**Supplemental Figures:**

Fig. S1. The SHP2 inhibitor 11a-1 is specific and reversible.

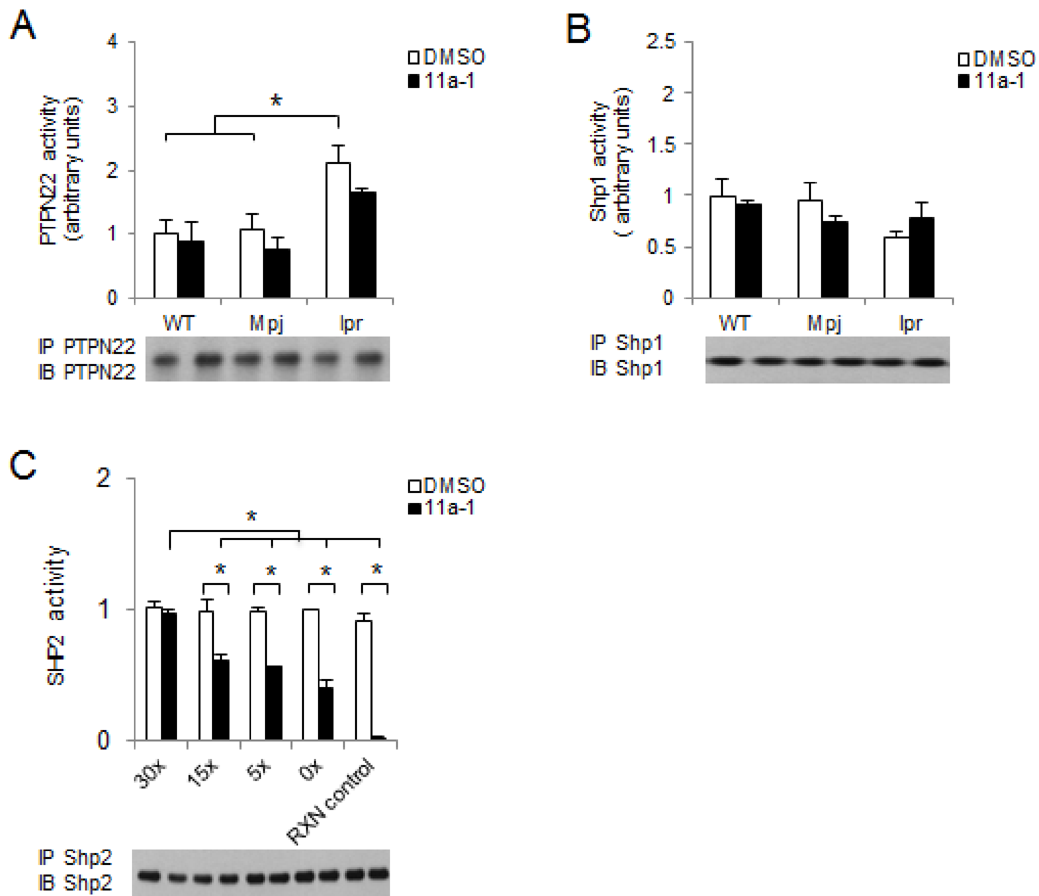
Fig. S2. Inhibition of SHP2 activity significantly improves kidney pathology in MRL/*lpr* mice.

Fig. S3. The SHP2 inhibitor specifically reduces the number of circulating DN T cells, but has no effect on red blood cells, platelets, monocytes, neutrophils, eosinophils, or basophils in MRL/*lpr* mice.

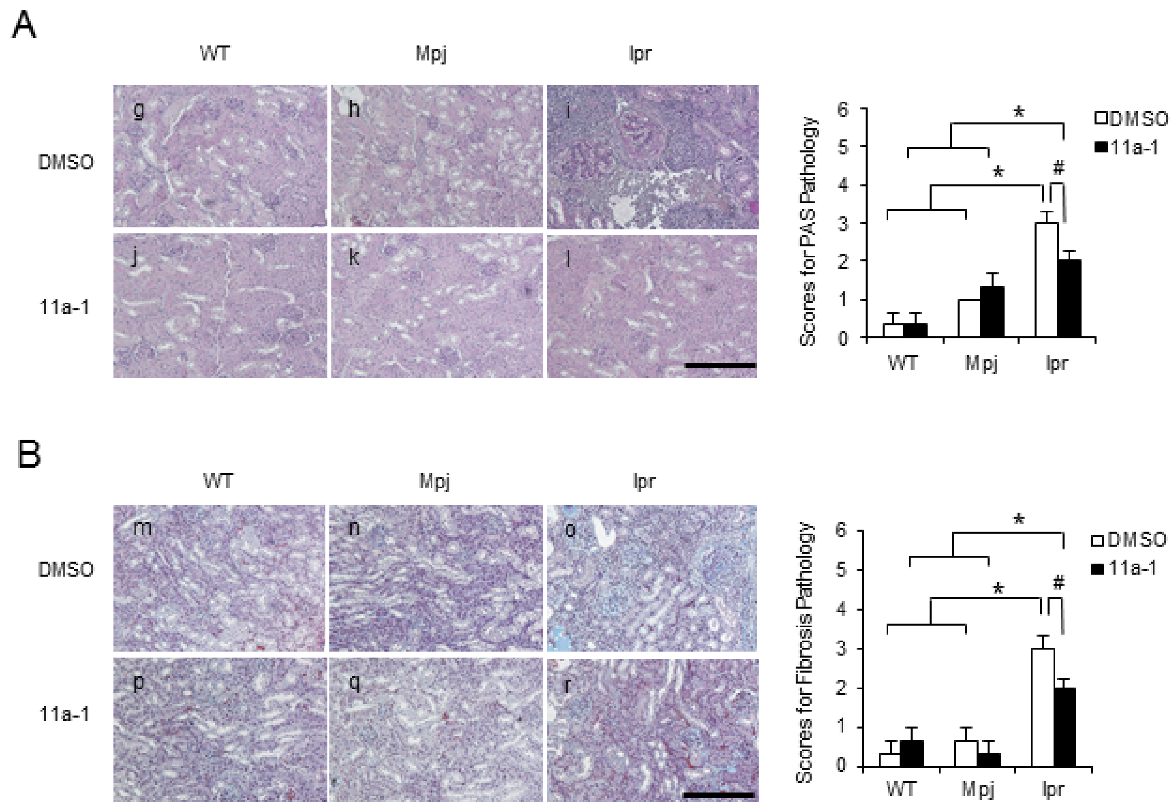
Fig. S4. SHP2 activity does not affect regulatory T cells in MRL/*lpr* spleens.

Fig.S5. The SHP2 inhibitor reduces inflammatory cell infiltration in MRL/*lpr* kidneys.

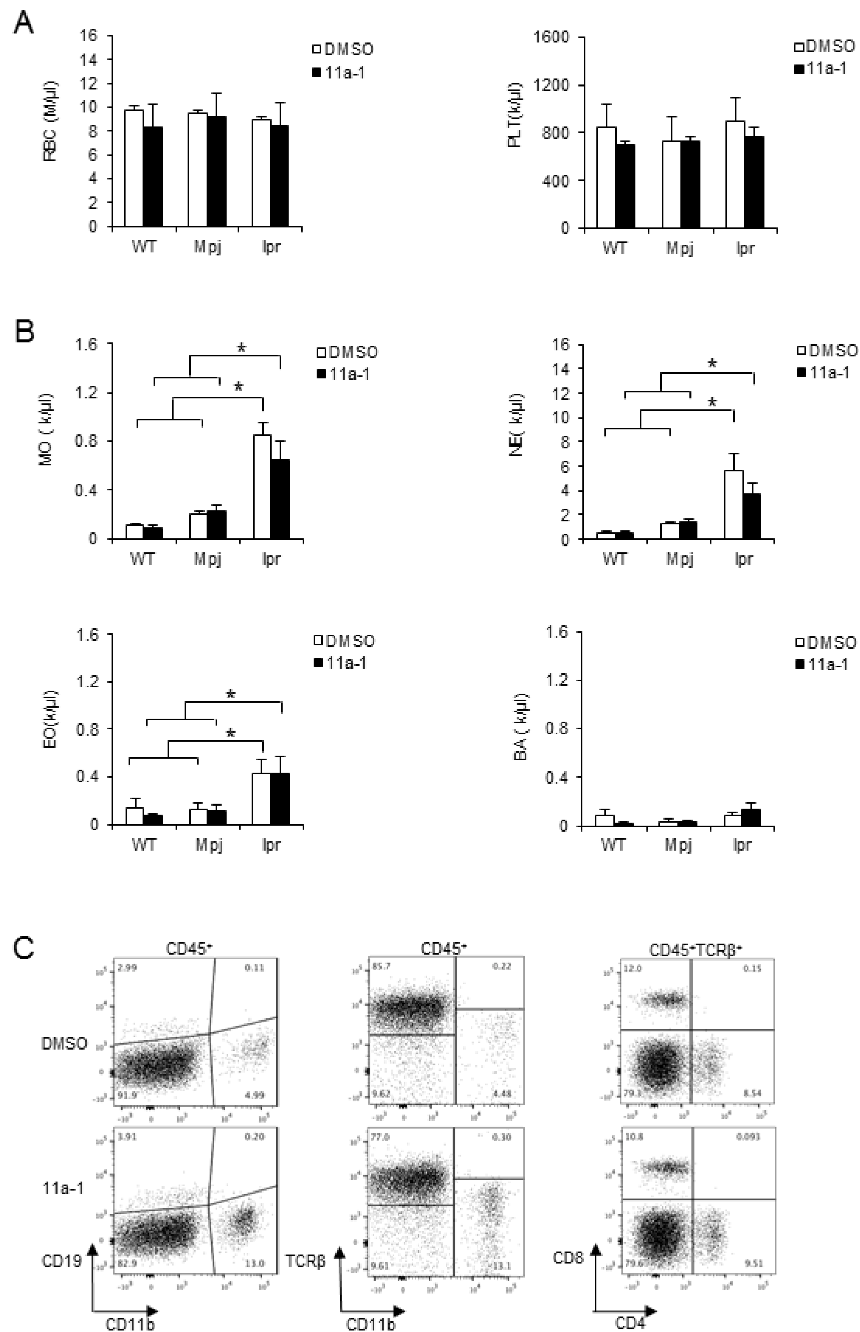
Fig. S6. The SHP2 inhibitor does not reduce IL-6, TNFα or IL-17A/A cytokine levels in MRL/*lpr* mice.



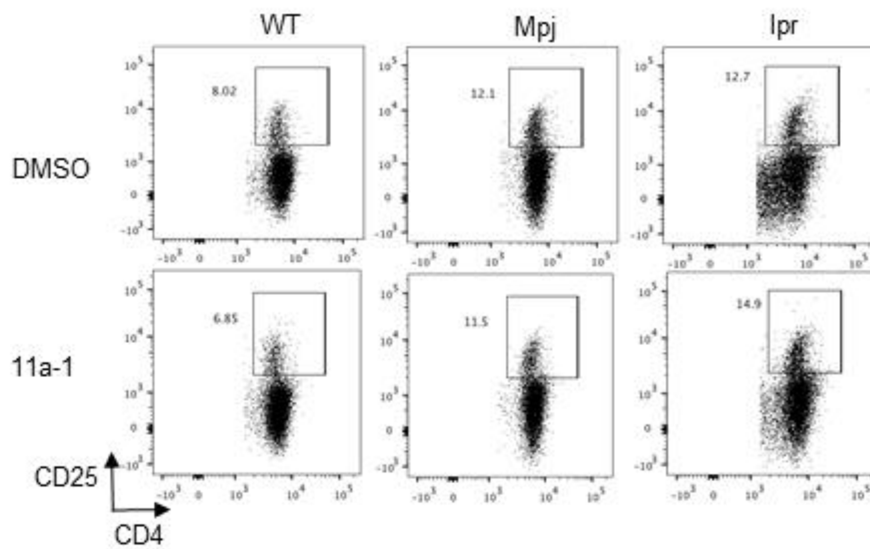

*Supplemental Figure 1.* **The SHP2 inhibitor 11a-1 is specific and reversible**. **A.** PTPN22 and **B.** SHP1 immune complex PTP assays were conducted using pNPP as a substrate on splenic lysates generated from 18 week-old WT, Mpj, and *lpr* female mice that were vehicle- or 11a-1-treated (7.5mg/kg/day) for 6 weeks, starting at 12 weeks of age. Immunoblot controls of immunoprecipitated PTPN22 or SHP1, showing comparable recovery respectively, are also shown. N=3-8 mice/group. **C.** SHP2 immune complexes from *lpr* splenic lysates were incubated *in vitro* with either 11a-1 (10µg/ml) or vehicle (DMSO) for 5 hours at $4^{o}$C, and then washed for the indicated number of times, to determine reversibility of the inhibitor. Immunoblot controls of immunoprecipitated SHP2 show comparable recovery. As a positive control for the reaction, SHP2 immune complexes were incubated directly with pNPP in reaction buffer. N=3 separate experiments; *p<0.05. P values were derived from one-way or two-way ANVOA with Holm-Sidak post-test when ANOVA was significant.



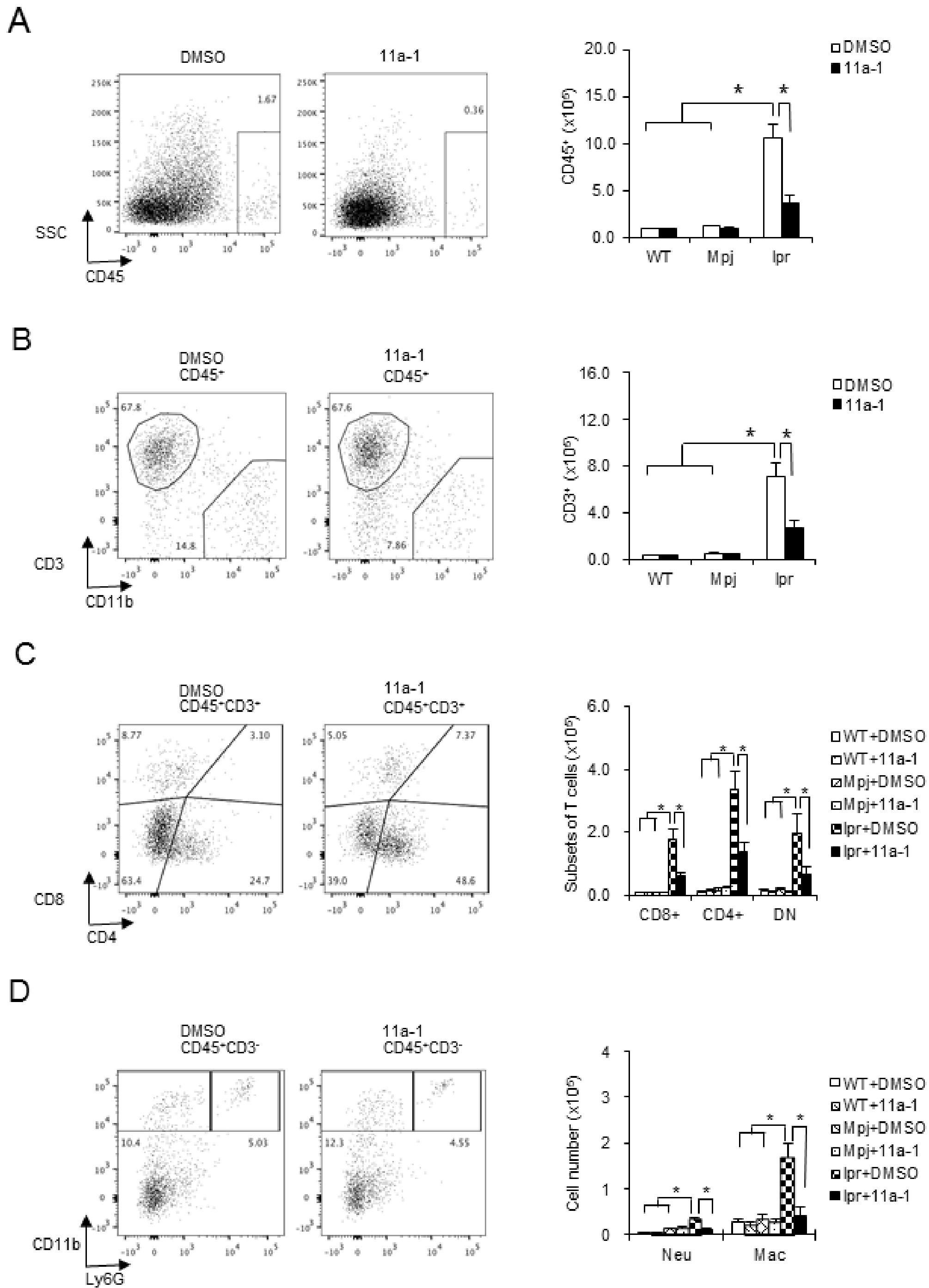

*Supplemental Figure 2.* **Inhibition of SHP2 activity significantly improves kidney pathology in MRL/*lpr* mice**. Representative **A.** PAS and **B.** Masson-trichrome-staining of kidney sections from 18 week-old WT, Mpj and *lpr* female mice treated for 6 weeks with vehicle or 11a-1 (7.5 mg/kg/day), with respective quantification of pathology scores indicated. *, p<0.01; #, p<0.05, where p values were derived from two-way ANOVA with Holm-Sidak post-test when ANOVA was significant. Scale bars: 500µm.



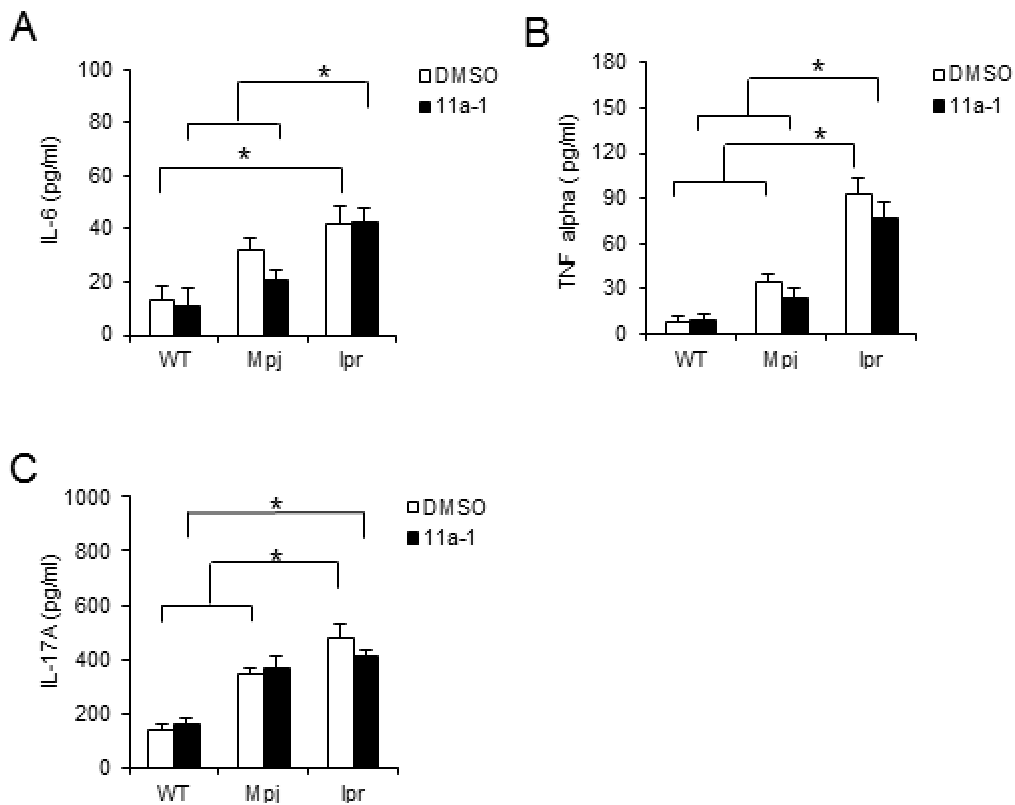

*Supplemental Figure 3.* **The SHP2 inhibitor specifically reduces the number of circulating DN T cells, but has no effect on red blood cells, platelets, monocytes, neutrophils, eosinophils, or basophils in MRL/*lpr* mice**. Total numbers of circulating **A.** red blood cells (RBCs), platelets and **B.** monocytes, neutrophils, eosinophils, and basophils in peripheral blood isolated from 18 week-old WT, Mpj and *lpr* female mice treated for 6 weeks with vehicle or SHP2 inhibitor (7.5 mg/kg/day). N=7-8 mice/group; **C.** Representative flow cytometry of B cells, T cells and the subset of T cells in peripheral blood collected from MRL/*lpr* mice treated for 6 weeks with vehicle or SHP2 inhibitor. N=4 mice/group. *p<0.05, where p value are derived from two-way ANOVA with Holm-Sidak post-test when ANOVA was significant.




*Supplemental Figure 4.* **SHP2 activity does not affect regulatory T cells in MRL/*lpr* spleens.** Total splenocytes were isolated from 18 week-old WT, Mpj and *lpr* female mice treated for 6 weeks with vehicle or 11a-1 (7.5 mg/kg/day) and assayed by flow cytometry for T regulatory cells ($CD4^+CD25^+$), gated at $CD3^+$.




*Supplemental Figure 5.* **The SHP2 inhibitor reduces inflammatory cell infiltration in MRL/*lpr* kidneys**. Kidney cells isolated from 18 week-old WT, MPJ and *lpr* female mice treated for 6 weeks with vehicle or 11a-1 (7.5 mg/kg/day) were assayed by flow cytometry for **A.** leukocytes ($CD45^+$), **B.** T cells ($CD3^+$) , gated at $CD45^+$, **C.** the subset of T cells: $CD4^+$, $CD8^+$ and $CD4^-CD8^-$, gated at $CD45^+CD3^+$, and **D.** macrophages and neutrophils ($CD11b^+Ly6G^-$, $CD11b^+Ly6G^+$), gated at $CD45^+CD3^-$.




*Supplemental Figure 6.* **The SHP2 inhibitor does not reduce IL-6, TNFα or IL-17A/A cytokine levels in MRL/*lpr* mice.** Circulating levels of **A.** Interleukin-6 (IL-6), **B.** Tumor necrosis factor alpha (TNFα), or **C.** Interleukin 17A homodimer (IL-17A/A) were measured in serum collected from 18 week-old WT, Mpj and *lpr* female mice treated for 6 weeks with vehicle or 11a-1 (7.5 mg/kg/day). N=7-8 mice/group; *p<0.05, where p values were derived from two-way ANOVA with Holm-Sidak post-test when ANOVA was significant.