Supplemental Figures:

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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.

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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°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 ANOVA 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.