Mucocutaneous	23
Musculoskeletal	23
Haematological	3
Renal	16
Neurological	3
Cardiorespiratory	2
Gastrointestinal	3
Ophthalmic	0
General	0
Hydroxychloroquine (%)	83
Other immunosuppressants (%)	
Methotrexate	14
Azathioprine	18
Mycophenolate mofetil	27
Cyclophosphamide	1
Oral steroids (%)	47

**Supplemental Table 1.** Clinical characteristics and treatment of SLE patients.

IFN <sup>low</sup> SLE pDCs vs. HC pDCs			
Gene	Fold Change (log2)	P value	FDR
ULBP2	19.757	< 0.001	< 0.001
C10orf35	18.302	< 0.001	< 0.001
TPSB2	18.228	< 0.001	< 0.001
TMEM216	-4.981	< 0.001	< 0.001
CXCL2	6.379	< 0.001	< 0.001
PLA2G7	9.712	< 0.001	< 0.001
DNAJB4	1.965	< 0.001	0.001
ZBP1	-7.254	< 0.001	0.001
LUCAT1	6.207	< 0.001	0.006
LOC100861532	2.839	< 0.001	0.007
LGALSL	6.161	< 0.001	0.007
SNORD95	4.390	< 0.001	0.007
LOC100008587	3.428	< 0.001	0.007
BBC3	2.962	< 0.001	0.011
SPR	6.792	< 0.001	0.015
FN1	4.352	< 0.001	0.015
PHF3	1.125	< 0.001	0.015
HSPB1	1.527	< 0.001	0.015
CLEC5A	8.287	< 0.001	0.015
CKAP4	-6.563	< 0.001	0.015
IRAIN	5.493	< 0.001	0.015
FAM157C	3.945	< 0.001	0.015
DNAJB1	2.108	< 0.001	0.015
ETV3	3.037	< 0.001	0.017
TPSAB1	9.650	< 0.001	0.020
SLC6A6	3.758	< 0.001	0.020
NPAS1	5.880	< 0.001	0.020
GADD45B	2.245	< 0.001	0.021
IFITM1	-3.619	< 0.001	0.022
COCH	-7.844	< 0.001	0.022
ANO8	3.516	< 0.001	0.022
LINC00623	3.718	< 0.001	0.022
HSPA4	-2.406	< 0.001	0.023
AOAH	-6.704	< 0.001	0.023
HOXB3	4.793	< 0.001	0.023
SLC8A2	5.243	< 0.001	0.023
NPL	4.663	< 0.001	0.025
ZNF678	4.063	< 0.001	0.025
CNST	2.130	< 0.001	0.025
RNY5	3.224	< 0.001	0.025
PLEKHA8P1	-4.947	< 0.001	0.025
DUSP1	2.903	< 0.001	0.027
LOC100008589	2.695	< 0.001	0.028
NRP2	6.969	< 0.001	0.028
EGR2	7.175	< 0.001	0.029
FCGR2B	-6.697	< 0.001	0.033
NRG2	5.224	< 0.001	0.033
LOC221946	5.139	< 0.001	0.033
PLCXD1	3.230	< 0.001	0.033
LACC1	4.975	< 0.001	0.033

**Supplemental Table 2.** Top 50 genes that are differentially expressed in pDCs of IFN<sup>low</sup> SLE patients in comparison with pDCs from healthy controls (HC).

Gene	IFN <sup>high</sup> SLE pDCs vs. HC pDCs		
	Fold Change (log2)	P value	FDR
IFI44	5.403	< 0.001	< 0.001
CAMP	7.261	< 0.001	< 0.001
OASL	6.812	< 0.001	< 0.001
SLC8A2	5.644	< 0.001	< 0.001
ATF3	5.870	< 0.001	< 0.001
CMPK2	7.710	< 0.001	< 0.001
BCL2	5.485	< 0.001	< 0.001
LGALS1	6.240	< 0.001	< 0.001
ORM1	8.011	< 0.001	< 0.001
NCMAP	4.931	< 0.001	< 0.001
HCG11	-3.108	< 0.001	< 0.001
PARP14	3.402	< 0.001	< 0.001
MSL2	2.238	< 0.001	0.001
DDX60L	6.470	< 0.001	0.001
PPDPF	1.798	< 0.001	0.001
IER2	2.552	< 0.001	0.001
NR4A1	5.230	< 0.001	0.002
TFB1M	-2.213	< 0.001	0.002
GFOD1	4.279	< 0.001	0.002
TP53INP2	5.236	< 0.001	0.002
TMEM177	-3.452	< 0.001	0.002
LIPT1	-2.499	< 0.001	0.002
JUND	2.486	< 0.001	0.002
THG1L	-2.089	< 0.001	0.002
CCDC121	6.073	< 0.001	0.002
SNORD14C	4.151	< 0.001	0.002
C2orf74	-2.833	< 0.001	0.002
CISD1	-2.392	< 0.001	0.002
HIST1H4F	-2.531	< 0.001	0.002
SEMA7A	3.150	< 0.001	0.002
ETV3L	3.865	< 0.001	0.002
CEACAM1	5.448	< 0.001	0.002
L3MBTL2	-1.887	< 0.001	0.002
ETV3	2.959	< 0.001	0.002
NPAS1	5.469	< 0.001	0.002
QRICH2	4.336	< 0.001	0.002
LTC4S	5.089	< 0.001	0.003
ARID5A	1.781	< 0.001	0.003
EIF2AK2	2.358	< 0.001	0.003
HES4	4.895	< 0.001	0.003
LINC00847	-2.487	< 0.001	0.003
NSUN7	5.334	< 0.001	0.003
DNAJB1	4.229	< 0.001	0.003
KLF8	-4.556	< 0.001	0.003
RSAD2	4.959	< 0.001	0.003
JUN	2.582	< 0.001	0.003
MON1A	-2.248	< 0.001	0.003
IFI44L	3.195	< 0.001	0.004
WDR87	6.155	< 0.001	0.004
IRAIN	4.774	< 0.001	0.004

**Supplemental Table 3.** Top 50 genes that are differentially expressed in pDCs of IFN<sup>high</sup> SLE patients in comparison with pDCs from healthy controls (HC).

Gene	IFN <sup>low</sup> SLE pDCs vs. HC pDCs			IFN <sup>high</sup> SLE pDCs vs. HC pDCs		
	Fold Change (log2)	P value	FDR	Fold Change (log2)	P value	FDR
ETV3	3.037	< 0.001	0.017	2.959	< 0.001	0.002
ATF3	3.914	< 0.001	0.052	5.209	< 0.001	0.000
LIN9	-3.716	< 0.001	0.058	-2.423	< 0.001	0.031
LGALS1	6.161	< 0.001	0.007	6.240	< 0.001	< 0.001
ZNF2	-4.108	< 0.001	0.058	-2.907	< 0.001	0.020
LIPT1	-3.224	< 0.001	0.050	-2.499	< 0.001	0.002
SEC24D	-2.559	< 0.001	0.051	-1.605	0.001	0.038
CXCL2	6.379	< 0.001	< 0.001	4.163	< 0.001	0.019
CBR4	-3.260	< 0.001	0.052	-1.546	< 0.001	0.011
DUSP1	2.903	< 0.001	0.027	2.386	< 0.001	0.021
LTC4S	5.509	< 0.001	0.033	5.089	< 0.001	0.003
SNORD95	4.390	< 0.001	0.007	3.106	< 0.001	0.016
PHF3	1.125	< 0.001	0.015	1.531	< 0.001	0.028
LOC441242	-2.798	0.001	0.068	-2.494	< 0.001	0.015
FUT10	-3.275	0.002	0.100	-2.388	< 0.001	0.016
LOC102724580	3.699	0.001	0.088	4.080	< 0.001	0.004
CCL19	4.468	< 0.001	0.057	3.828	< 0.001	0.020
CTSL	6.460	< 0.001	0.040	4.114	< 0.001	0.020
PUDP	-2.632	< 0.001	0.058	-2.752	< 0.001	0.008
ATP7A	-4.215	< 0.001	0.035	-2.853	< 0.001	0.020
SAT1	1.642	< 0.001	0.036	1.805	< 0.001	0.009
MIR6087	2.376	< 0.001	0.050	2.411	< 0.001	0.028
ZFP91	2.619	< 0.001	0.046	2.147	0.001	0.043
PAAF1	-3.453	0.001	0.066	-1.973	< 0.001	0.033
DUSP8	6.050	0.001	0.085	6.392	< 0.001	0.006
IRAK3	6.179	< 0.001	0.045	4.152	< 0.001	0.007
PLEKHA8P1	-4.947	< 0.001	0.025	-2.810	< 0.001	0.009
ACVR1B	5.196	0.001	0.059	4.169	< 0.001	0.017
RN7SL1	2.867	< 0.001	0.049	2.648	< 0.001	0.034
RN7SL2	3.107	< 0.001	0.033	2.806	< 0.001	0.021
ATG14	2.520	< 0.001	0.058	1.640	< 0.001	0.028
REREP3	3.757	< 0.001	0.046	3.672	< 0.001	0.019
IRAIN	5.493	< 0.001	0.015	4.774	< 0.001	0.004
CDH1	3.795	0.001	0.061	2.895	< 0.001	0.028
SCARNA21	2.549	0.001	0.074	2.980	0.001	0.041
C5AR1	6.724	0.002	0.098	5.210	< 0.001	0.031
SLC8A2	5.243	< 0.001	0.023	5.644	< 0.001	< 0.001
IER2	2.416	< 0.001	0.050	2.552	< 0.001	0.001
DNAJB1	2.108	< 0.001	0.015	4.097	< 0.001	0.005
NPAS1	5.880	< 0.001	0.020	5.469	< 0.001	0.002
LOC100008589	2.695	< 0.001	0.028	2.969	< 0.001	0.006
MIR3687-1	3.321	0.002	0.098	3.448	< 0.001	0.007
MIR3687-2	3.321	0.002	0.098	3.448	< 0.001	0.007
LOC100861532	2.839	< 0.001	0.007	2.930	< 0.001	0.005
WRB	-2.306	0.001	0.068	-2.027	< 0.001	0.008
<b>pDC-specific transcription factors</b>						
E2-2 (TCF4)	0.691	0.118	0.537	0.313	0.578	0.852
SPIB	0.657	0.279	0.719	0.235	0.744	0.922

**Supplemental Table 4.** Genes that are differentially expressed in pDCs of both IFN<sup>low</sup> and IFN<sup>high</sup> SLE patients in comparison with pDCs from healthy controls (HC).