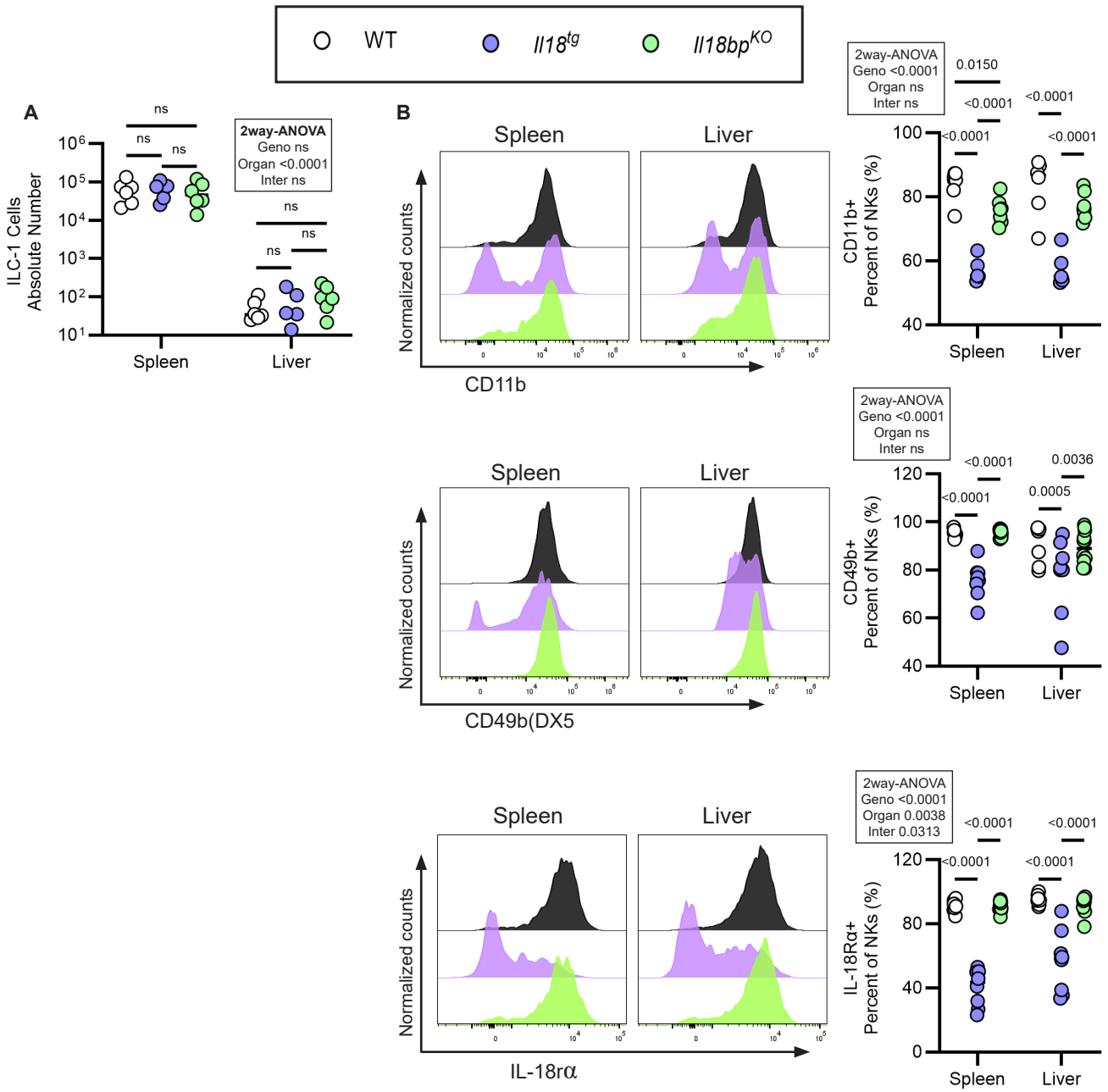
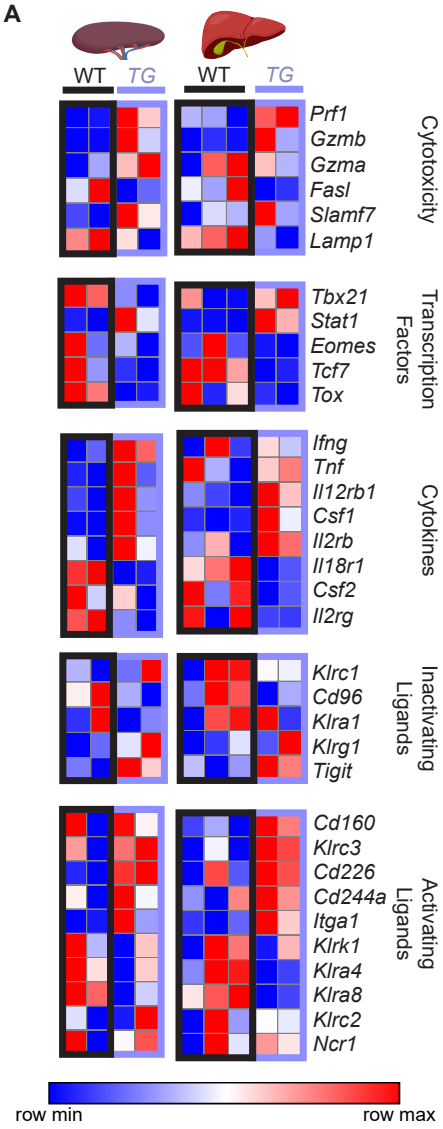


Supplemental Figure 1. Altered NK cell phenotype in resting *Il18*^{tg} more than *Il18bp*^{KO} mice. Companion to Figure 1. (**A**) ILC1 enumeration from spleen and liver. (**B**) Representative and aggregate homeostatic NK cell CD11b, CD49b, and IL-18Rα expression from NK cells. Significance: 2-way ANOVA (inset box) with Tukey's pairwise comparisons of all three genotype combinations within each organ; Data representative of 3 independent experiments (A) and combined from 2 independent experiments (B). "ns" = adjusted p-value < 0.05; ns results omitted in (B).

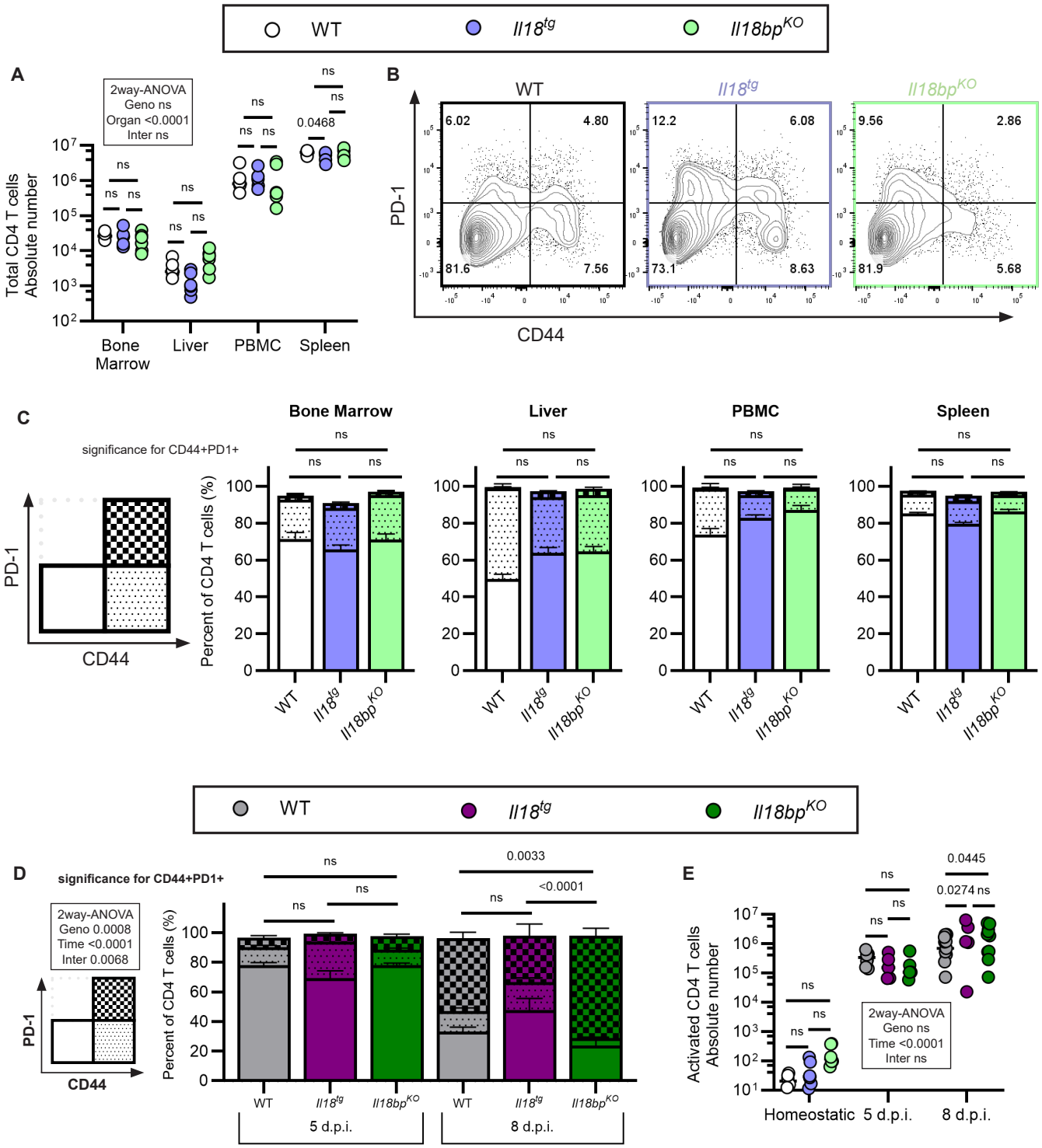
A



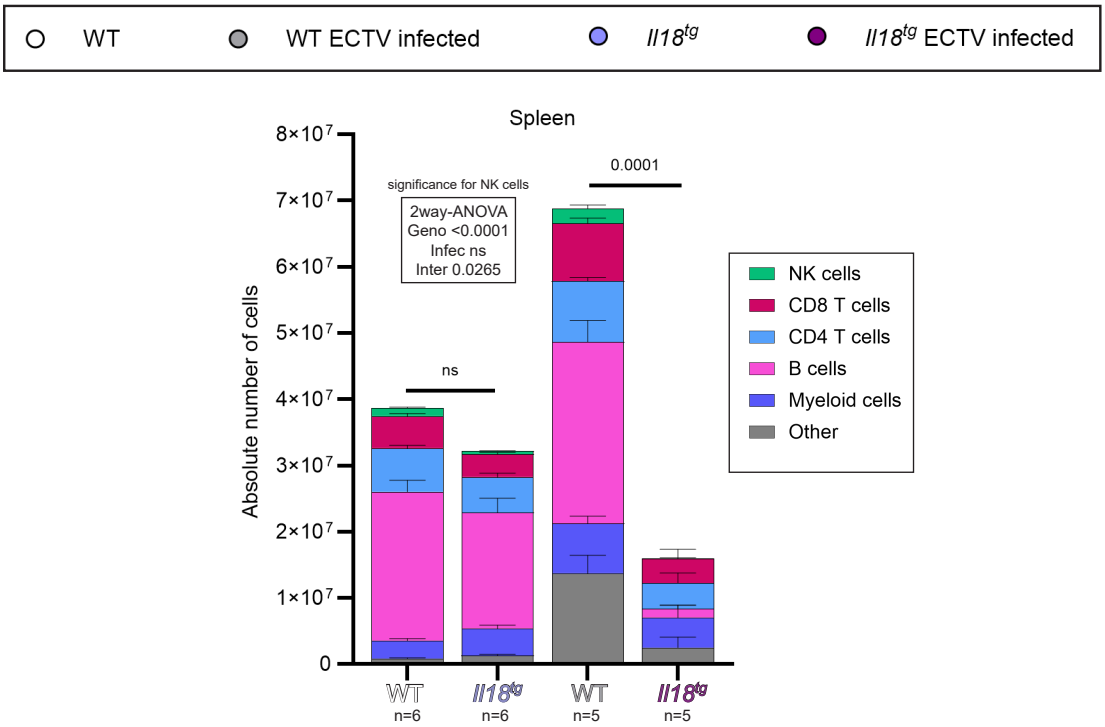
B

GSEA			
Geneset Source	Enriched Gene Sets	NES	FDR q-val
M7	CUI_TREG_IFNG_RESPONSE_UP	2.4761052	0
M7	CUI_T_CELL_CD4_IL18_RESPONSE_UP	2.47261	0
M7	CUI_CDC2_IFNK_RESPONSE_UP	2.4371073	0
M7	CUI_MONOCYTE_IFNG_RESPONSE_UP	2.4316566	0
M7	CUI_B_CELL_IL18_RESPONSE_UP	2.4298909	0
M7	CUI_NK_CELL_IL1A_RESPONSE_UP	2.4158356	0
M7	CUI_T_CELL_GD_IL27_RESPONSE_UP	2.4120698	0
M7	CUI_T_CELL_CD4_IFNG_RESPONSE_UP	2.4099748	0
M7	CUI_T_CELL_CD4_IL12_RESPONSE_UP	2.387173	0
M7	CUI_T_CELL_CD8_IFNG_RESPONSE_UP	2.3699746	0
M2	WP_CELL_CYCLE	2.425232	0
M2	REACTOME_RESOLUTION_OF_SISTER_CHROMATID_COHESION	2.2397768	5.44E-04
M2	WP_G1_TO_S_CELL_CYCLE_CONTROL	2.305113	6.61E-04
M2	REACTOME_EXTRACELLULAR_MATRIX_ORGANIZATION	2.2171535	6.69E-04
M2	REACTOME_ACTIVATION_OF_THE_PRE_REPLICATIVE_COMPLEX	2.2512186	6.80E-04
M2	REACTOME_MHC_CLASS_II_ANTIGEN_PRESENTATION	2.2720602	9.07E-04
M2	REACTOME_GPCR_LIGAND_BINDING	2.191582	9.47E-04
M2	REACTOME_G_ALPHA_I_SIGNALLING_EVENTS	2.166227	0.0013218

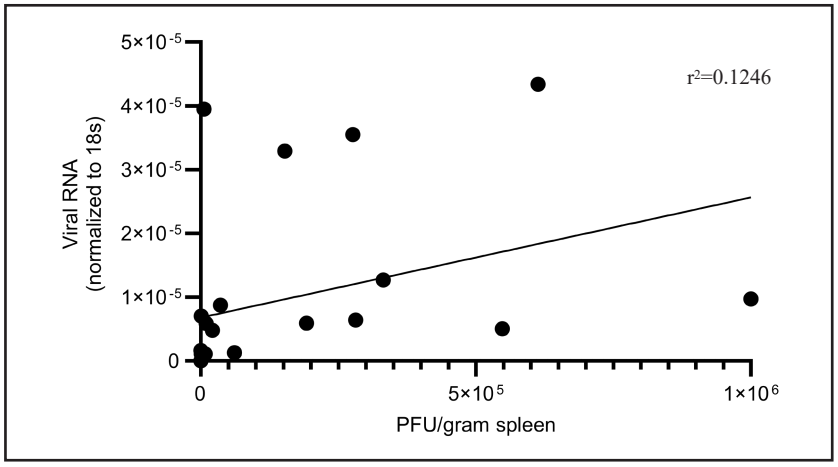
Supplemental Figure 2. Transcriptomic analysis of NK and ILC1 cells from WT and *Il18*^{tg} mice.
(**A**) Row- and organ-normalized heatmap of Transcripts Per Million (TPM) values from selected canonical transcripts from bulk RNAseq of sorted Splenic & Liver NK cells (see methods and Supplemental Dataset 1). (**B**) Top MSigDB M7-Immunologic Signature and M2-Canonical Pathway gene sets enriched in liver and spleen *Il18*^{tg} NK cells relative to WT (See also Supplemental Data 1). GSEA=Gene Set Enrichment Analysis; NES=Normalized Enrichment Score; FDR=False-Discovery Rate.



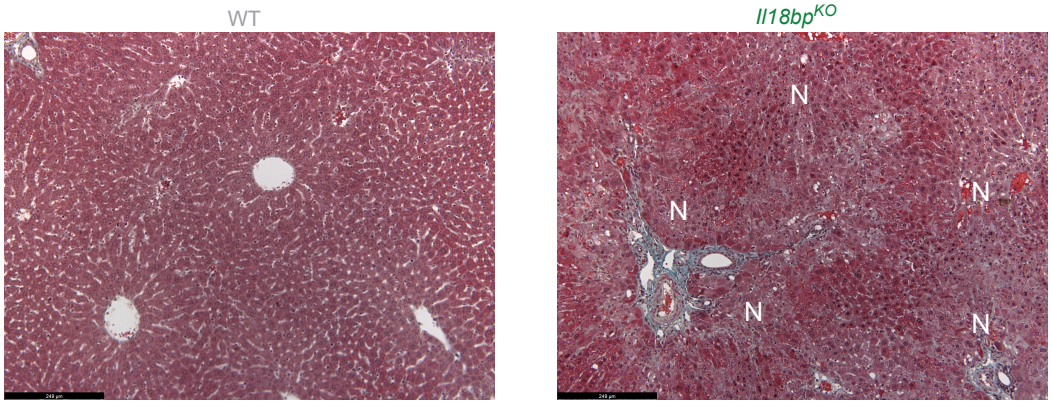
Supplemental Figure 3. Excess IL-18 does not induce spontaneous CD4 T-cell hyperactivation. Companion to Figures 2, 4, and 5. (**A**) Total CD4 T cells per organ or peripheral blood mononuclear cells (PBMC) per mL. Representative contour plots (**B**, from spleen) and aggregate data (**C**) of CD4 T-cell subsets as a proportion of all CD4 T cells from various organs of uninfected mice, n=6/genotype. Proportion of all CD4 T cells (**D**) and absolute numbers (**E**) of splenic CD4 T-cell subsets five and eight days post mousepox infection. Day 5: WT n=10, *Il18*^{tg} n=5, *Il18bp*^{KO} n=5; and Day 8: WT n=11, *Il18*^{tg} n=5, *Il18bp*^{KO} n=10). Significance: 2-way ANOVA (inset box) with Tukey's pairwise comparisons (line with p-value) of genotypes within each organ (A,C), timepoint (D,E). For C and D only CD44^{+}PD-1^{+} CD4 T cells were compared between genotypes. Data representative of 3 independent experiments. "ns" = adjusted p-value < 0.05.



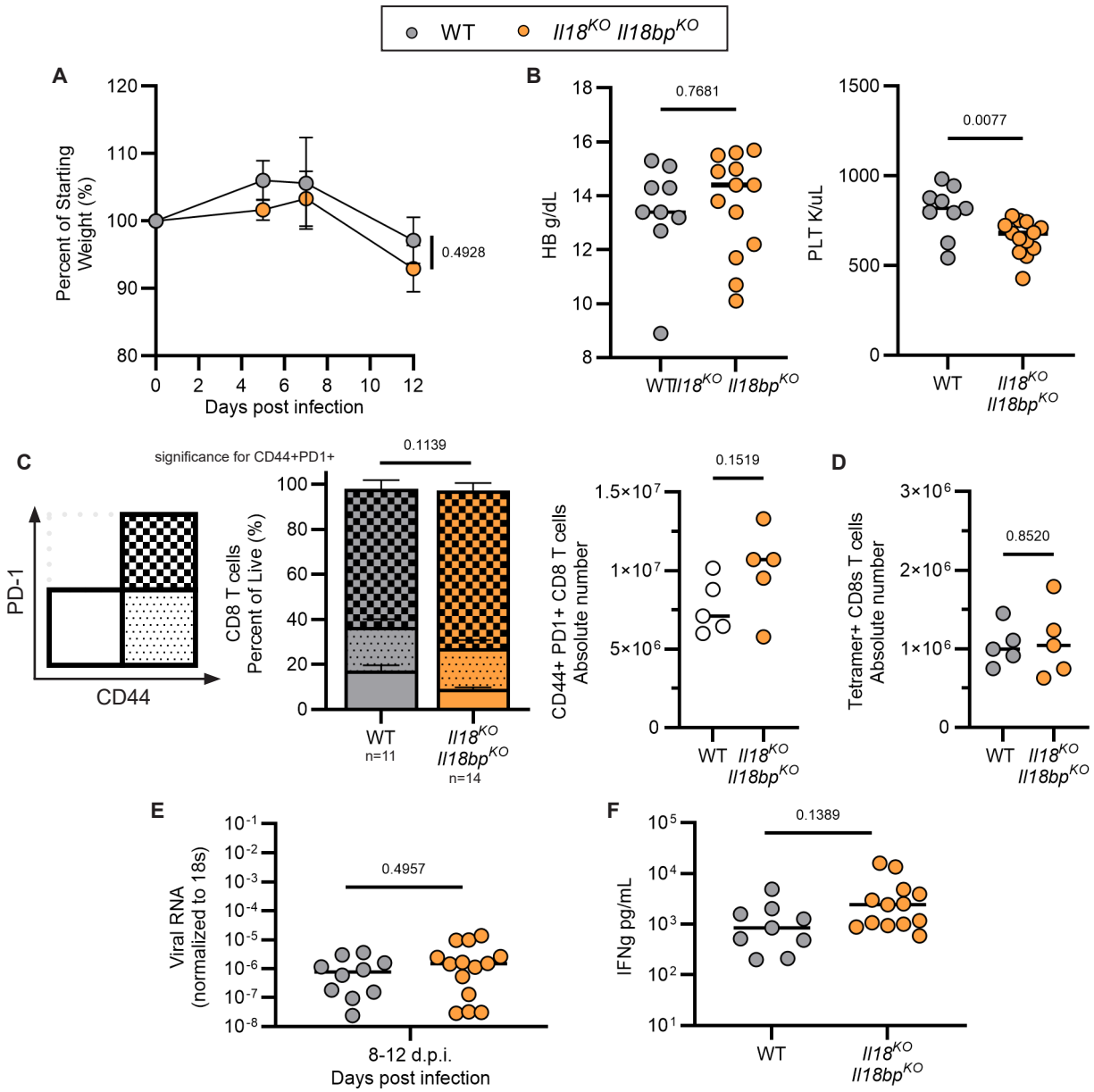
Supplemental Figure 4. NK and other immune cell composition in spleens of *Il18*^{tg} mice, Day 5 of ECTV infection. Companion to Figure 3A. Composition of NK cells compared to other cells. NK cell data is same as in Figure 3A. Significance: 2-way ANOVA (inset box) of only NK cell numbers with Šídák's multiple comparisons test (line with p-value) of genotypes within timepoints (B). "ns" = adjusted p-value < 0.05.



Supplemental Figure 5. Mousepox viral RNA correlates with Plaque-Forming Units (PFU). Viral RNA was measured via qPCR of the ECTV TNF binding protein I1R (*Evm003)* gene and normalized to 18s endogenous mouse RNA. PFU determined via plaque assay of spleen from day 5, 8 and 12. R^2 value established by simple linear regression.



Supplemental Figure 6. Trichrome staining reveals extensive necrosis in *Il18bp*^{KO} livers. Companion to Figure 5. Representative photomicrographs of liver sections after trichrome staining from mice 8 days post infection. "N" denotes sites of necrosis.



Supplemental Figure 7. Susceptibility of *Il18bp^{KO}* mice to fulminant ECTV-HLH requires IL-18. WT and *Il18^{KO}Il18bp^{KO}* mice were infected with mousepox (ECTV) and assessed for weight loss (**A**, n=4-5). (**B**) Endpoint (Day 8-12) hemoglobin (HB) and platelet count (PLT). (**C**) CD8 T-cell activation as proportion of all CD8 T cells and absolute number of cells/spleen. (**D**) ECTV-peptide B8R-specific (Tetramer+) CD8 T cells. Mousepox viral RNA from spleen (**E**), and plasma IFNg (**F**) from 8-12 d.p.i. Significance: Mixed Effects Model comparing genotypes (A) and unpaired t-test (B-F). In (C), comparison was restricted to PD-1+ CD44+ CD8 T cells. Data representative of 2 independent experiments (A-B), combined from 2 independent experiments (C-F). "ns" = adjusted p-value < 0.05.