Supplementary table 1

A. Characteristics of SLE patients and controls (cohort A discovery)

	SLE (n= 30)	HC (n=30)
Age, mean (SD) years	43 (14)	43 (14)
Gender, n females (%)	25 (83)	25 (83)
Ethnic background, n caucasian (%)	27 (90)	27 (90)
Disease duration since diagnosis, mean (SD) months	86 (73)	-
Disease activity according to the PGA, mean score (SD)	0.8 (0.8)	-
Immunosuppressive therapy*, n patients with (%)	16 (53)	-

B. Characteristics of SLE patients and controls (cohort B validation)

	SLE (n= 64)	pSS (n=14)	Sarc (n=14)	HC (n=39)
Age, mean (SD) years	45 (13)	48 (18)	48 (14)	42 (14)
Gender, n females (%)	56 (87)	14 (100)	2 (14)	22 (56)
Ethnic background, n caucasian (%)	44 (69)	10 (71)	12 (86)	-
Disease duration since diagnosis, mean (SD) months	142 (175)	50 (49)	19 (38)	-
Disease activity according to the PGA, mean score (SD)	0.9 (0.9)	1.6 (0.5)	1.6 (1.2)	-
Immunosuppressive therapy*, n patients with (%)	33 (52)	1 (1)	3 (21)	-

SLE: systemic lupus erythematosus, pSS: primary Sjögren syndrome, Sarc: sarcoidosis, HC: healthy controls, PGA: physician global assessment score, SD: standard deviation. *Defined as treatment with prednisolone or equivalent $\geq$ 10 mg per day and/or any immunosuppressive drugs.

Supplementary Table 2. Detailed characteristics of SLE patients from cohort A and B

	Cohort A				Cohort B			
	Total SLE patients (n=30)	Inactive (n=17)	Moderate (n=8)	Active (n=5)	**Total SLE patients (n=63)**	Inactive (n=28)	Moderate (n=25)	Active (n=10)
Age, mean (SD) years	**43 (14)**	42 (14)	48 (12)	36 (13)	**45 (13)**	44 (12)	47 (15)	45 (11)
Female sex, no. (%)	**25 (83)**	15 (88)	6 (75)	4 (80)	**56 (88)**	22 (79)	23 (92)	10 (100)
Ethnic background, no. (%) :								
Caucasian	**27 (90)**	16 (94)	8 (100)	3 (60)	**44 (69)**	21 (75)	16 (64)	7 (70)
Africans	**1 (3)**	0	0	1 (20)	**7 (11)**	2 (7)	3 (12)	0
Asian	**2 (7)**	1 (6)	0	1 (20)	**9 (14)**	4 (14)	5 (20)	2 (20)
Hispanic	**0**	0	0	0	**3 (5)**	1 (4)	1 (4)	1 (10)
Disease duration, mean (SD)	**86 (73)**	99 (78)	93 (68)	35 (32)	**142 (175)**	135 (145)	129 (153)	115 (113)
Physician Global Assessment score, mean (SD) score	**0.8 (0.8)**	0.3 (0.5)	1.1 (0.6)	1.8 (0.7)	**0.9 (0.9)**	0.5. (0.7)	1.0 (0.8)	1.7 (0.6)
Active manifestations at study[&], no. (%)								
Fever	**1 (3)**	0	0	1 (20)	**2**	0	0	2 (20)
Renal	**4 (13)**	0	0	4 (80)	**25**	0	19 (76)	6 (60)
Hematologic	**3 (10)**	0	1 (13)	2 (40)	**36**	11 (39)	17 (68)	8 (80)
Musculoskeletal	**4 (13)**	0	2 (25)	2 (40)	**11**	0	5 (20)	6 (60)
Mucocutanous	**8 (27)**	0	3 (38)	2 (40)	**14**	0	9 (36)	5 (50)
Serositis	**0**	0	0	0	**2**	0	2 (8)	0
Neurologic	**0**	0	0	0	**9**	0	1 (4)	8 (80)
Low C3 and/or C4 at study, no. (%)	**13 (43)**	5 (29)	3 (38)	3 (60)	**18 (33)**	4 (14)	8 (32)	6 (55)
Positive anti-dsDNA antibodies at study, no. (%)	**16 (53)**	7 (41)	5 (63)	4 (80)	**30 (48)**	12 (43)	13 (52)	5 (55)
Treatments past month[#] :								
No treatment	**7 (23)**	3 (18)	2 (25)	1 (20)	**7 (11)**	4 (14)	3 (12)	0
Antimalarials only, no. (%)	**8 (27)**	5 (29)	2 (25)	1 (20)	**17 (27)**	9 (32)	6 (24)	2 (20)
Systemic glucocorticoids,no. (%)	**12 (40)**	7 (41)	2 (25)	3 (60)	**33 ()**	11 (39)	15 (60)	7 (70)
Dose, mean mg/d	**10**	10	15	12	**9**	8	11	8
Immunosuppressant agent, no. (%)	**10 (33)**	6 (35)	2 (25)	2 (40)	**39 (48)**	9 (32)	13 (52)	7 (70)

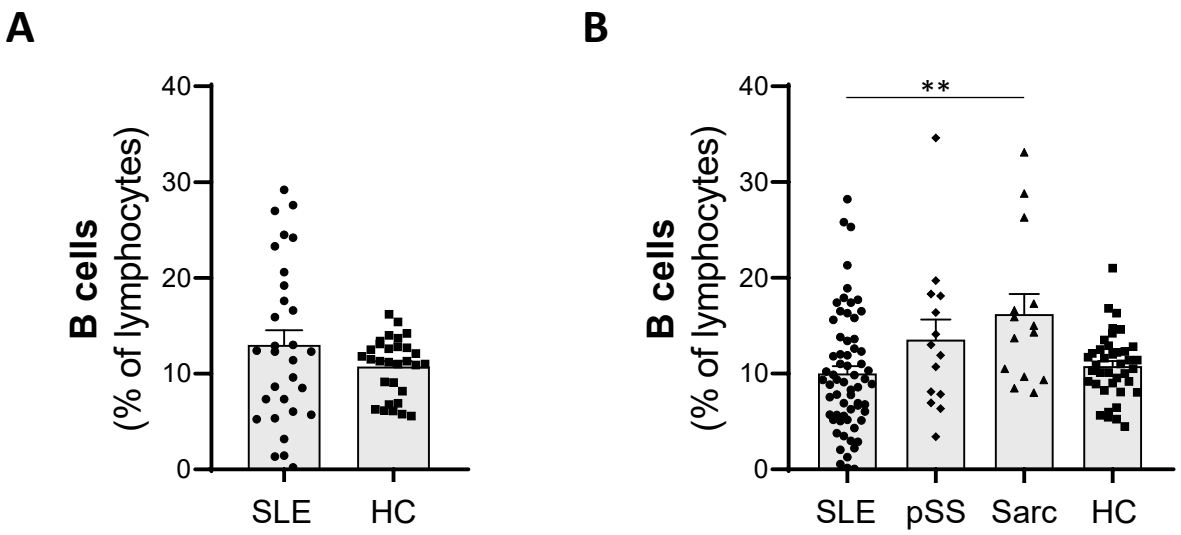
[&] Clinical manifestations according to the SELENA-SLEDAI items. [#]Dose of systemic glucocorticoids corresponds to prednisone or equivalent, and immunosuppressant agents included azathioprine, methotrexate, and mycophenolate mofetil used during the last 4 weeks.

Supplementary table 3. Antibody inventory

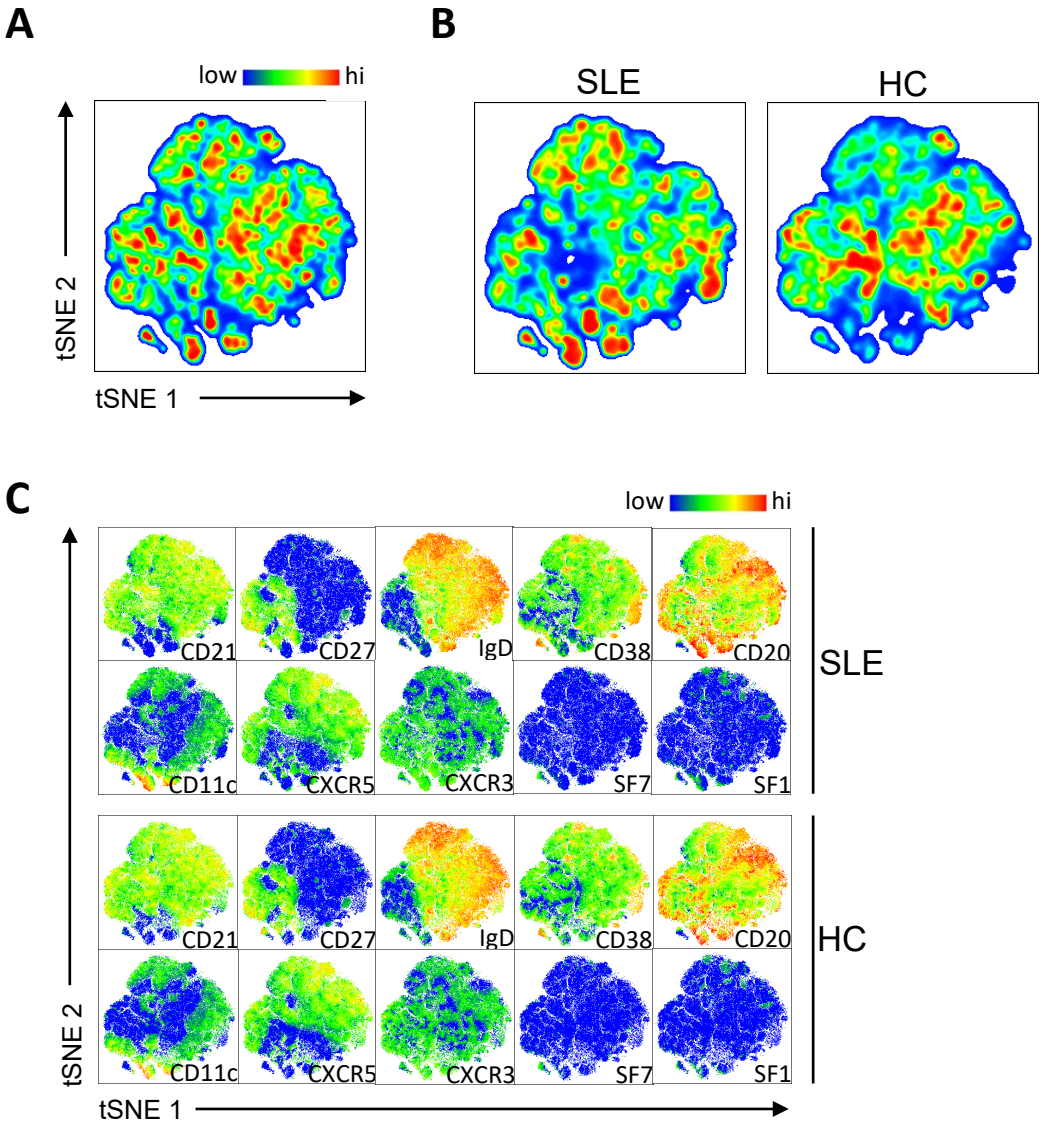
Flow Cytometry Antibody	Format	Clone	Company
CD38	V450	HB7	BD bioscience
CD19	APC-Cy7	SJ25C1 (= SJ25-C1)	BD bioscience
IgM	FITC	MHM-88	Biolegend
CD21	PE-Cy7	B-ly4	BD bioscience
IgD	PE	IA6-2 (= δ-IA6-2)	BD bioscience
CD45	PerCP	2D1	BD bioscience
CD27	APC	M-T271	BD bioscience

Mass Cytometry Antibody	Format	Clone	Company
CD45	89Y	HI30	Fludigm
Live/Dead	103Rh	-	Fludigm
CD8	113 In	RPA-T8	Biolegend
CD4	115 In	RPA-T4	Biolegend
CD19	142 Nd	HIB19	Fludigm
CD352 / SLAM 6	143 Nd	NT-7	Fludigm
CD38	144 Nd	HIT2	Biolegend
CD127	145 Nd	A019D5	Biolegend
IgD	146 Nd	IA6-2	BD bioscience
CD7	147 Sm	CD7-6B7	Fludigm
CD45	148 Nd	HI30	Conju-Biolegend
CCR4	149 Sm	205410	Fludigm
CD3	150 Nd	UCH-T1	BD bioscience
PD-1	151 Eu	EH12.2H7	Biolegend
CD21	152 Sm	BL13	Fludigm
CD45RA	153 Eu	HI100	BD bioscience
CD84 / SLAM 5	154 Sm	CD84.1.21	Fludigm
CD27	155 Gd	L128	Fludigm
SLAMF 7 (CD319)	156 Gd	162.1	Biolegend
CXCR3	158 Gd	1C6/CXCR3	BD bioscience
CCR7	159 Tb	G043H7	Biolegend
CD14	160 Gd	M5E2	Fludigm
CD150 / SLAM 1	161 Dy	A12(7D4)	Biolegend
CD11c	162 Dy	clone 3.9	Fludigm
CRTh2 (Fluidigm)	163 Dy	BM16	Fludigm
CD48 / SLAM 2	164 Dy	BJ40	Biolegend
CD45RO	165 Ho	UCHL1	Fludigm
CD45	166 Er	HI30	Conju-Biolegend
CXCR5	167 Er	RF8B2	Biolegend
ICOS	168 Er	C398.4A	Biolegend
CD25	169 Tm	2A3	Fludigm
TCR va24-Ja18 (6B11)	170 Er	Witek	Fludigm
CD20	171Yb	2H7	Fludigm
TCR$\alpha\beta$	172 Yb	IP26	Biolegend
HLA-DR	173 Yb	L243	Fludigm
CD229 / SLAM 3	174 Yb	HLy9.1.25	Fludigm
CD244 / SLAM 4	175Lu	C1.7	Biolegend
CD56	176Yb	R19-760	Fludigm

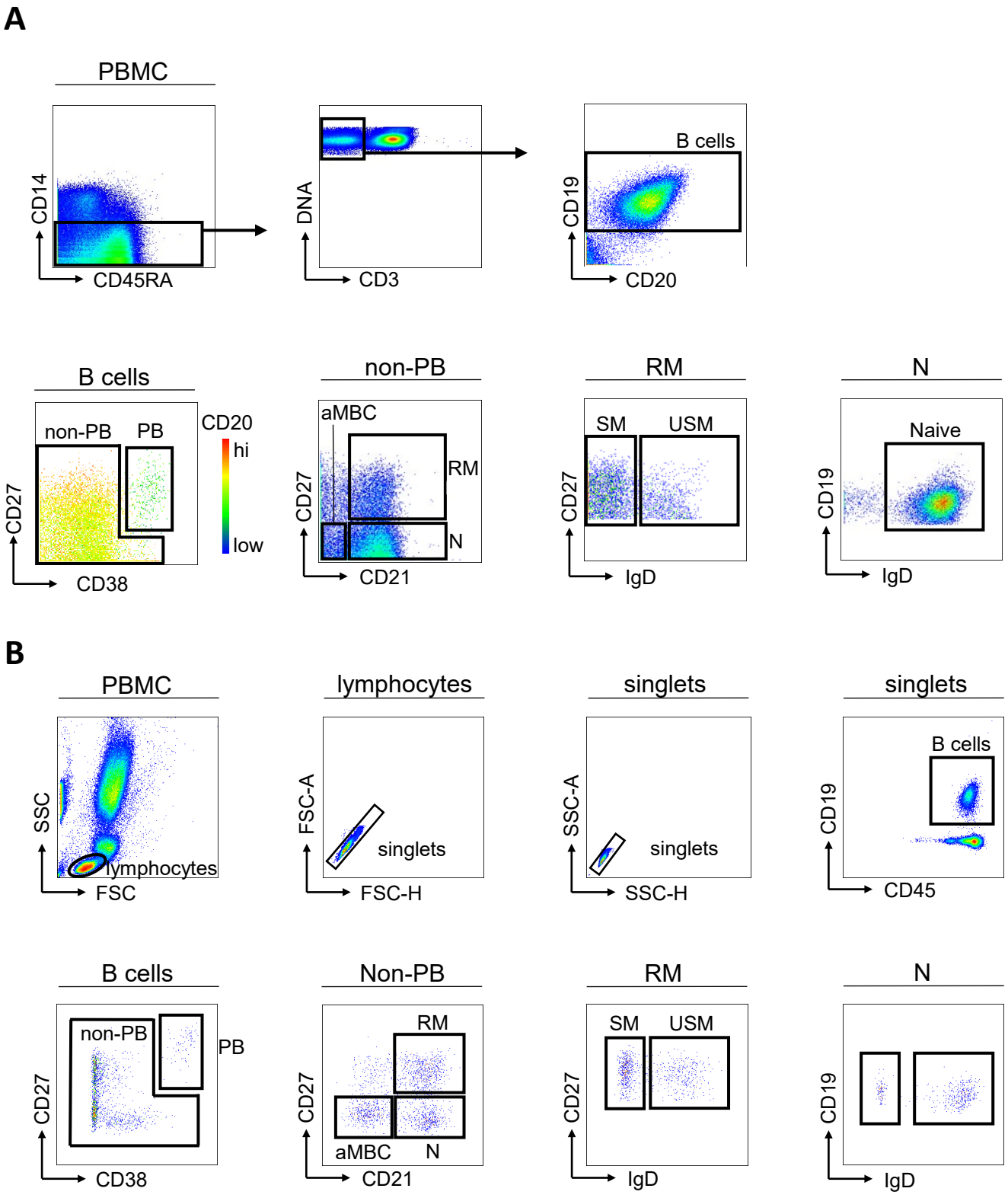
CD57 (CHUV)	194 Pt	NK1	Conju-BD bioscience
CD45	198 Pt	HI30	Conju-Biolegend
CD16	209Bi	3G8	Fludigm



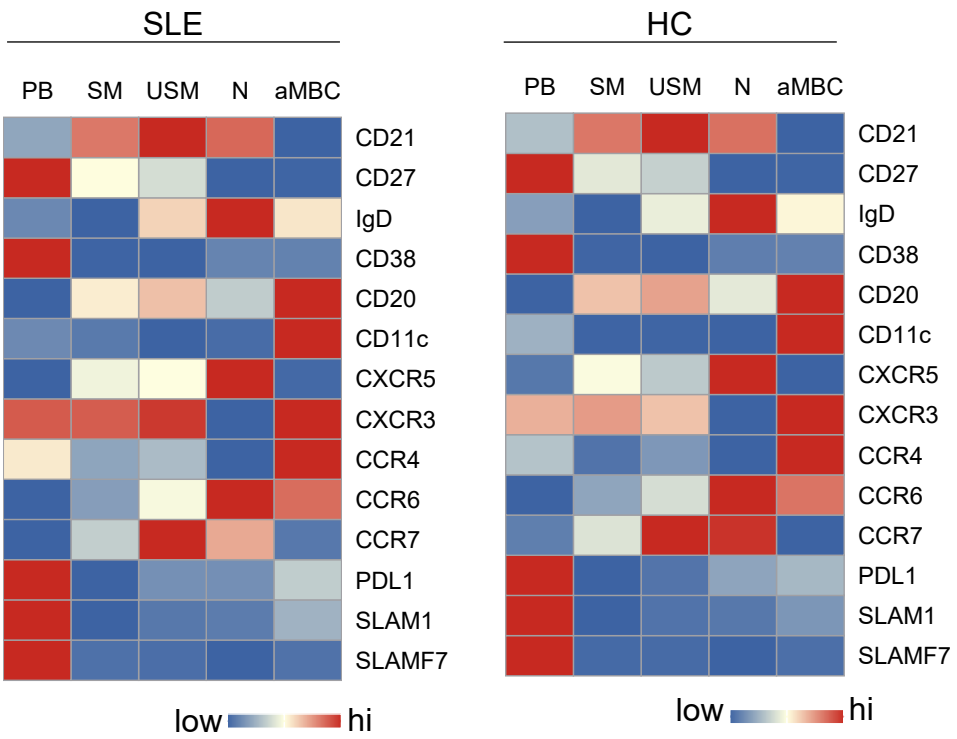
Supplementary figure 1. Frequency of B cells (CD19+) in systemic lupus erythematosus (SLE) patients compared to controls in two separate cohorts. (A) Frequency of B cells in SLE patients compared to healthy controls (HC) : B cell analysis by mass cytometry followed by manual gating in 30 SLE and 30 HC (cohort A). **(B)** Frequency of B cells in SLE patients compared to other autoimmune diseases and HC : B cell analysis by flow cytometry in fresh blood of 63 SLE patients, 14 primary Sjögren's syndrome, 14 sarcoidosis and 39 HC (cohort B). Scatter plots represents mean ± SEM. Statistical analysis were performed on log-transformed data to obtain normal distributions, *p value < 0.05, **p value < 0.01, ***p value < 0.001.



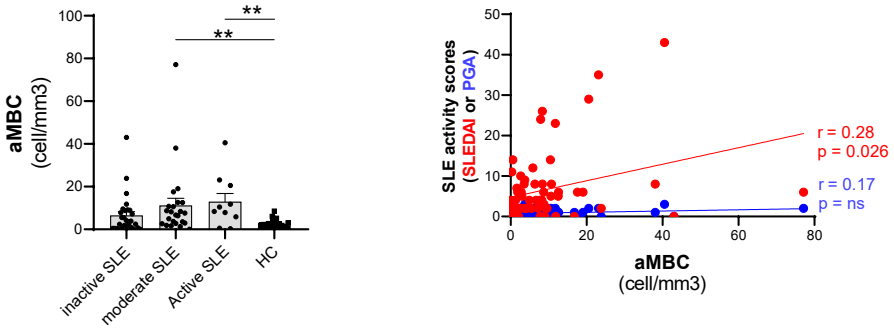
Supplementary figure 2. B cell phenotype analysis. (A) Density map of a merged tSNE analysis of B cells (CD19+) incorporating a total of 240,000 B cells, including 120,000 B cells from 30 healthy Controls (HC) and 120'000 B cells from 30 systemic lupus erythematosus (SLE) patients. **(B)** Density tSNE plots of B cells for both groups (120,000 B cells each). **(C)** tSNE plots showing the expression of surface markers in SLE and HC.



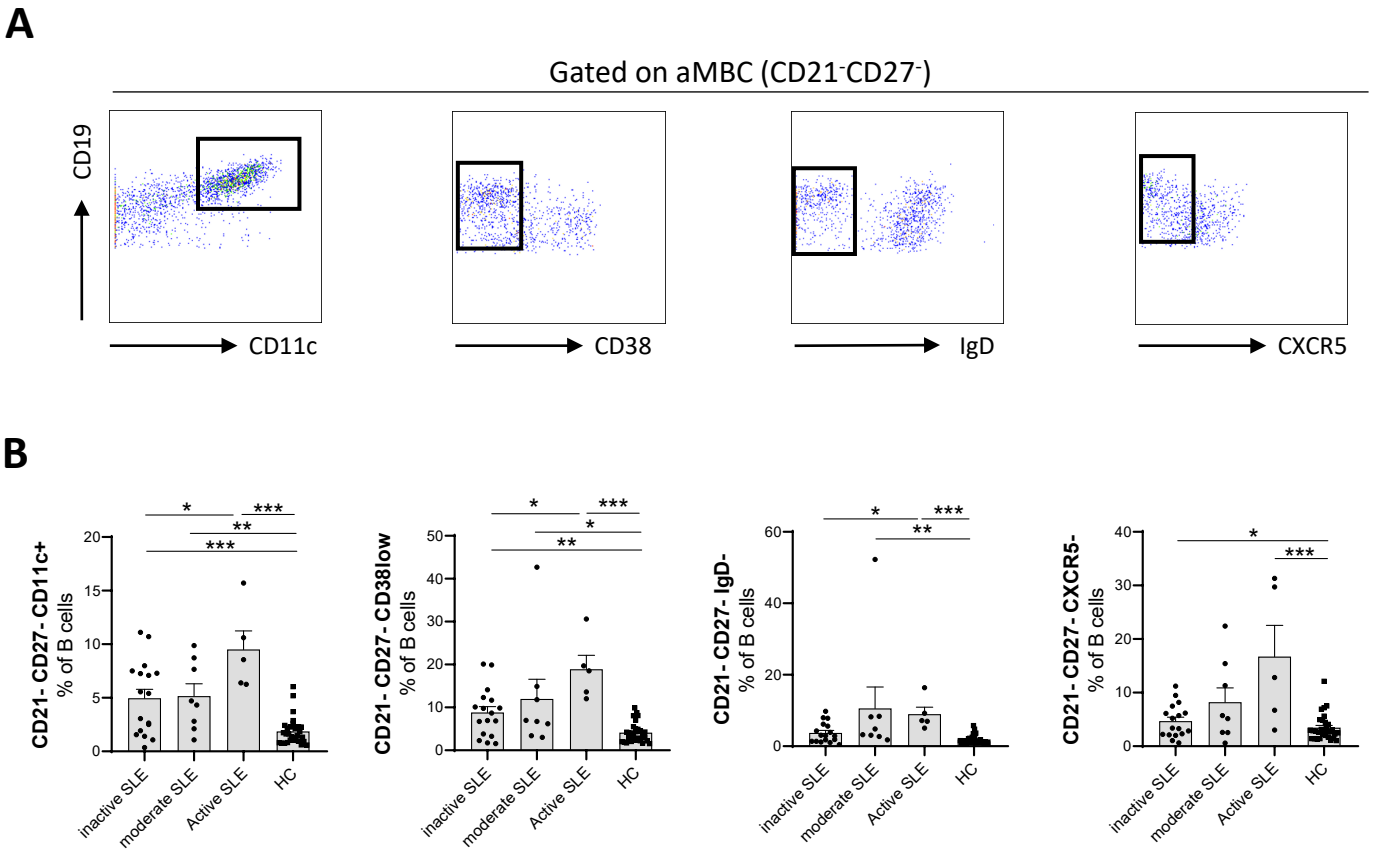
Supplementary figure 3. Manual gating strategy of B cell subsets analysis for mass cytometry data analysis **(A)** and flow cytometry data analysis **(B)**.



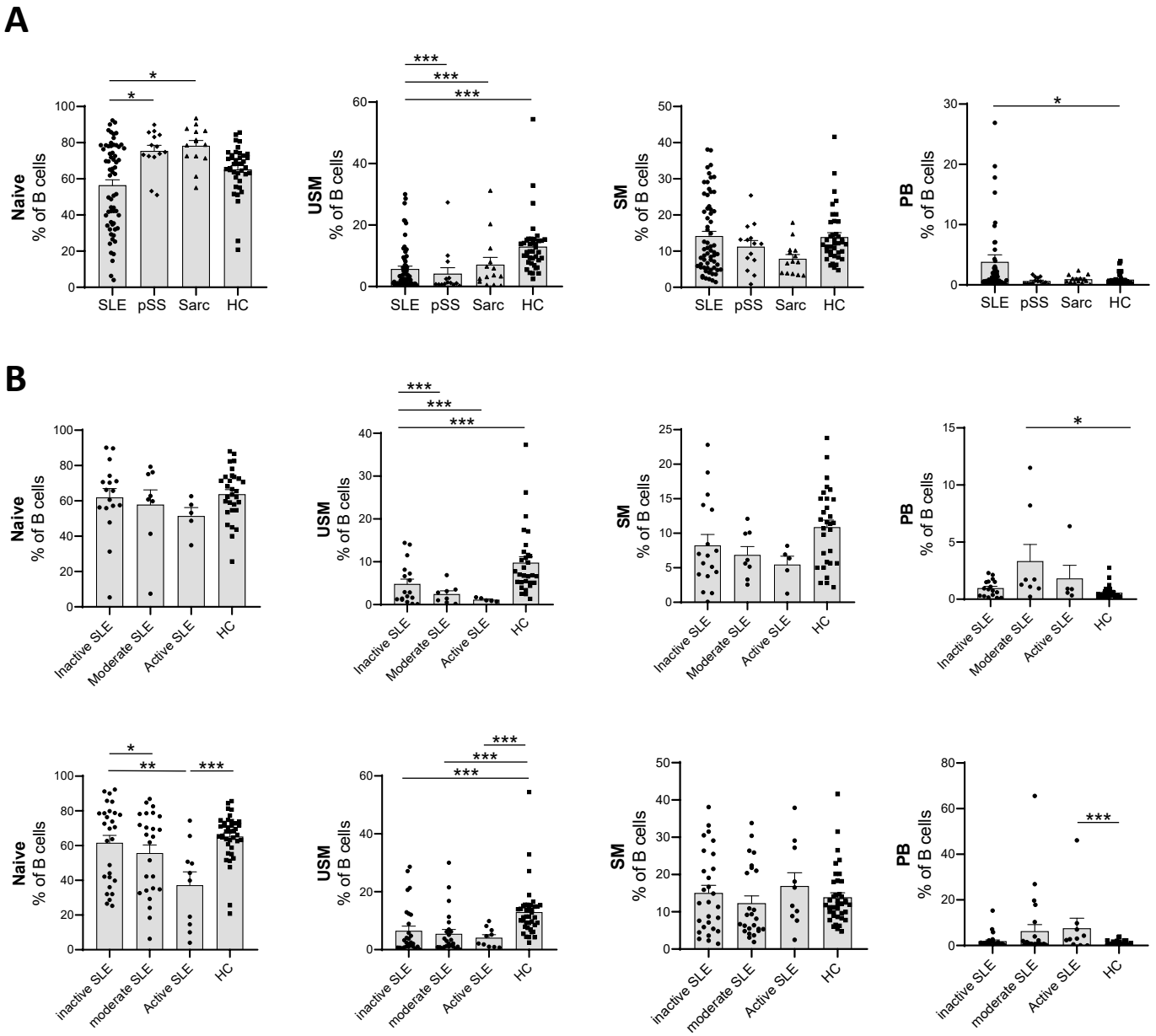
Supplementary figure 4. Heatmap showing mean levels of expression of surface markers in manually gated B cell subsets : naive (N), switched memory (SM), unswitched memory (USM), atypical memory B cells (aMBC) and plasmablast (PB) in 30 systemic lupus erythematosus patients (left panel) and 30 healthy controls (right panel). B cells were analyzed by mass cytometry (cohort A). Data was normalized by rows.



Supplementary figure 5. aMBC numbers correlate with disease activity (data shown for cohort B). Frequency of aMBC according to disease activity. Statistical analysis using two-way ANOVA followed by Bonferroni's correction on log-transformed data. Correlation between aMBC frequency and two SLE disease activity scores (spearman's rho correlation). ** p value < 0.01, p value considered significant if < 0.05.



Supplementary figure 6. Using additional surface markers to define aMBC did not improve discrimination of disease activity in SLE. **(A)** Gating strategy. **(B)** Frequencies of atypical memory B cells (aMBC, CD21- CD27-) using additional surface markers expressions (IgD-, CD38low, CD11c+, CXCR5-) in SLE patients according to disease activity and compared to HC. B cell subsets were analyzed by mass cytometry in 30 SLE patients and 30 HC (cohort A). Scatter plots represents mean ± SEM. Statistical analysis were performed on log-transformed data to obtain normal distributions, *p value < 0.05, **p value < 0.01, ***p value < 0.001.



Supplementary figure 7. Frequencies of B cell subsets identified by manual gating other than atypical memory B cells. **(A)** Frequency of B cells in SLE patients compared to controls (B cell analysis by flow cytometry of fresh blood in 63 SLE patients, 14 primary Sjögren's syndrome, 14 sarcoidosis and 39 HC = cohort B). **(B)** Frequency of B cells in SLE patients according to their disease activity and compared to HC in cohort A (upper panels, B cell analysis by mass cytometry in 17 inactive SLE, 8 moderate SLE, 5 active SLE and 30 HC) and cohort B (lower panels, B cell analysis by flow cytometry in 28 inactive SLE, 25 moderate SLE, 10 active SLE and 39 HC). Scatter plots represents mean ± SEM. Statistical analysis were performed on log-transformed data to obtain normal distributions, *p value < 0.05, **p value < 0.01, ***p value < 0.001.