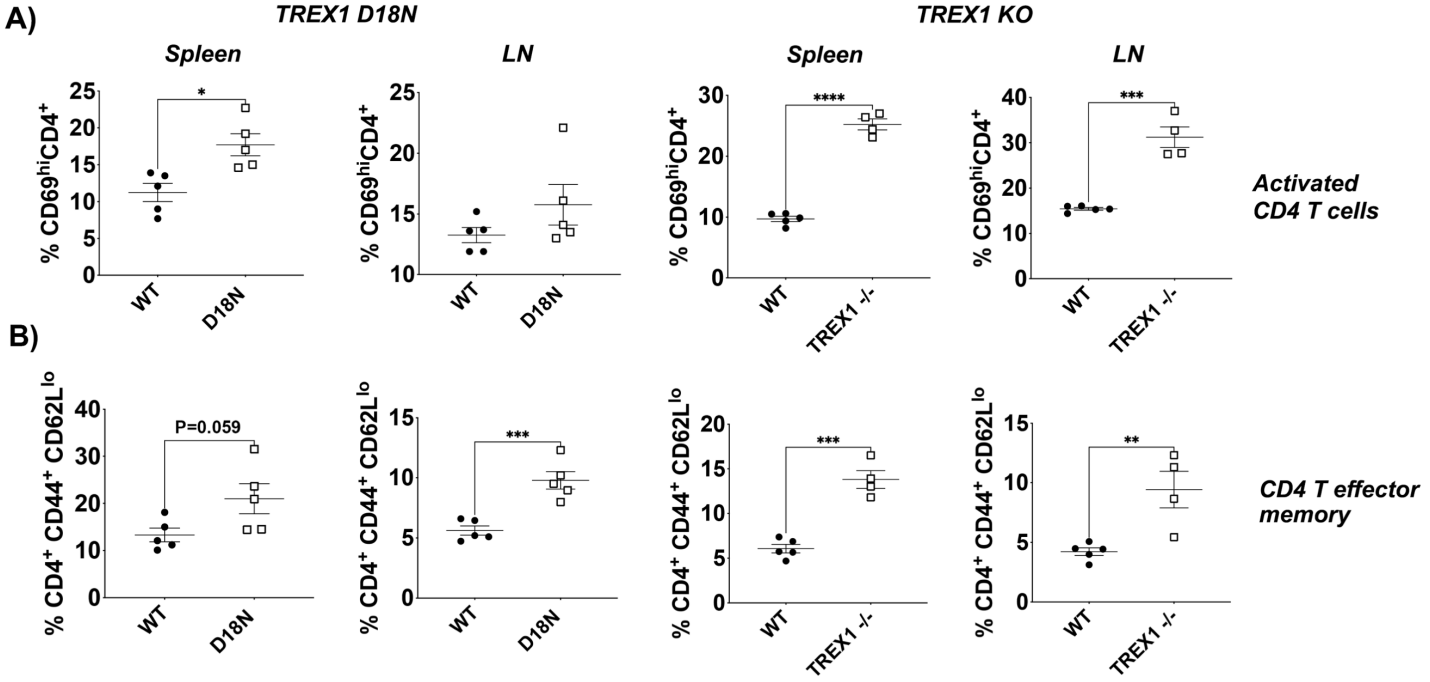
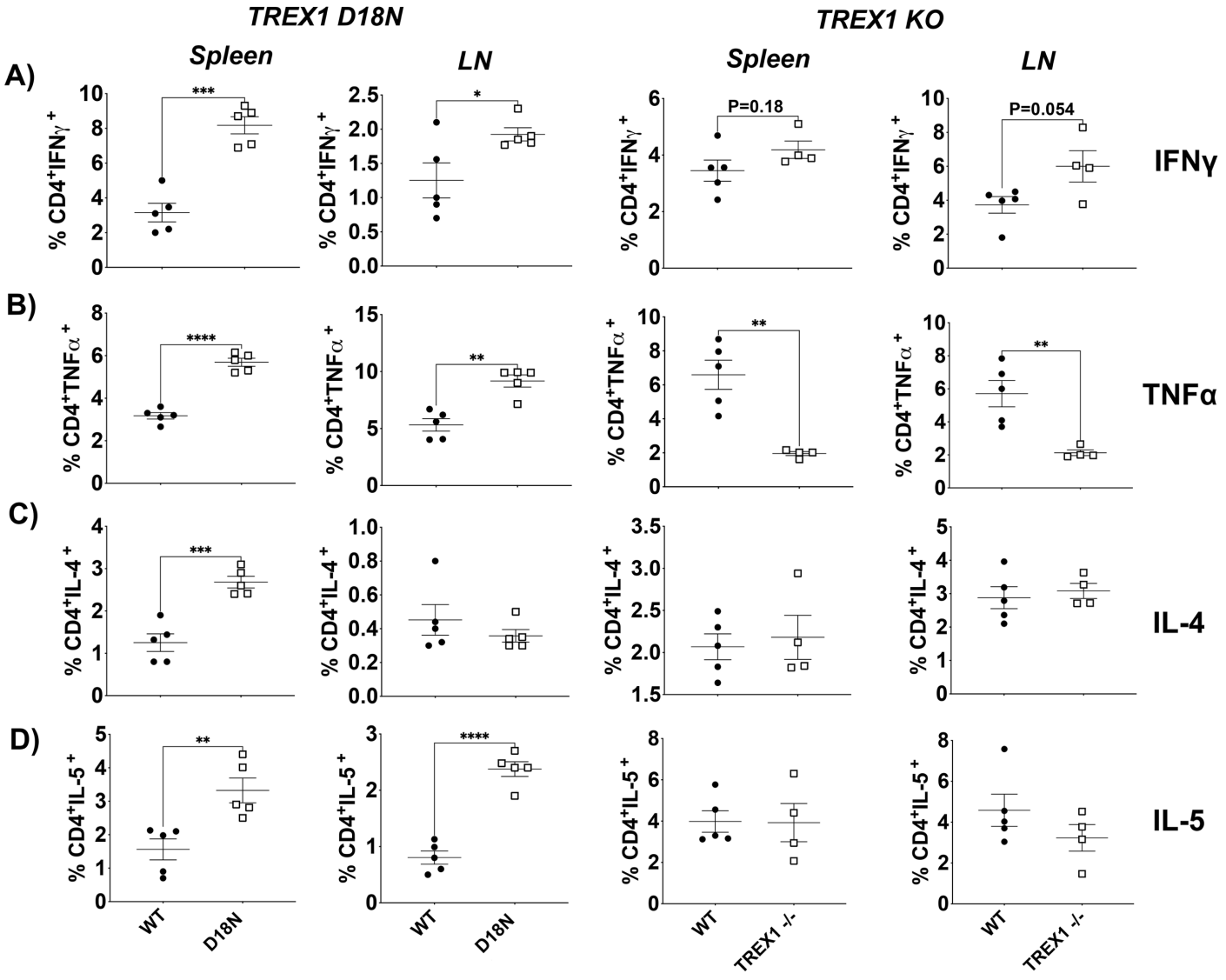
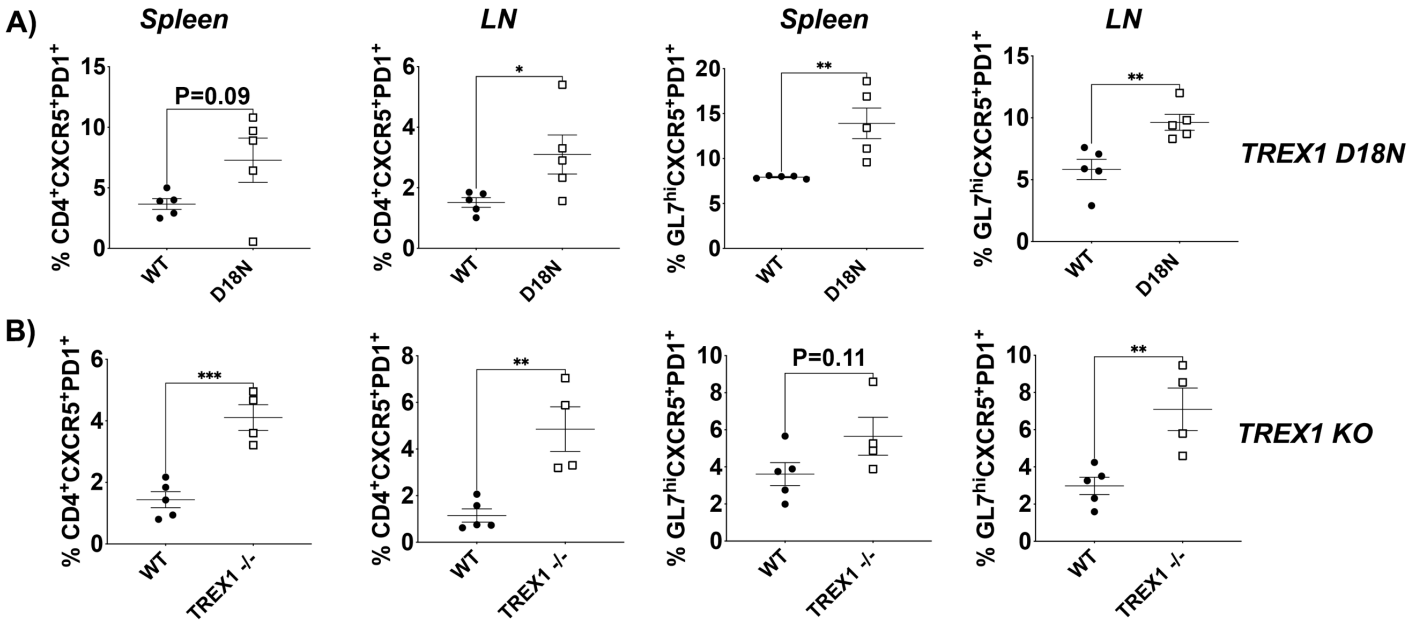
Supplementary Figure 1. Elevated levels of CD4 T helper cells and T effector memory in TREX1 deficiency. Spleen and pooled peripheral lymph nodes (cervical, axillary, brachial and inguinal lymph nodes) were obtained from female 8-12 weeks old TREX1 D18N and TREX1 knockout mice and levels of A) activated $CD4^+$ T cells ($CD4^+CD69^{hi}$) and B) Tem status ($CD4^+CD44^+CD62L^{lo}$) were analyzed by flow cytometry. Percentage data presented as mean ± S.E.M relative to WT mice (normalized absolute numbers) and show a total of 4-5 mice per group over 3 independent experiments, with the dots representing individual mice. *p < 0.01, ** p < 0.001 as calculated by 2-tailed unpaired Student's t-test and Mann-Whitney test.



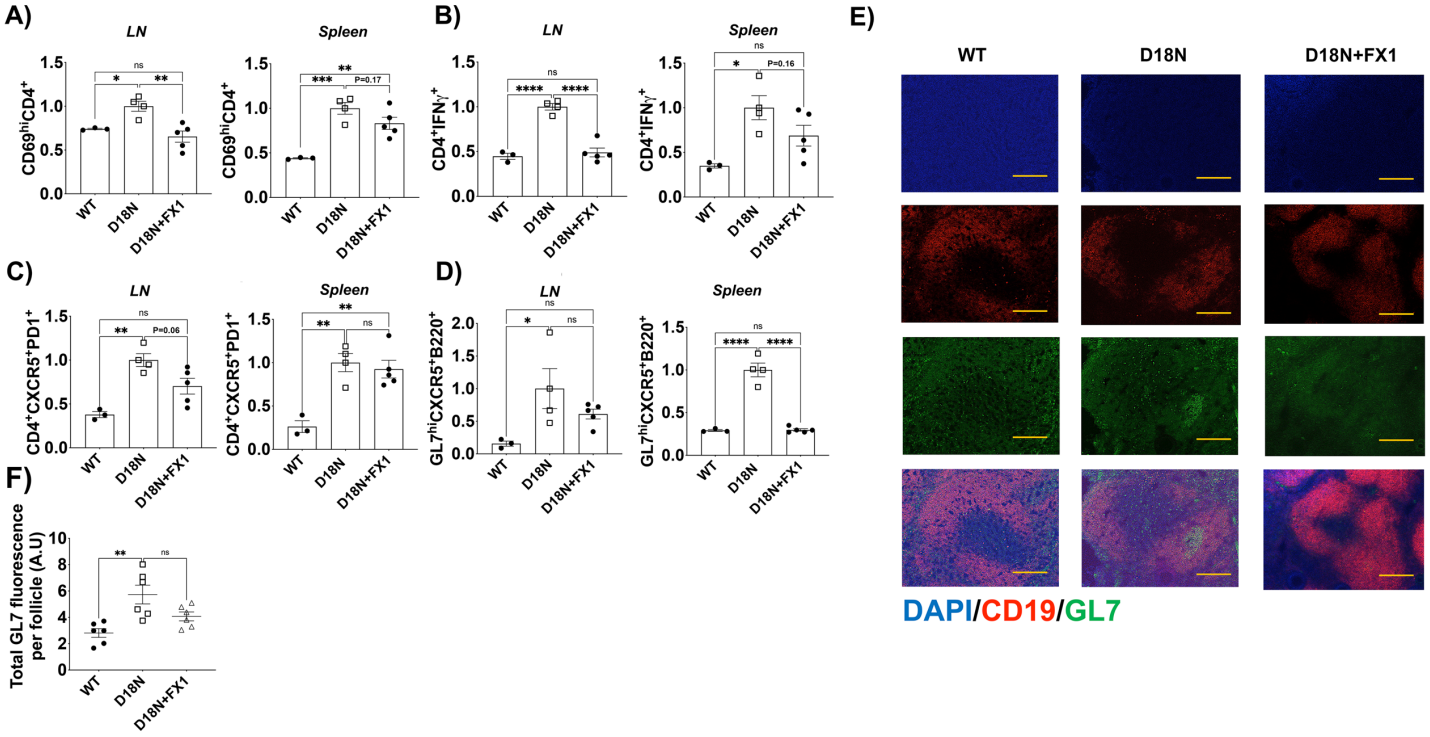
Supplementary Figure 2. Status of T-helper cytokines in TREX1 deficiency. Spleen and lymph nodes (LN) from female TREX1 D18N and TREX1 knockout mice were stimulated with PMA/Ionomycin for 5 hours and levels of Th1 cytokines % IFNγ$^+$ **(A)**, % TNFα$^+$ **(B)** and Th2 cytokines % IL-4$^+$ **(C)** and % IL-5$^+$ **(D)** in the CD4 T cell gate were analyzed by flow cytometry. Data presented as mean ± S.E.M relative to WT mice (normalized percentage data) and show a total of 4-5 mice per group over 3 independent experiments, with the dots representing individual mice; or three independent experiments for *in vitro* assays. *p < 0.01, ** p < 0.001 as calculated by 2-tailed unpaired Student's t-test.



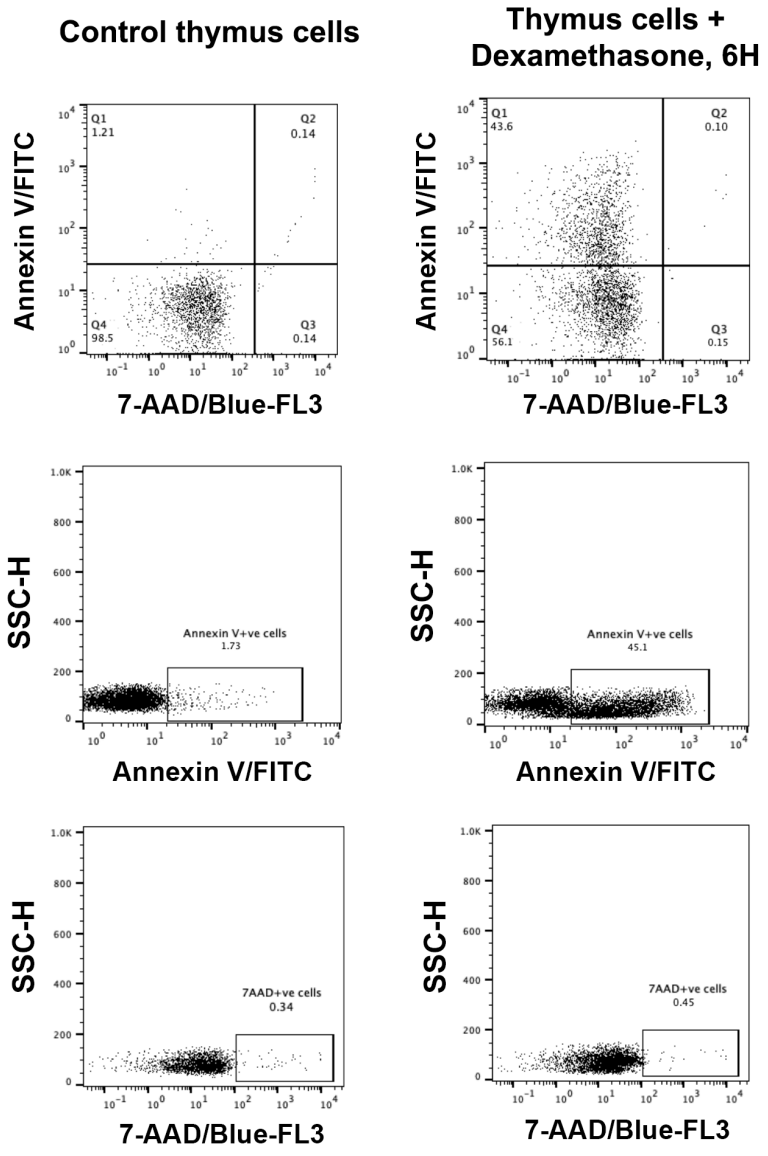
Supplementary Figure 3. Elevated T-Follicular helper cell response and B-cell activation in TREX1 deficiency. Levels of TfH cells (% $CD4^+CXCR5^+PD1^+$) and % $GL7^{hi}CXCR5^+B220^+$ B-cells in the CD4 and B220 gated cells. (A) TREX1 D18N and (B) TREX1 KO female mice analyzed by flow cytometry. Data presented as mean ± S.E.M relative to WT mice (normalized percentage data) and show a total of 4-5 mice per group over 3 independent experiments, with the dots representing individual mice. *p < 0.01, ** p < 0.001, *** p < 0.0001 as calculated by 2-tailed unpaired Student's t-test.



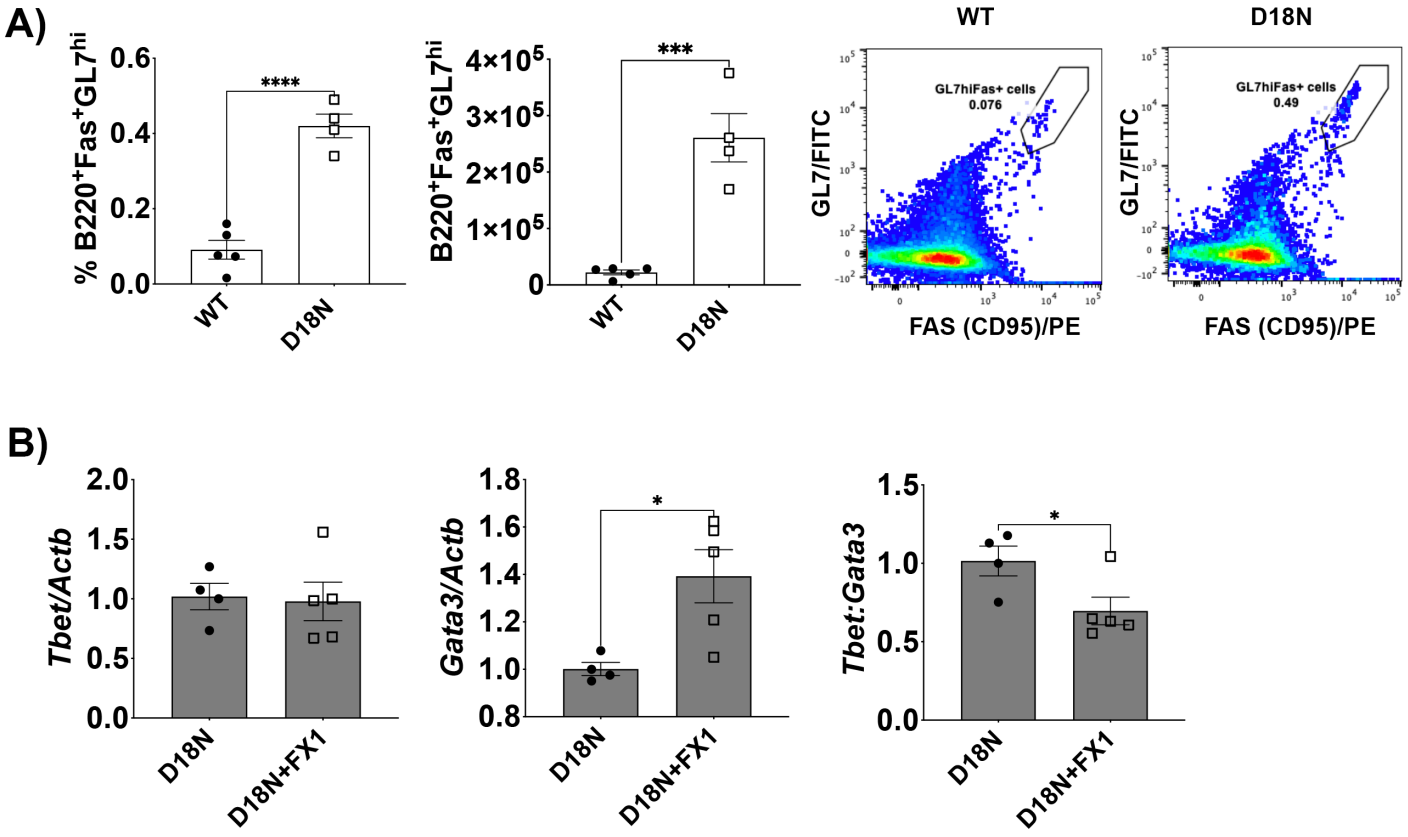
Supplementary Figure 4. Bcl6 inhibition rescues autoimmunity in TREX1 D18N mutant animals. Mice were treated as described in materials and methods and analyzed by flow cytometry for fold changes over D18N control mice in A) % $CD69^{+}CD4^{+}$ B) % $IFN\gamma^{+}CD4^{+}$ T cells C) % $CD4^{+}CXCR5^{+}PD1^{+}$ T follicular helper cells and D) % $B220^{+}GL7^{hi}CXCR5^{+}$ B cells E) Immunofluorescence for GC B cells (GL7/CD19), Scale bars 50 µm and F) Quantification of total GL7 fluorescence per splenic follicle by ImageJ. Data are shown as mean ± S.E.M and with a total of 3 to 5 mice per group over 3 independent experiments and shown as relative to D18N animals. *p < 0.01, ** p < 0.001, *** p < 0.0001 as calculated by multiple comparison by one way ANOVA.



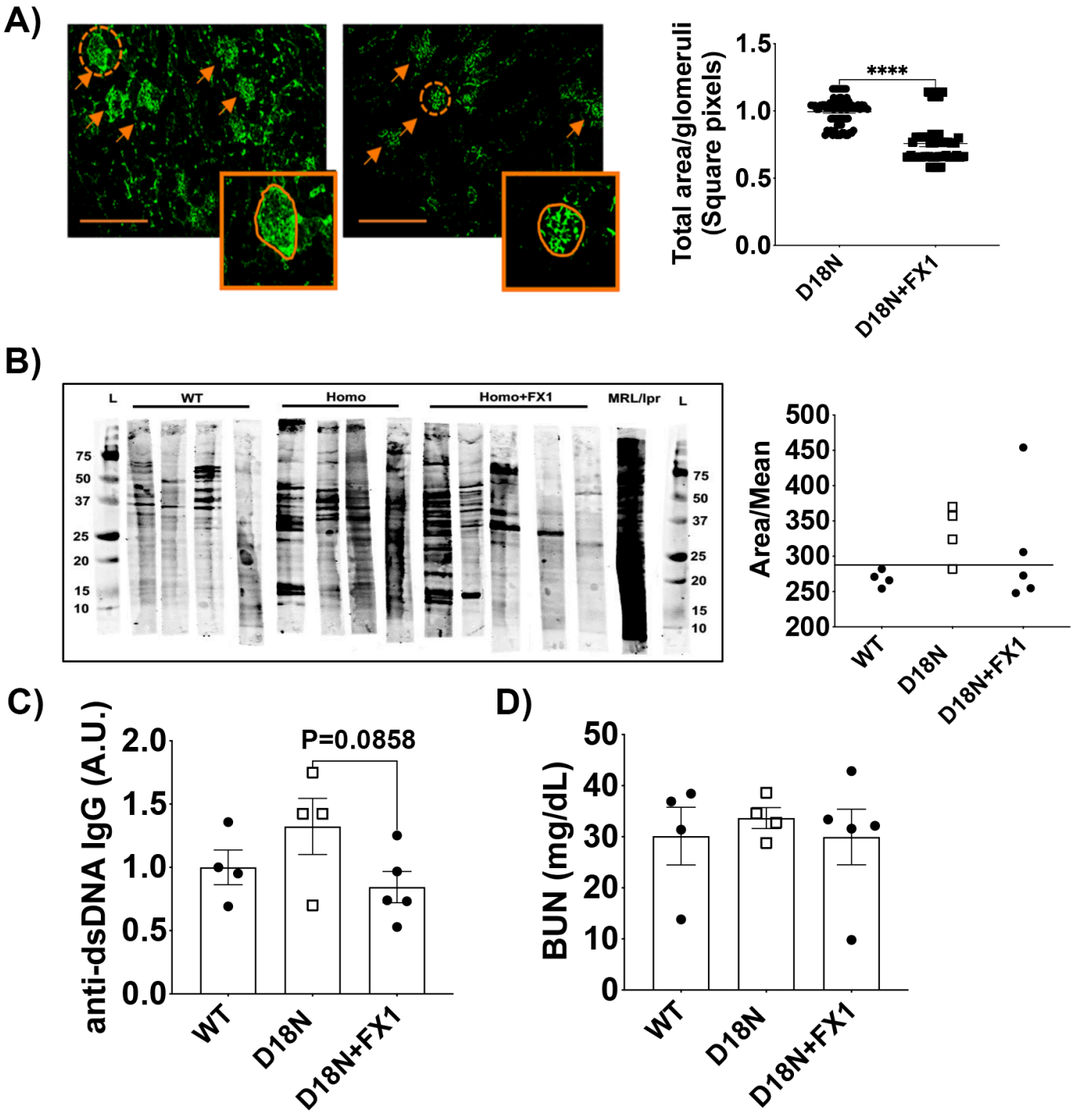
Supplementary Figure 5. Flow cytometry analysis to confirm apoptotic cell generation for *in vitro* analysis.

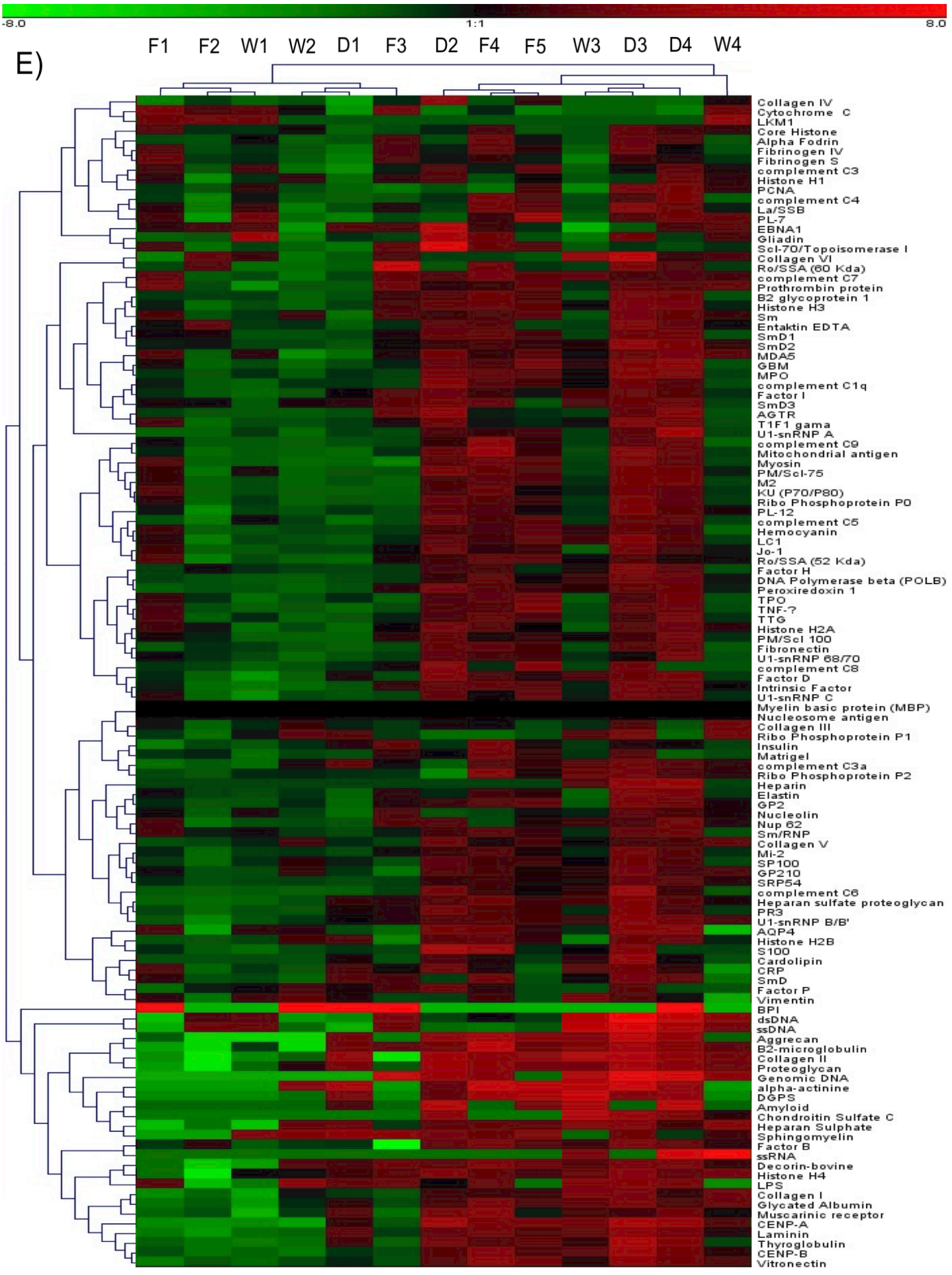


Supplementary Figure 6. Elevated germinal center formation in TREX1 deficiency and attenuated Th1 response in FX1 treated TREX1 D18N animals. A) Levels of germinal center B-cells ($B220^{+}GL7^{hi}Fas^{+}$) in TREX1 D18N female mice analyzed by flow cytometry. Both percentage data and absolute number data are shown. Data presented as mean ± S.E.M representative of 4 to 5 animals per group and shown as both percentages (left) and absolute numbers (right). Flow cytometry plots are representative images showing gating strategy. *p < 0.01, ** p < 0.001, *** p < 0.0001 as calculated by 2-tailed unpaired Student's t-test. **B)** Transcript levels of *Tbx21 (T-bet)* and *Gata3* were measured by Real-time PCR in TREX1 D18N mice and mice treated with FX1. Data are presented as mean ± S.E.M of a total of 4 to 5 mice per group over 2-independent experiments normalized to TREX1 D18N vehicle control. *p < 0.01 as calculated by 2-tailed unpaired Student's t-test.



Supplementary Figure 7. Bcl6 inhibition rescues autoimmunity in TREX1 D18N mutant mice. Mice were treated as described in materials and methods and analyzed for A) Total glomerular IgG deposition in the kidneys B) Analysis of serum autoantibodies by Western blot analysis and its quantification by ImageJ; WT- wild type, Homo – TREX D18N, Homo+FX1 – TREX1 D18N treated with FX1 C) Circulating anti-dsDNA IgG levels as tested by ELISA D) Levels of Blood Urea Nitrogen (BUN) in WT, TREX1 D18N (D18N) and D18N - FX1 treated animals. E) Heat map and cluster analysis of autoantibody array showing differential regulation in serum samples from WT (W1-W4), untreated TREX1 D18N (D1-D4) and FX1 treated TREX1 D18N (F1-F5) mice (next page). Data are shown as mean ± S.E.M and show a total of 4 to 5 mice per group over 2 independent experiments and are shown as relative to D18N animals. **** $p < 0.0001$ as calculated by 2-tailed unpaired Student's t-test.

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F1
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D4
W4
Collagen IV
Cytochrome C
LKM1
Core Histone
Alpha Fodrin
Fibrinogen IV
Fibrinogen S
complement C3
Histone H1
PCNA
complement C4
La/SSB
PL-7
EBNA1
Gliadin
Scl-70/Topoisomerase I
Collagen VI
Ro/SSA (60 Kda)
complement C7
Prothrombin protein
B2 glycoprotein 1
Histone H3
Sm
Entaktin EDTA
SmD1
SmD2
MDA5
GBM
MPO
complement C1q
Factor I
SmD3
AGTR
T1F1 gama
U1-snRNP A
complement C9
Mitochondrial antigen
Myosin
PM/Scl-75
M2
KU (P70/P80)
Ribo Phosphoprotein P0
PL-12
complement C5
Hemocyanin
LC1
Jo-1
Ro/SSA (52 Kda)
Factor H
DNA Polymerase beta (POLB)
Peroxiredoxin 1
TPO
TNF-?
TTG
Histone H2A
PM/Scl 100
Fibronectin
U1-snRNP 68/70
complement C8
Factor D
Intrinsic Factor
U1-snRNP C
Myelin basic protein (MBP)
Nucleosome antigen
Collagen III
Ribo Phosphoprotein P1
Insulin
Matrigel
complement C3a
Ribo Phosphoprotein P2
Heparin
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GP2
Nucleolin
Nup 62
Sm/RNP
Collagen V
Mi-2
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Collagen II
Proteoglycan
Genomic DNA
alpha-actinine
DGPS
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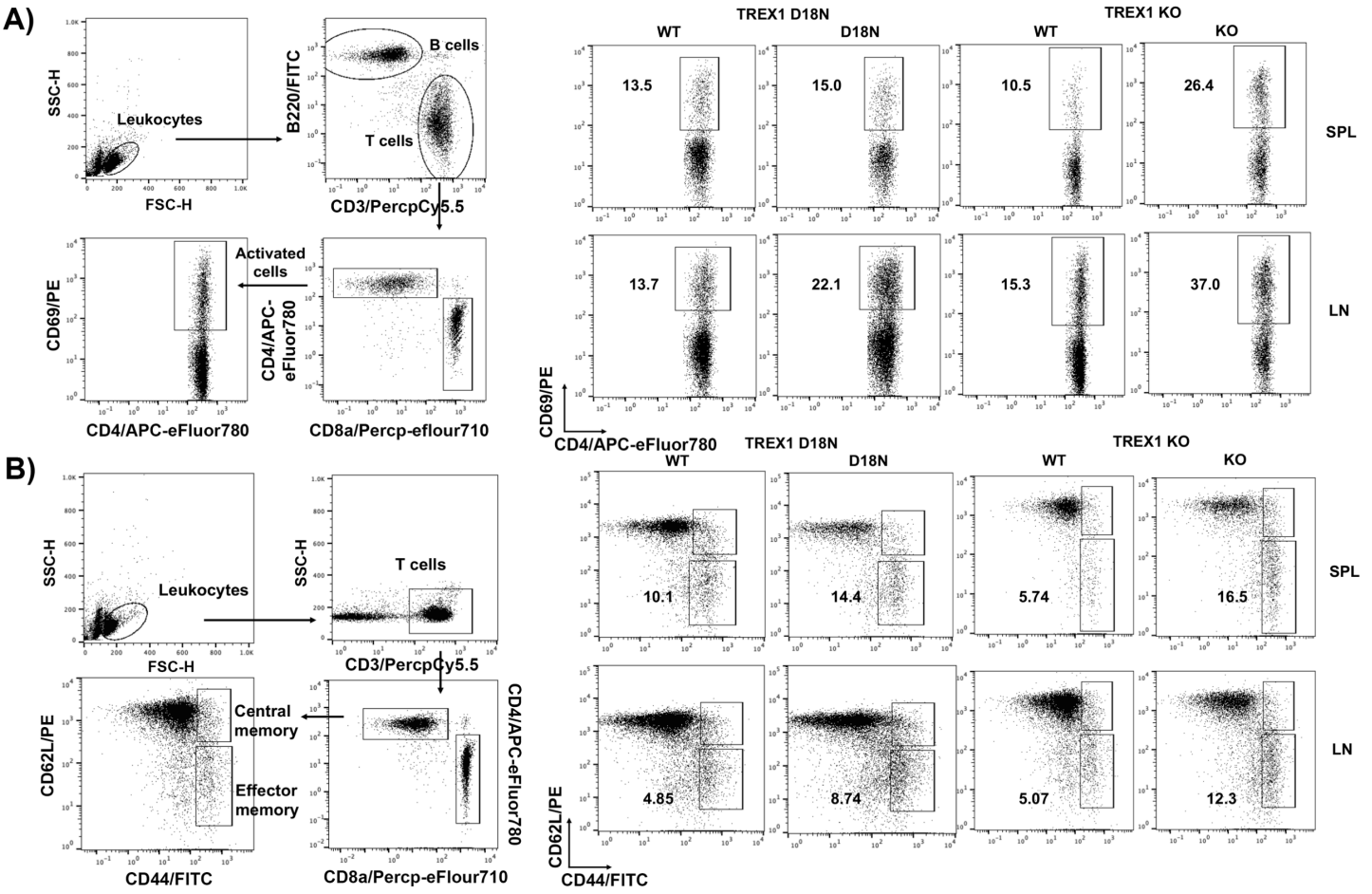
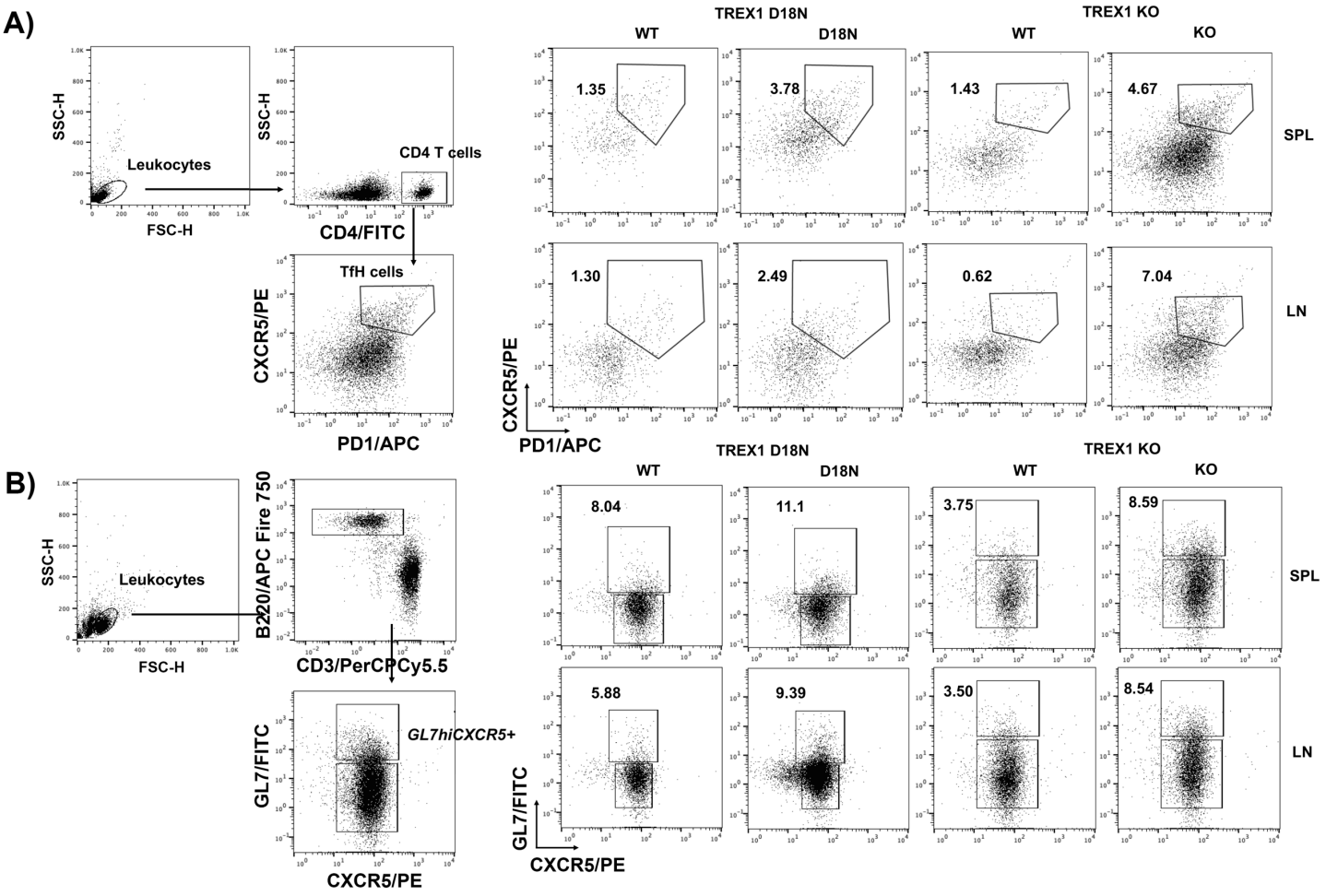
Sphingomyelin
Factor B
ssRNA
Decorin-bovine
Histone H4
LPS
Collagen I
Glycated Albumin
Muscarinic receptor
CENP-A
Laminin
Thyroglobulin
CENP-B
Vitronectin

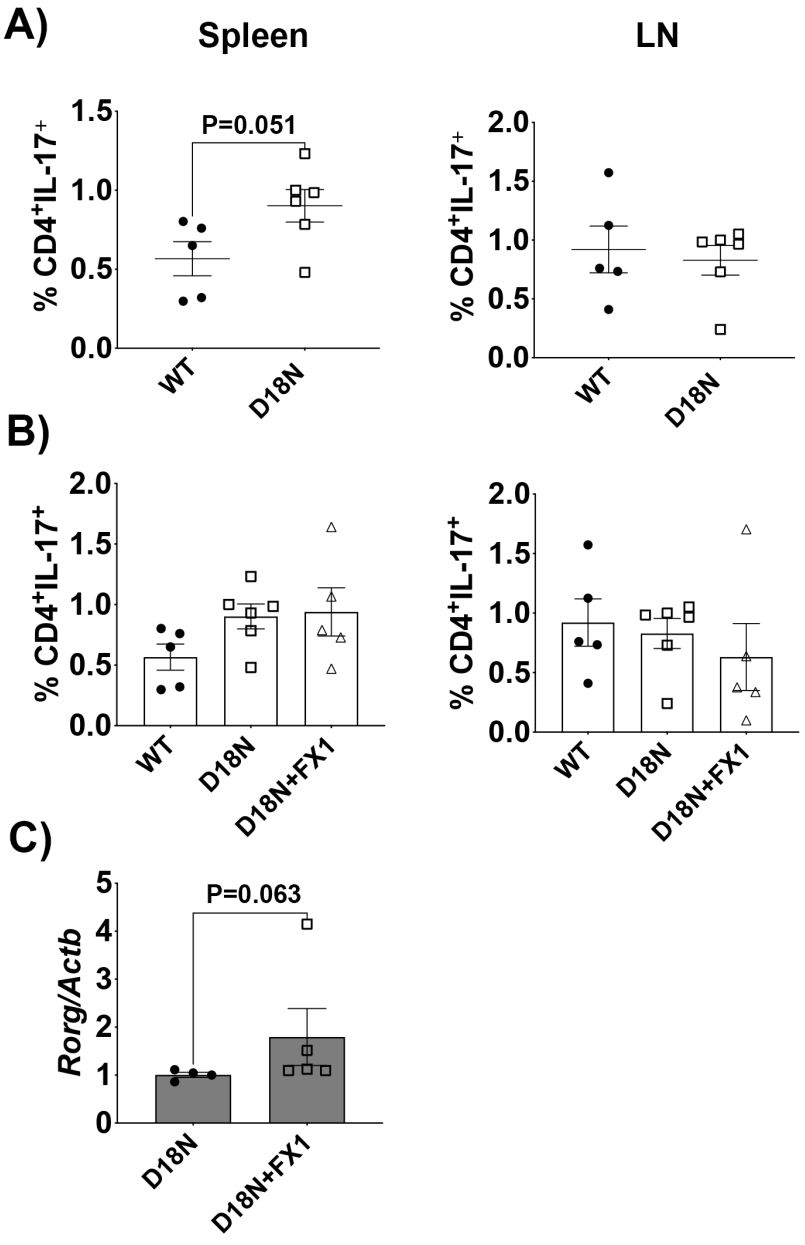
Supplementary Figure 8. Flow cytometry gating strategy used for the analysis of A) recently activated cells and B) memory cells. Representative flow plots between TREX1 D18N and TREX1 KO animals are shown. Inset numbers represents percentage changes observed between WT and TREX1 deficient animals.



Supplementary Figure 9. Flow cytometry gating strategy used for the analysis of A) T follicular helper (Tfh) cells and B) GL7^{hi}CXCR5^{+} B cells. Representative flow plots between TREX1 D18N and TREX1 KO animals are shown. Inset numbers represents percentage changes observed between WT and TREX1 deficient animals.



Supplementary Figure 10. Status of T-helper cytokines in TREX1 deficiency. A) Spleen and lymph nodes (LN) from female TREX1 D18N and TREX1 knockout mice were stimulated with PMA/Ionomycin for 5 hours and levels of Th17 cytokine IL-17 was analyzed by flow cytometry. **B)** Spleen and lymph nodes (LN) from female TREX1 D18N animals and animals treated with FX1 were stimulated with PMA/Ionomycin for 5 hours and levels of Th17 cytokine IL-17 was analyzed by flow cytometry. **C)** Transcript levels of *Rorg* was investigated by Real-time PCR in TREX1 D18N animals and animals treated with FX1. Data presented as mean ± S.E.M and show a total of 4-5 animals per group over 2-independent experiments. The 2-tailed unpaired Student's t-test and multiple comparison by one way ANOVA were employed for statistical evaluations.



Supplementary Table 1: Details of antibodies used for flow cytometry.

Antigen	Conjugate	Catalog No.	Vendor
CD4	APC-eFluor 780	47-0041-82	Invitrogen
CD4	FITC	11-0041-85	eBioscience
CD69	PE	104507	BioLegend
CD44	FITC	11-0441-82	eBioscience
CD62L	PE	12-0621-83	eBioscience
IL-4	PE	504104	BioLegend
IL-5	PE	504303	BioLegend
TNFα	FITC	506304	eBioscience
IFNγ	FITC	505806	eBioscience
CXCR5	PE	145504	BioLegend
PD1	APC	109112	BioLegend
GL7	Alexa Fluor 488	144612	BioLegend
B220	FITC	103206	BioLegend
B220	APC/Fire 750	103260	BioLegend
CD3	PercpCy5.5	100328	BioLegend
CD3	APC-eFluor780	47-0033-82	eBioscience
Fas	PE	152607	BioLegend