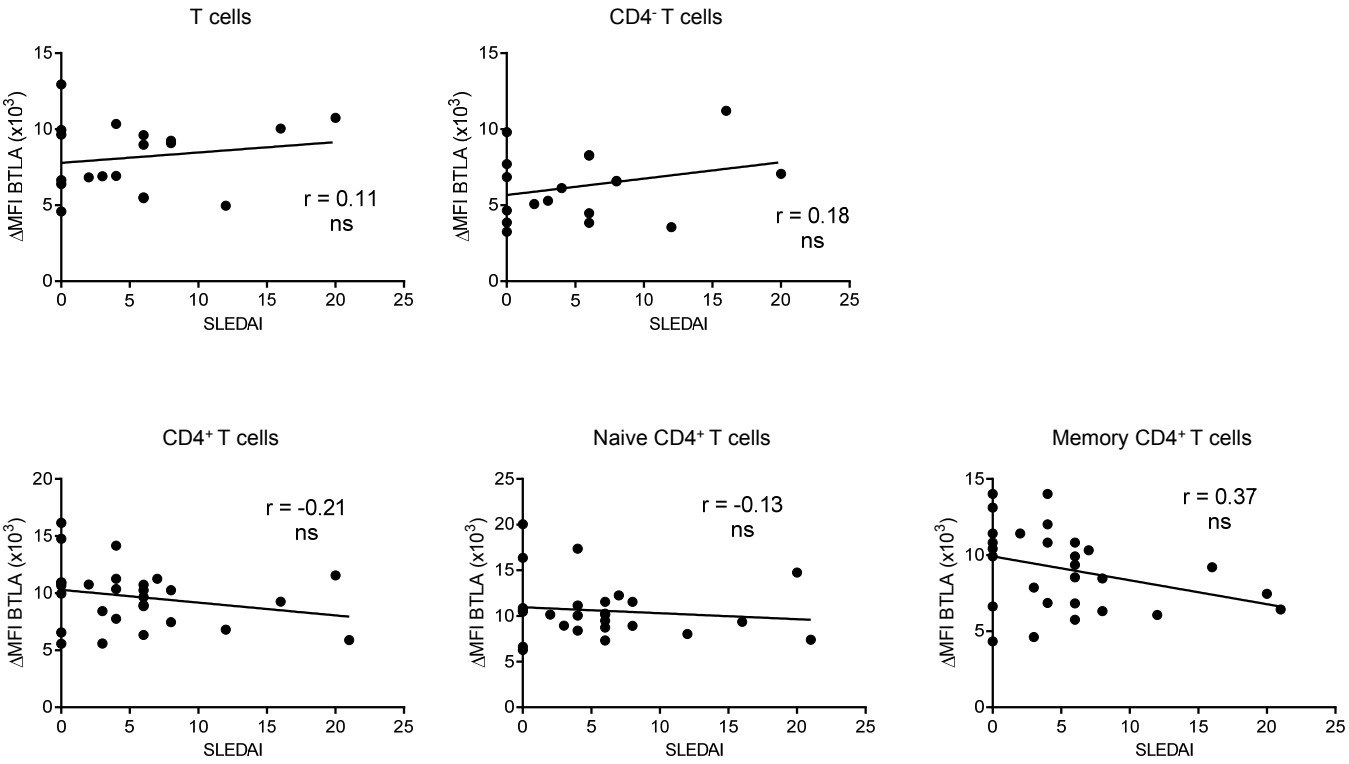
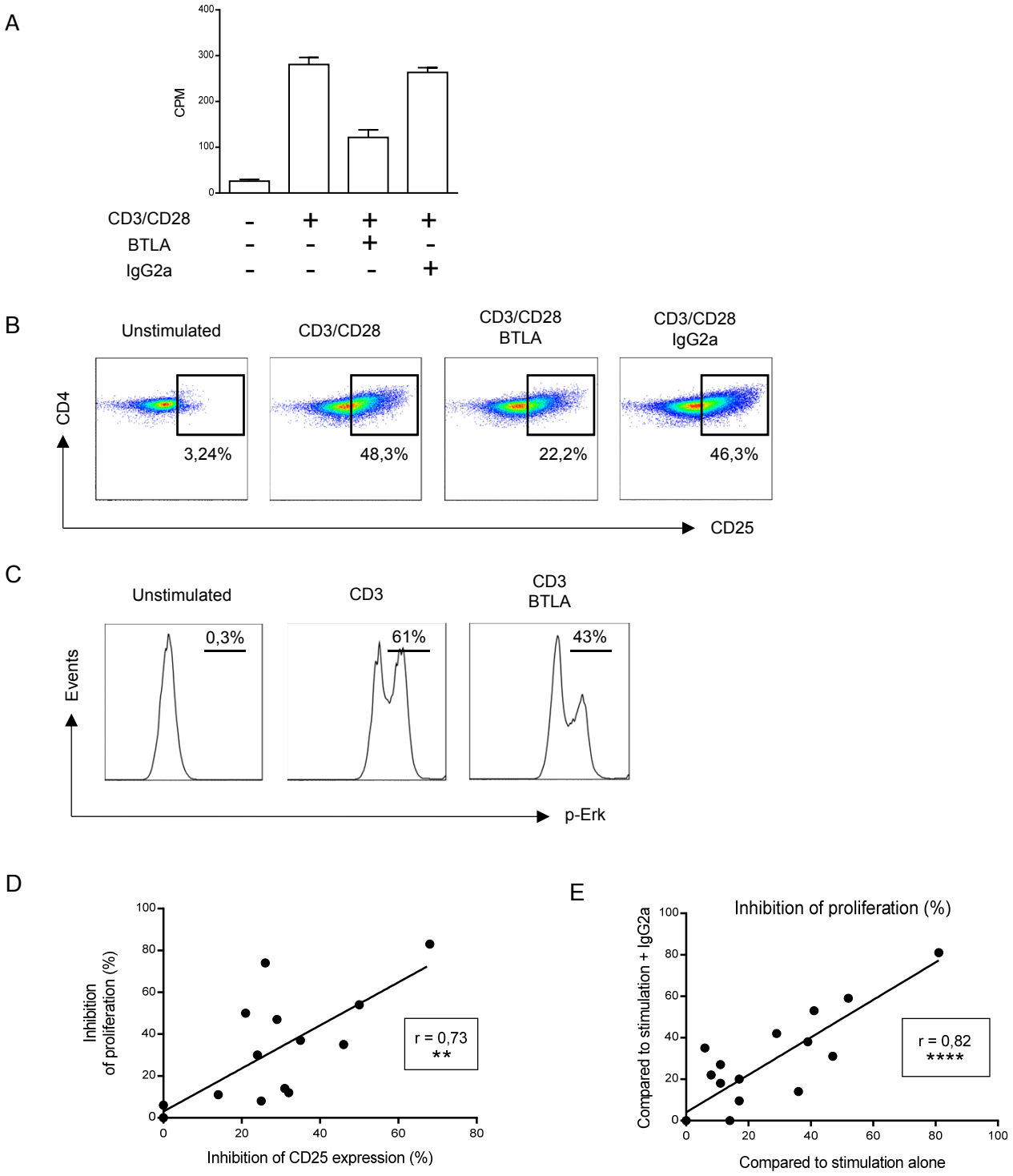
Supplemental Table 1: Clinical and biological characteristics of SLE patients.

	SLE patients (*n*=48)
Sex (F/M)	43/5
Age (years), median (range)	46 (17-82)
SLEDAI, median (range)	4 (0-24)
Clinical manifestations*	
Fever	4
Rash	12
Mucosal ulcers	1
Alopecia	1
Arthritis	18
Pleurisy	3
Pericarditis	2
Nephritis	5
Biological features	
Anti-dsDNA**	25
Anemia	10
Lymphopenia	11
Leucopenia	5
Thrombocytopenia	5
Hematuria	4
Low complements	19
Proteinuria	7
Treatment; median (range)	
None	10
CS < 10mg/day; 5 (2-7.5)	11
CS ≥ 10mg/day; 10 (10-20)	10
HCQ (mg/day); 400 (200-400)	22
MTX (mg/week); 17.5 (10-20)	6

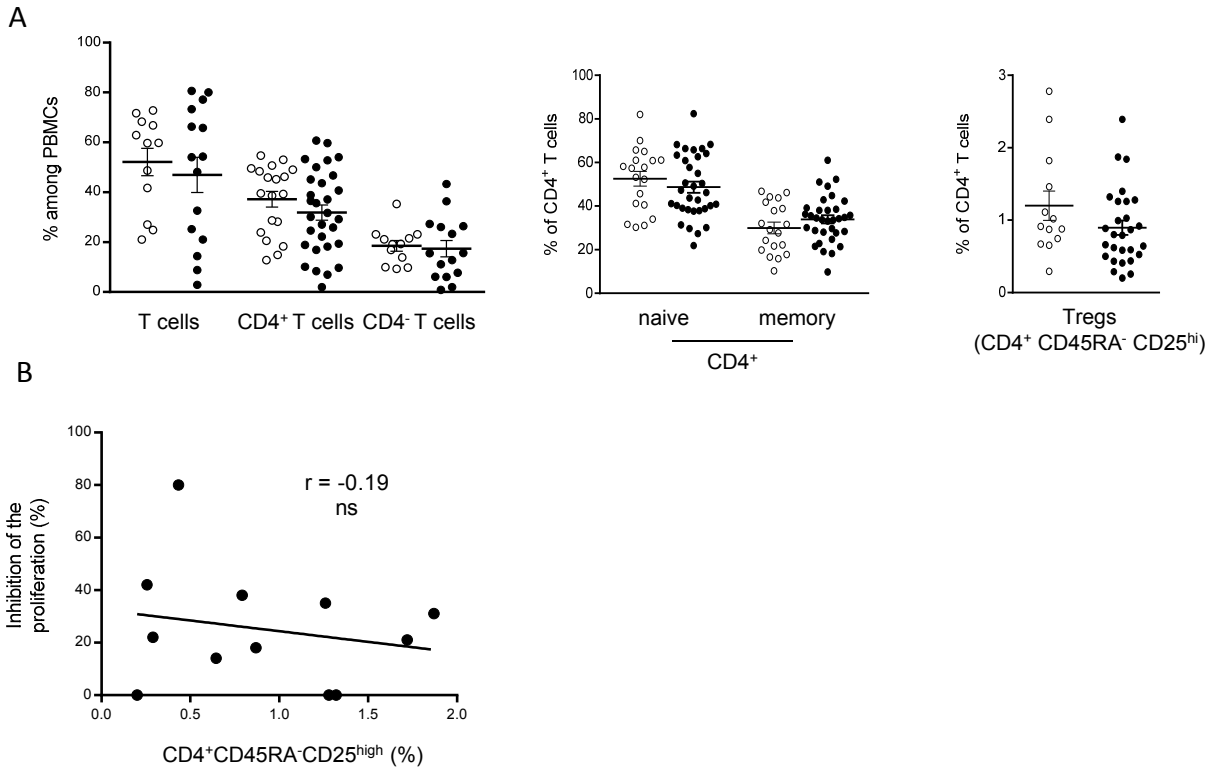
F, female; M, male; SLEDAI, SLE disease activity index; CS, corticosteroids; HCQ, hydroxychloroquine; MTX, methotrexate.
* at the time of blood drawn ** considered positive when the titer was ≥50 IU/ml as measured by ELISA.



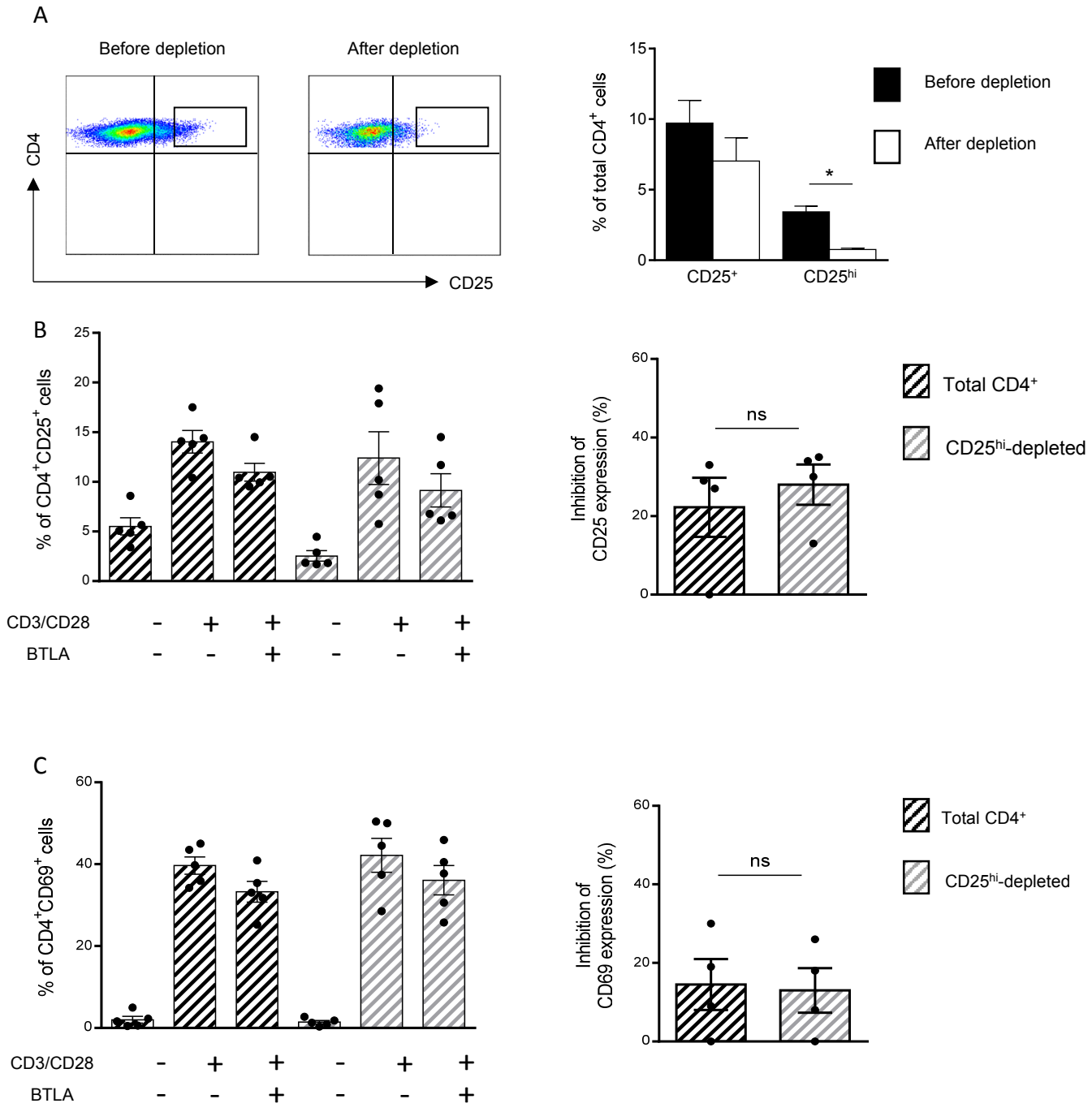
Supplemental Figure 1: Relationship between BTLA expression on various T cell subsets and SLEDAI score. Correlation between BTLA expression and the disease activity defined by the SLEDAI (*n*=17-25). Each dot represents one individual. r=Spearman correlation coefficient. ns=not significant.



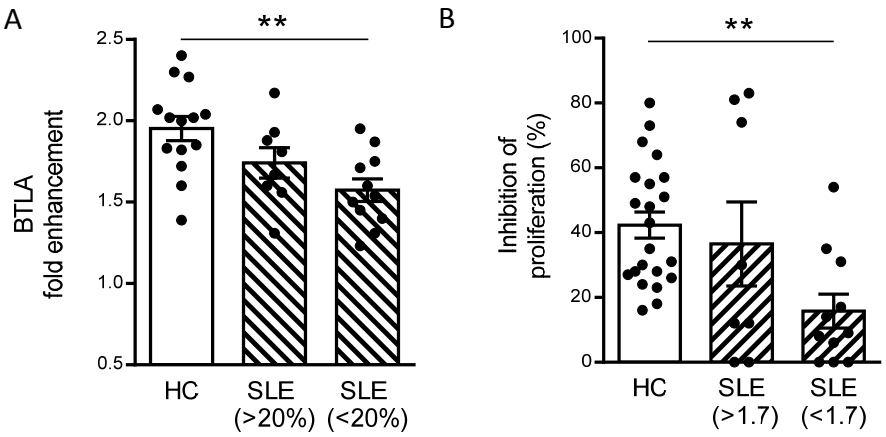
Supplemental Figure 2: Evaluation of BTLA functionality in CD4$^+$ T cells from HCs. Purified CD4$^+$ T cells were cultured for 48h in presence or not of TCR stimulation (anti-CD3/CD28 mAbs) ± the agonistic anti-BTLA mAb or its isotype control (IgG2a). Representative data obtained with CD4$^+$ T cells from one HC are shown. **(A)** CD4$^+$ T cells were cultured for 3 days and [^{3}H] thymidine was added during the last 16-18h. Results are expressed as cpm ± SEM. **(B)** CD25 expression was assessed by flow cytometry on stimulated CD4$^+$ T cells following 2 days of culture. (**C**) Erk phosphorylation was determined by flow cytometry on purified CD4$^+$ T cells stimulated for 5 minutes with anti-CD3 mAb in presence or not of the agonistic anti-BTLA mAb. **(D-E)** Correlations between the inhibition of proliferation and CD25 expression **(D)** and between the inhibition of proliferation in the presence or not of the isotype control **(E)** were calculated with Spearman's correlation and r represents the Spearman's correlation coefficient; **p<0.01; ****: p<0.0001.



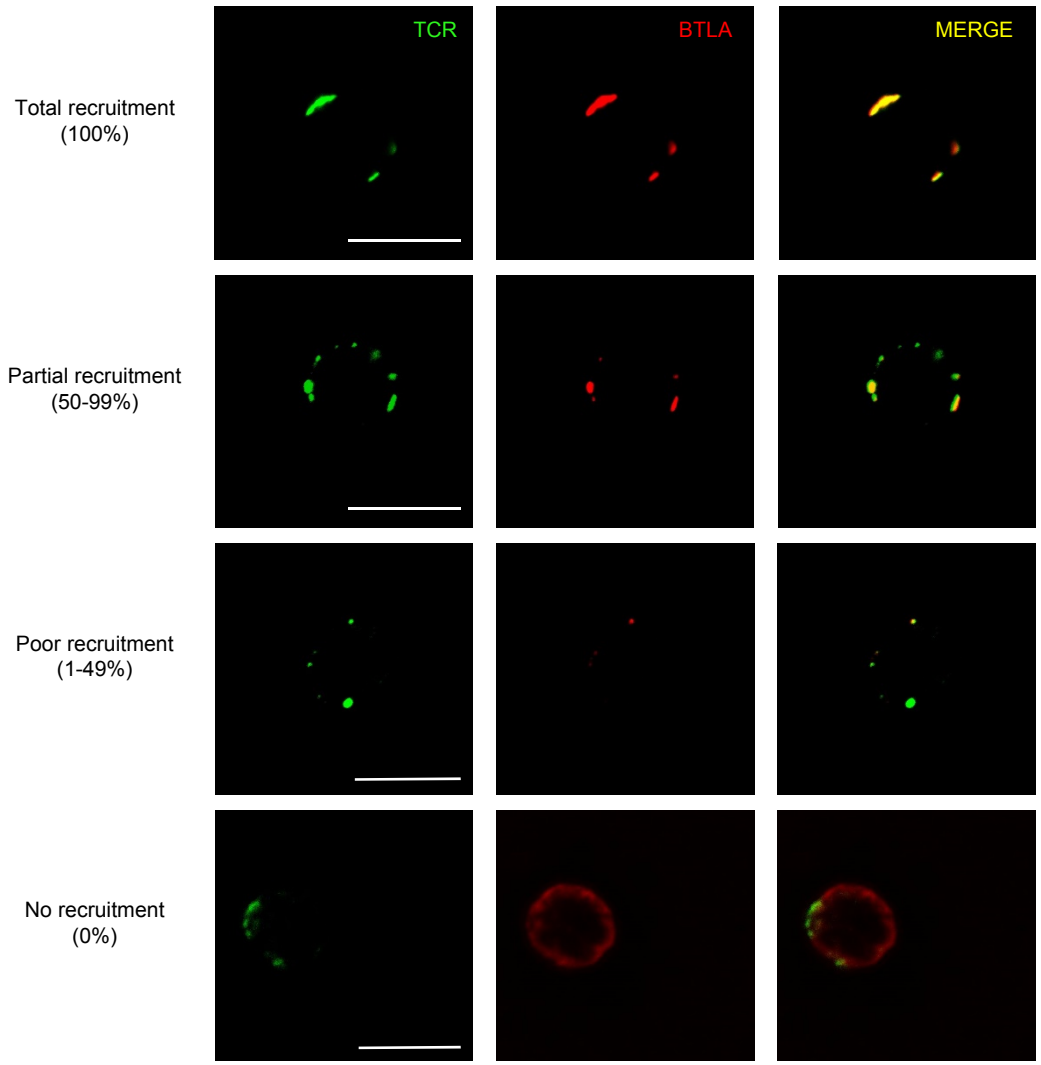
Supplemental Figure 3: Frequency of human T cell subsets in HCs and SLE patients. (A) Comparison of the frequency of total T cells ($CD3^+$), $CD4^+$ T cells ($CD3^+CD4^+$) and $CD8^+$ T cells ($CD3^+CD4^-$) among total PBMCs from HCs (white bars, *n*=10-21*)* and SLE patients (hatched bars, *n*=21-30*)*. **(B-C)** Comparison of the frequency of naive ($CD3^+CD4^+CD45RA^+$) and memory ($CD3^+CD4^+CD45RA^-$) $CD4^+$ T cells **(B)** and aTregs (**C**: $CD3^+CD4^+CD45RA^-CD25^{hi}$) among total $CD4^+$ T cells from HCs (white bars) and SLE patients (hatched bars). **(D)** Correlation between aTreg frequency and the inhibition of proliferation (%, n=12) Results are expressed as mean ± SEM and each dot represents one individual. r=Spearman correlation coefficient. ns=not significant.



Supplemental Figure 4: Absence of Treg impact on the analysis of BTLA functionality. **(A)** Example of CD25 staining following Treg depletion. **(B-C)** $CD4^+$ T cells and $CD25^{hi}$-depleted $CD4^+$ T cells were stimulated with anti-CD3+anti-CD28 mAbs ± the agonistic anti-BTLA mAb or its isotype control. CD25 and CD69 expression were analyzed after 2 days by flow cytometry and the inhibition of CD25 expression **(B)** and of CD69 expression **(C)** were compared in total and in $CD25^{hi}$-depleted $CD4^+$ T cells from SLE patients (*n*=4). Results are expressed as mean ± SEM. (ns: not significant, *p<0.05; Mann-Whitney).



Supplemental Figure 5: Low BTLA fold enhancement is associated with high BTLA functional deficiency. (A) BTLA fold enhancement was compared between HCs and SLE patients harboring either more than 20% inhibition of $CD4^+$ T cell proliferation (SLE>20%; *n*=11) or less than 20% inhibition (SLE<20%; *n*=8). **(B)** Percentage of inhibition of the proliferation was compared between HC and SLE patients whose $CD4^+$ T cells harbor a fold enhancement of BTLA expression higher than 1.7 (SLE>1.7; *n*=8) or lower than 1.7 (SLE<1.7; *n*=11). Results are expressed as mean ± SEM. (**p<0.01, One way ANOVA/Tukey comparison).



Supplemental Figure 6: Profiles of BTLA recruitment to TCR clusters. To quantify BTLA (in red) recruitment to TCR (in green) clusters cell by cell, we measured the percentage of TCR/BTLA-colocalized clusters over the total number of clusters for each cell. Four different profiles of recruitment are defined: total recruitment (100% of colocalized clusters); partial recruitment (50-99%); poor recruitment (1-49%) and no recruitment (0% of colocalized clusters). White bar=10µm.

Figure S6