Supplementary Information

The lipid-sensor TREM2 aggravates disease in a model of LCMV-induced hepatitis

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Fig. S1 Serum lipid changes on day 2 and Ppar-δ reporter assay. (**A**) Serum from WT mice infected with LCMV strain WE two days previously was used for targeted metabolomics (n=4 mice per group). Bubble plot of individual glycerophospholipids (circles) and sphingolipids (triangles) depicting fold-change (x-axis), p-value (y-axis) and the absolute change (size of symbols). Red symbols reflect metabolites with a fold-change >1.5 and a p-value <0.05. (**B-C**) Ppar-δ reporter assay results from WT and *Trem2*$^{-/-}$ mouse embryonic fibroblasts stimulated with serum-extracted lipids (**B**, n=3-4) or pure lipids (**C**, n=4) as described in Methods. Statistical significance was calculated by unpaired t-test. Bars represent the mean ± SEM.

Fig. S2 Similar kidney-specific serum parameters in WT and *Trem2*$^{-/-}$ mice. (**A-B**) WT and *Trem2*$^{-/-}$ mice were infected with LCMV strain WE. Serum levels of blood urea nitrogen (BUN) (**A**) and creatinine (**B**) were measured eight and ten days post infection (n=5 mice per group, representative of two independent experiments). Statistical significance was calculated by Two-way ANOVA with Bonferroni correction. Bars represent the mean ± SEM.

Fig. S3 Similar viral propagation in primary WT and *Trem2*$^{-/-}$ macrophages. BMDMs from WT and *Trem2*$^{-/-}$ mice were isolated *ex vivo* and left uninfected or infected with LCMV strain WE

(MOI 0.01). Viral loads from cell culture supernatants were quantified by immunological focus assay (n=3 mice per group, representative of two independent (similar) experiments). Symbols represent the mean ± SEM.

Fig. S4 $CD8^+$ and $CD4^+$ effector memory T cell responses and FACS gating strategy for intracellular cytokine staining. WT and *Trem2*$^{-/-}$ mice were infected with LCMV strain WE **(A-F)**. $CD44^{hi}$ $CD62^{lo}$ $CD8^+$ effector memory T cells were quantified in liver and spleen **(A-B)** before, four and eight days post infection (n=4 mice per genotype). $CD44^{hi}$ $CD62^{lo}$ $CD4^+$ effector memory T cells were quantified in liver and spleen **(C-D)** before, four and eight days post infection (n=4 mice per group). Statistical significance was calculated by Two-way ANOVA. Bars represent the mean ± SEM. **(E-F)** FACS gating strategy for data shown in Fig. 4.

Fig. S5 Concanavalin A induced acute hepatitis in WT and *Trem2*$^{-/-}$ mice. (**A**) WT and *Trem2*$^{-/-}$ mice received either PBS or 10 mg/kg concanavalin A i.p. **(A-B).** Serum kinetics of ALT (A) and AST (B) were measured 24 hours post treatment (n=6 infected mice and one untreated mouse per genotype). Statistical significance was calculated by unpaired t test. Bars represent the mean ± SEM.

Fig. S6 Profiling of lymphocyte populations in LCMV-infected WT and *Trem2*$^{-/-}$ mice. WT and *Trem2*$^{-/-}$ mice were infected with LCMV strain WE **(A-F)**. γ/δ T cell ($CD19^-$ $CD3^+$ $TCR\gamma/\delta^+$), NK cells ($CD19^-$ $CD3^-$ $NK1.1^+$), NKT cells ($CD19^-$ $CD3^+$ $NK1.1^+$), neutrophils ($CD19^-$ $Ly6G^+$) and macrophages ($CD19^-$ $CD11c^-$ $F4/80^+$) were quantified in liver and spleen before, four and eight days post infection (n=4 mice per group). Statistical significance was calculated by Two-way ANOVA. Bars represent the mean ± SEM.

Fig. S7 Serum cytokine responses in LCMV-infected WT and *Trem2*$^{-/-}$ mice. WT and *Trem2*$^{-/-}$ mice were infected with LCMV WE, and serum was collected at various time points post infection **(A-C)**. Serum kinetics of **(A)** IFNα (12-15 infected and 3 uninfected mice per genotype pooled from three independent experiments), **(B)** interleukin-6 (8-9 mice per genotype pooled from two independent experiments), and **(C)** CXCL1 (4-9 mice per genotype pooled from two independent experiments). Statistical significance was calculated by Two-way ANOVA with Bonferroni correction. Symbols respectively bars represent the mean ± SEM.

Fig. S8 Confirmation of bone marrow reconstitution. Reconstitution of relevant cell types was confirmed by FACS analysis of WT mice that were reconstituted with bone marrow of *CD45.1* mice. Bars represent the mean of 2 mice (**A**). FACS gating strategy (**B**).

Fig. S9 *Trem2* expression in primary macrophages and hepatocytes. (**A**) Bone marrow-derived macrophages and (**B**) primary mouse hepatocytes were seeded at $1x10^6$ cells per well and infected with LCMV at an MOI of 0.01. Expression of *Trem2* and *GAPDH* was analyzed by real-time PCR at the respective time points and normalized to *Eef1a*. Symbols represent the mean ± SEM.

Table S1 Quantification of serum metabolites

Figure S1: Serum lipid changes on day 2 and Ppar-δ reporter assay

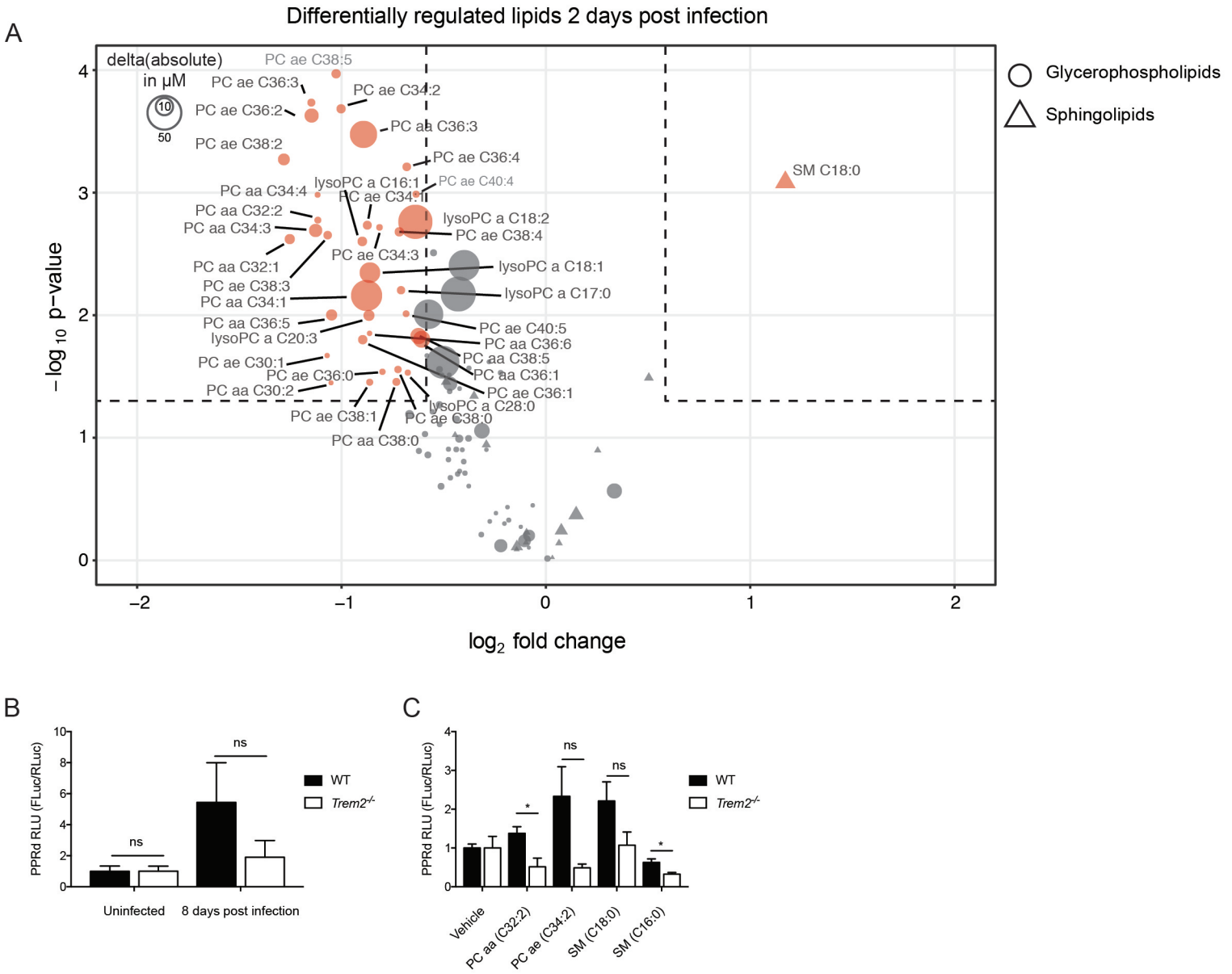


Figure S2: Similar kidney-specific serum parameters in WT and *Trem2*$^{-/-}$ mice

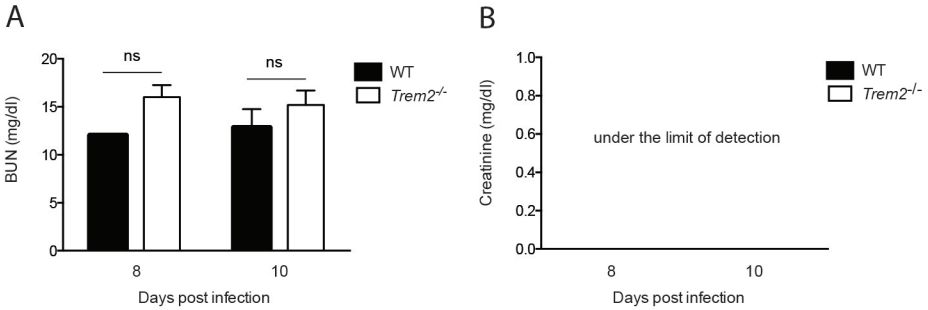


Figure S3: Similar viral propagation in primary WT and *Trem2*$^{-/-}$ macrophages

A

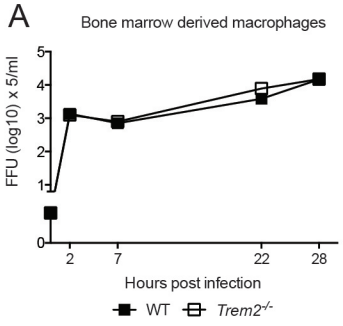


Figure S4: Effector memory T cell responses and FACS gating strategy for intracellular cytokine staining

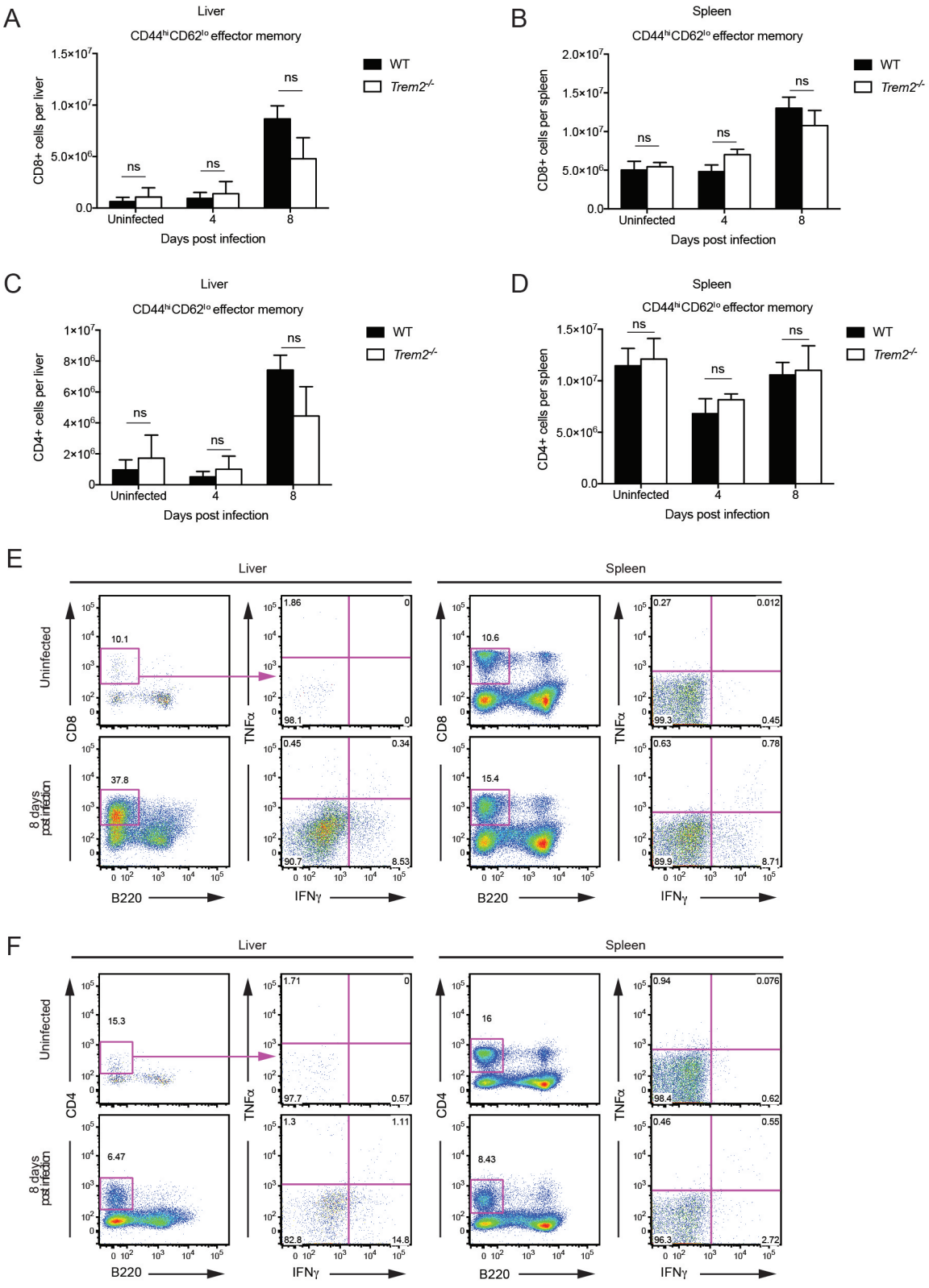


Figure S5: Concanavalin A induced acute hepatitis in WT and *Trem2*$^{-/-}$ mice

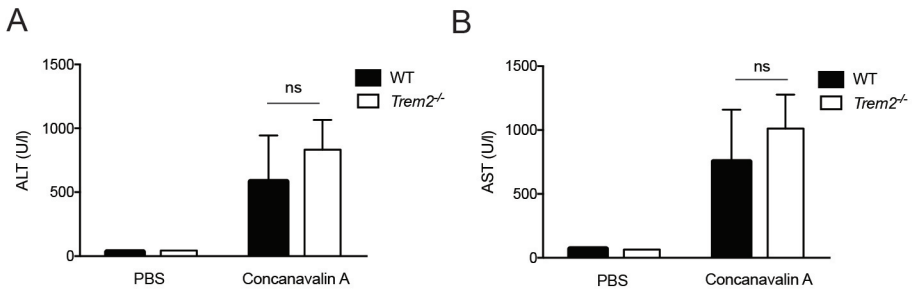


Figure S6: Profiling of lymphocyte populations in LCMV-infected WT and *Trem2*$^{-/-}$ mice

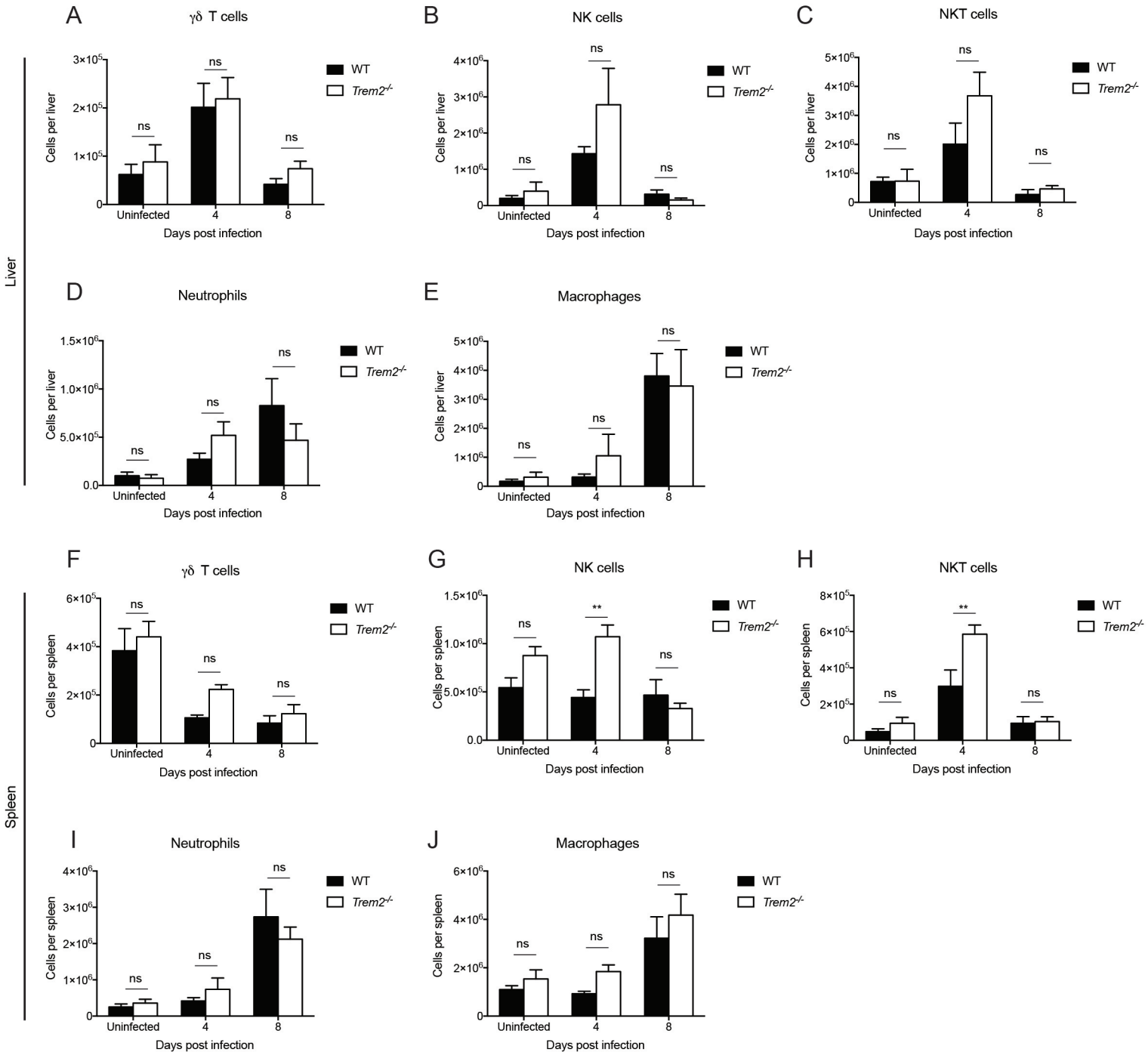


Figure S7: Serum cytokine responses in LCMV-infected WT and *Trem2*$^{-/-}$ mice

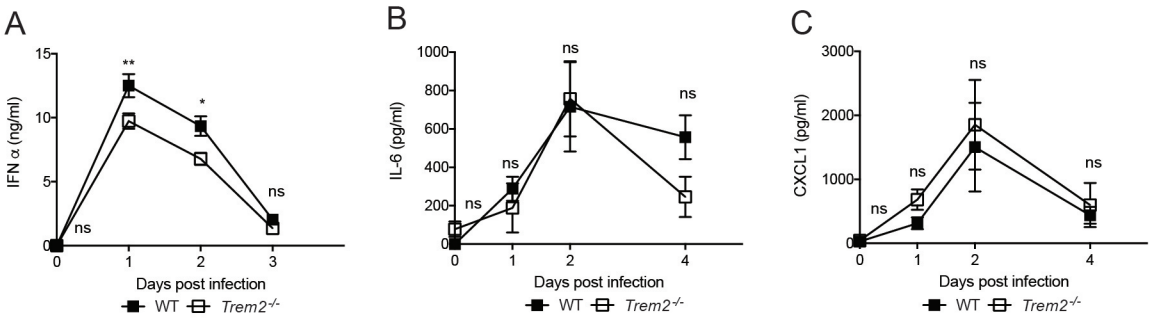
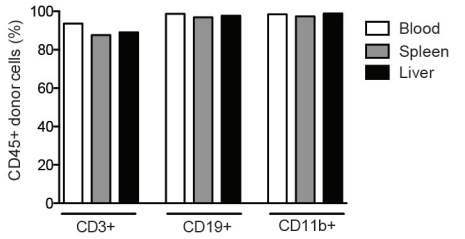


Figure S8: Confirmation of bone marrow reconstitution

A



B

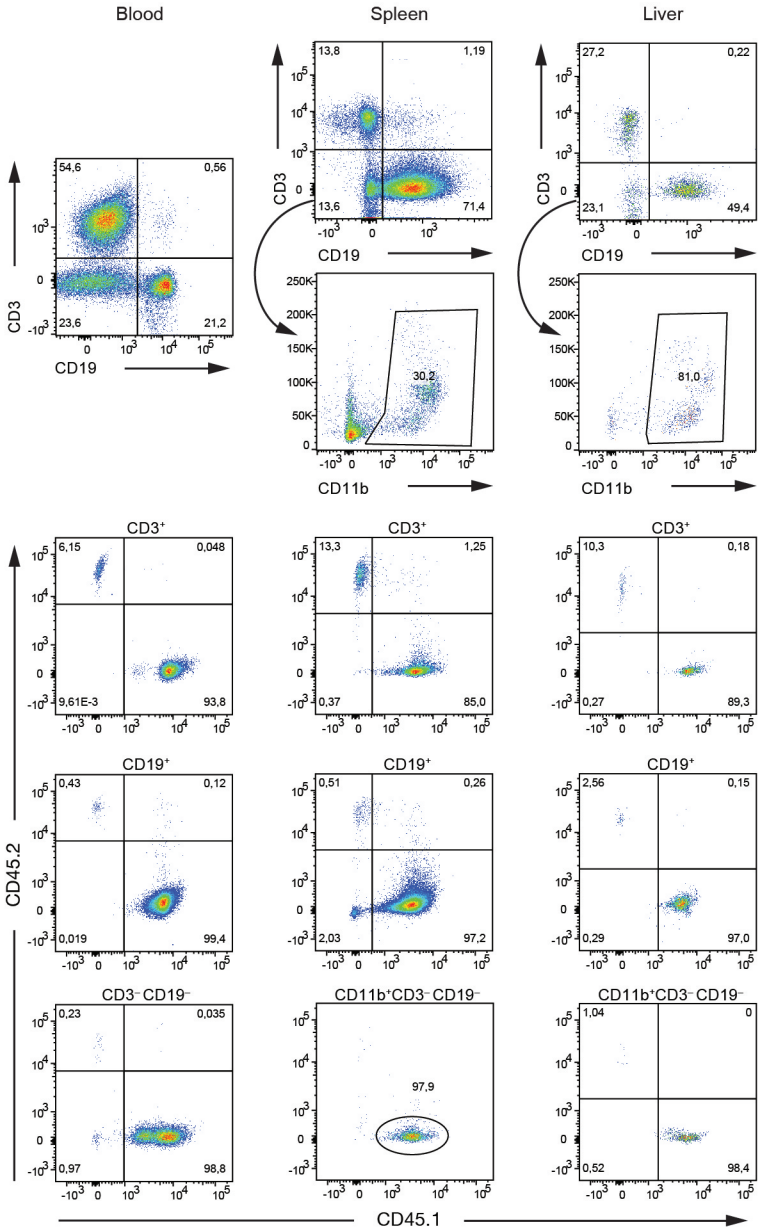


Figure S9: *Trem2* expression in primary mouse hepatocytes