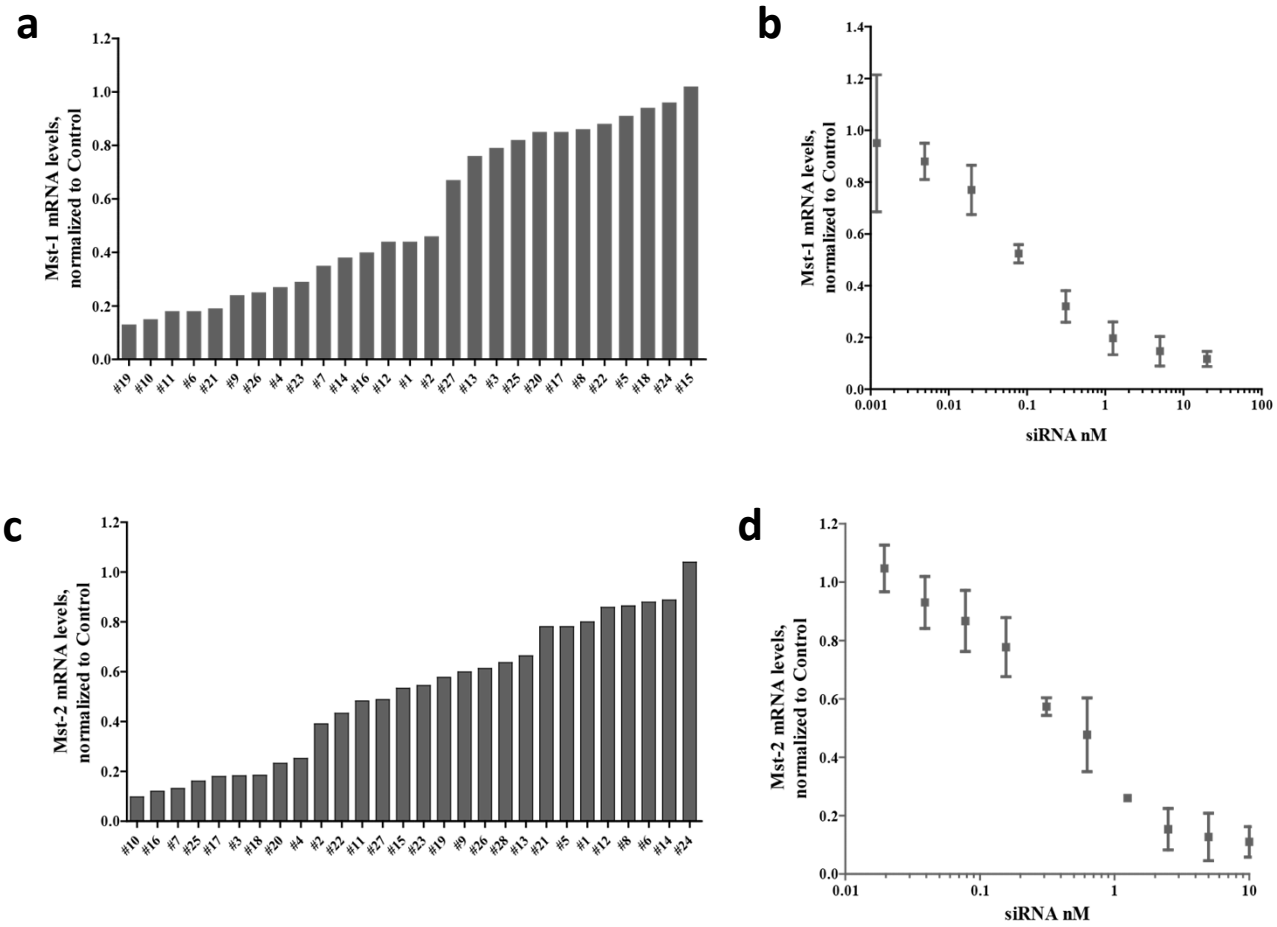
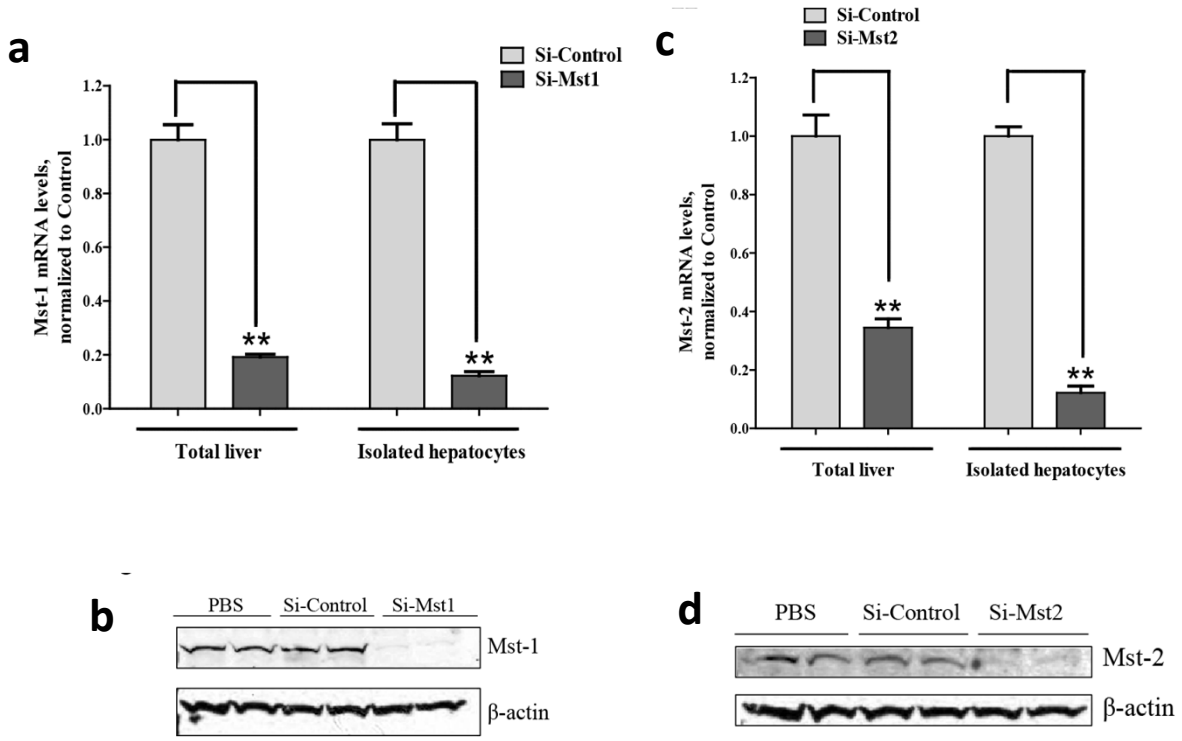
Fig 1S



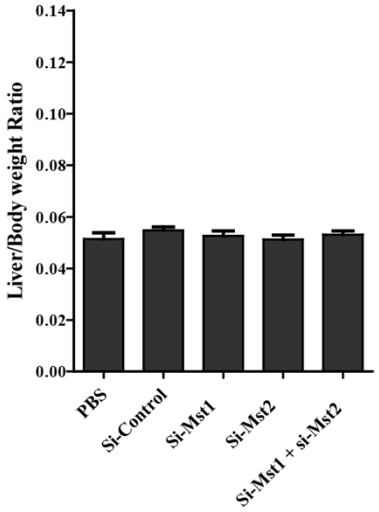
Supplementary Figure 1. Screening of siRNAs against Mst-1 and Mst-2. The mRNA levels were analyzed 16-18 hours post transfection of siRNA in NIH3T3 cells. a, mRNA down-regulation by 5nM of specific siRNA against Mst-1. b, Dose-dependence of Mst-1 mRNA down-regulation by #19 siRNA from (a). c, mRNA down-regulation by 5nM of specific siRNA against Mst-2 in NIH3T3 cells. d, Dose-dependence of Mst-2 mRNA down-regulation by #10 siRNA from (c).

Fig. 2S



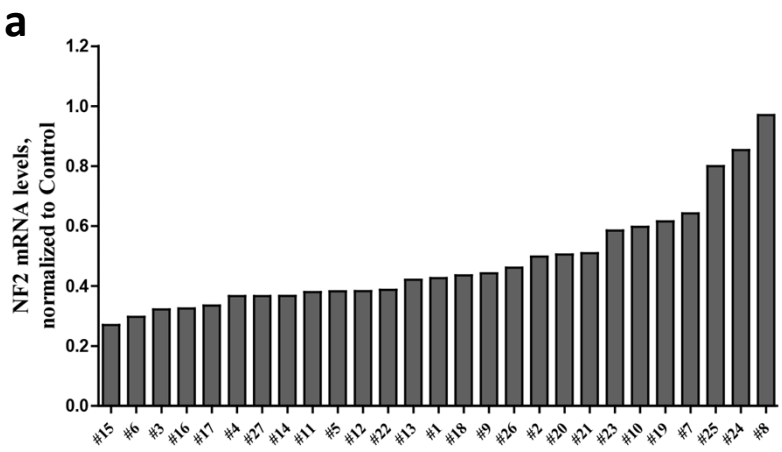
Supplementary Figure 2. Validation of *in vivo* knock-down of Mst-1 or Mst-2, a, C57BL/6 mice were treated with 0.5mg/kg si-Mst1 or dose matched si-control. Two days after injection, livers were perfused and digested, and then hepatocytes separated. The mRNA levels of Mst-1 in total liver and hepatocytes were analyzed. **, $p<0.01$. ($N\geq3$). b, Protein lysate was made and western blot was performed to detect Mst-1. c, C57BL/6 female mice were treated with 0.5mg/kg si-Mst2 or dose matched si-control. Two days after injection, livers were perfused and digested, and then hepatocytes separated. The mRNA levels of Mst-2 in total liver and hepatocytes were analyzed. **, $p<0.01$. ($N\geq3$). d, Liver lysate was made and western blot was performed to detect Mst-2.

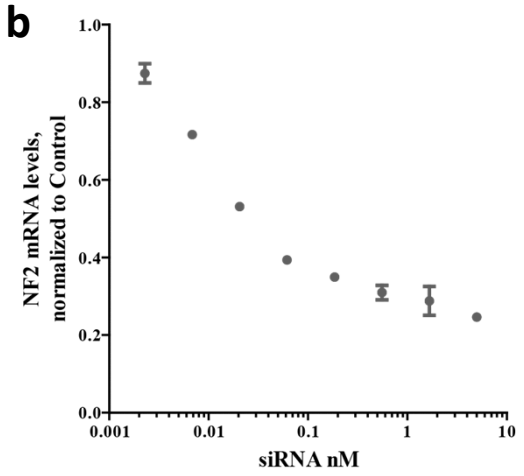
Fig 3S



Supplementary Fig. 3. Double Knockdown of Mst1 and Mst2 is not efficient to induce liver growth. C57BL/6 mice were treated with si-Mst1, si-Mst2, combination of si-Mst1 and si-Mst2, dose matched si-Control or PBS. Livers were taken 16 days after treatment, and weight of liver was recorded.

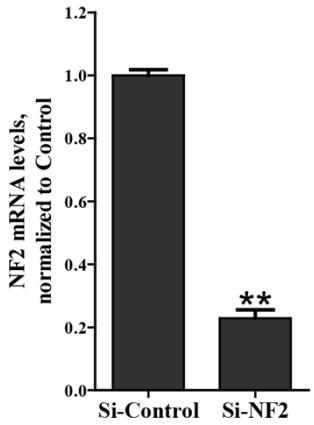
Fig 4S





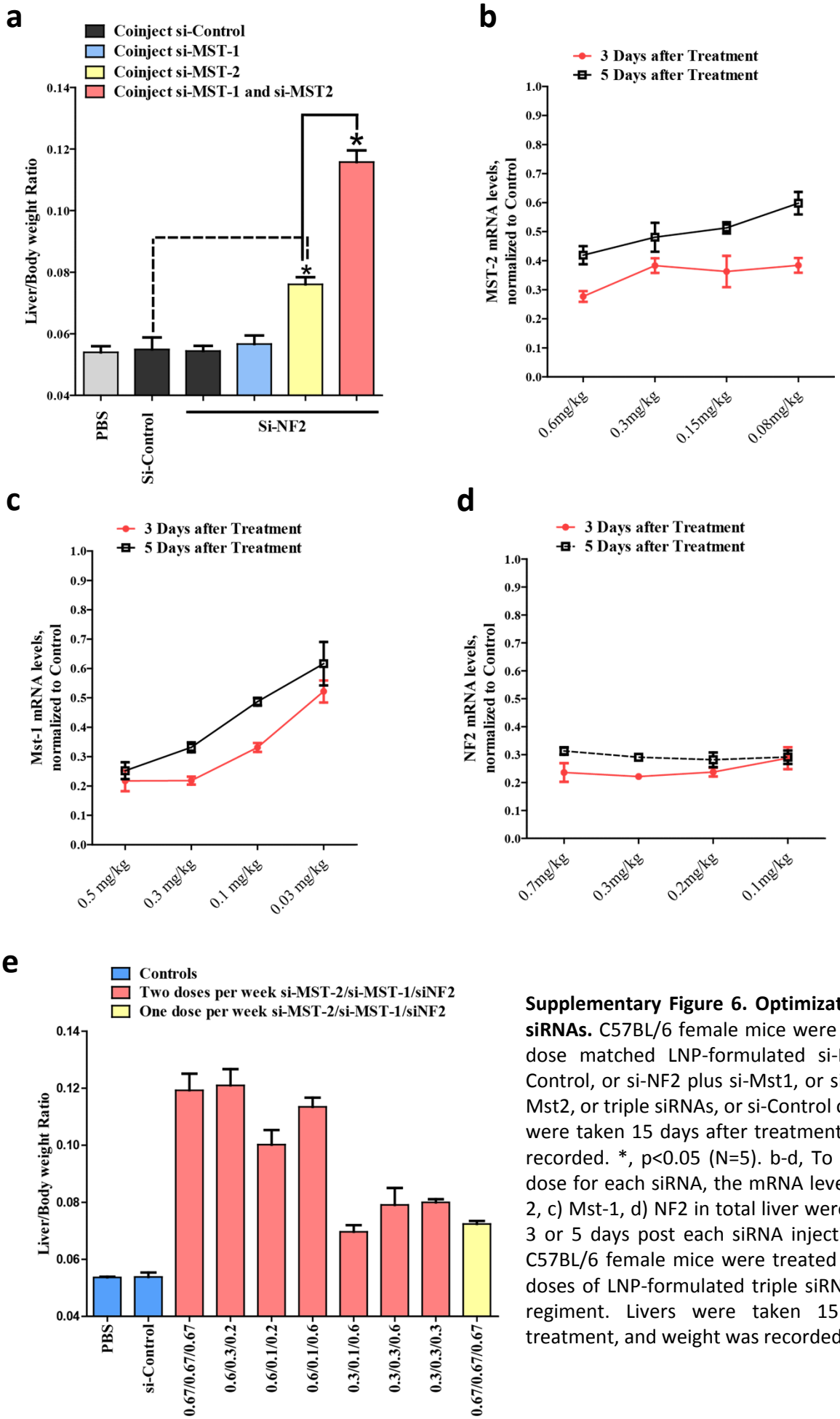
Supplementary Figure 4. Screening of siRNAs against NF2. The mRNA levels were analyzed 16-18 hours post transfection of siRNA in NIH3T3 cells. a, mRNA down-regulation by 5nM of specific siRNA against NF2. b, Dose-dependence of NF2 mRNA down-regulation by #15 siRNA from (a).

Fig 5S



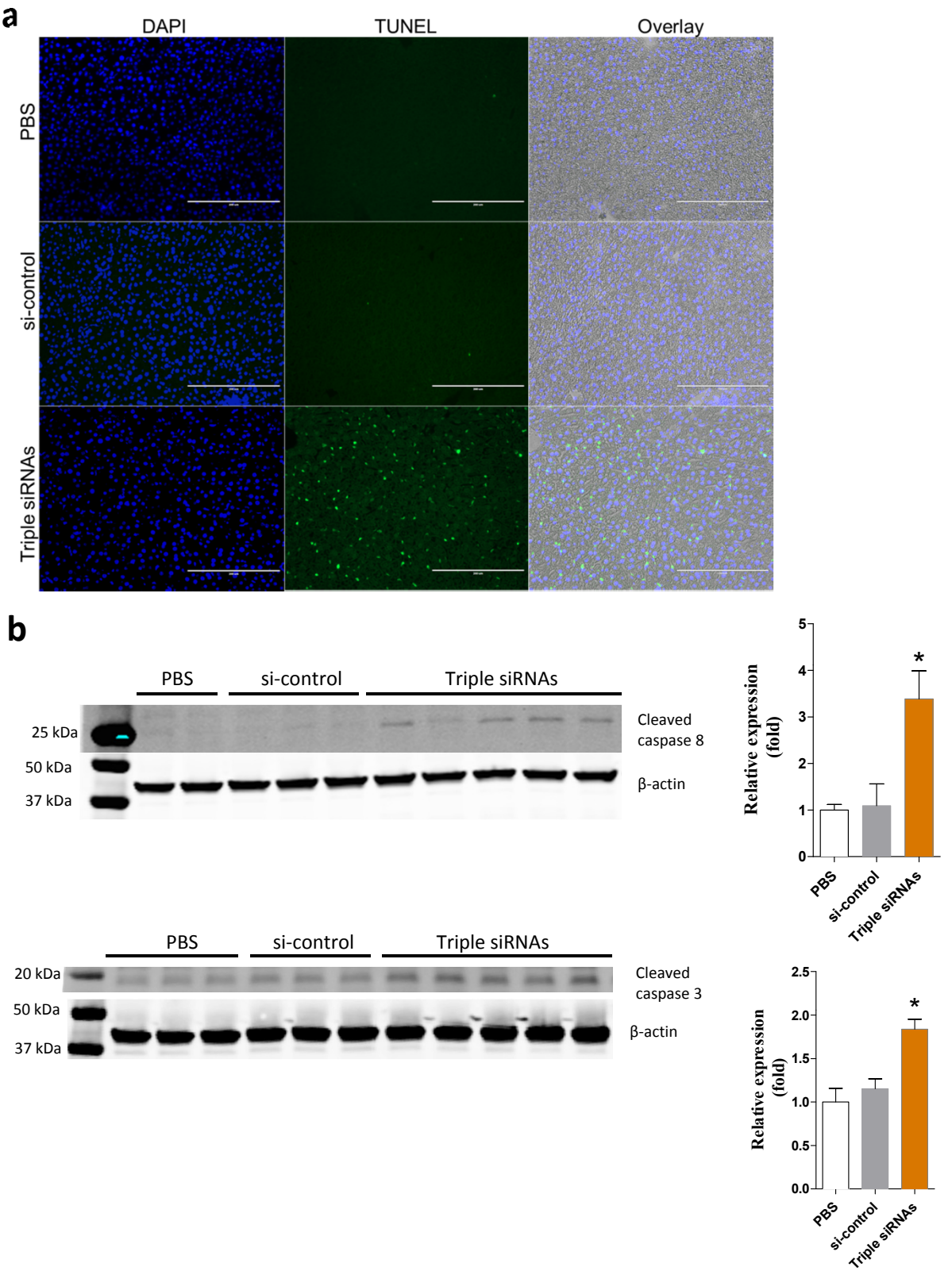
Supplementary Figure 5. Validation of NF2 knockdown *in vivo*. C57BL/6 mice were treated with LNP-formulated si-NF2 (0.5mg/kg) or dose matched si-Control. Two days after injection, the mRNA levels of NF2 in total liver were analyzed. **, $p<0.01$. (N=3).

Fig 6S



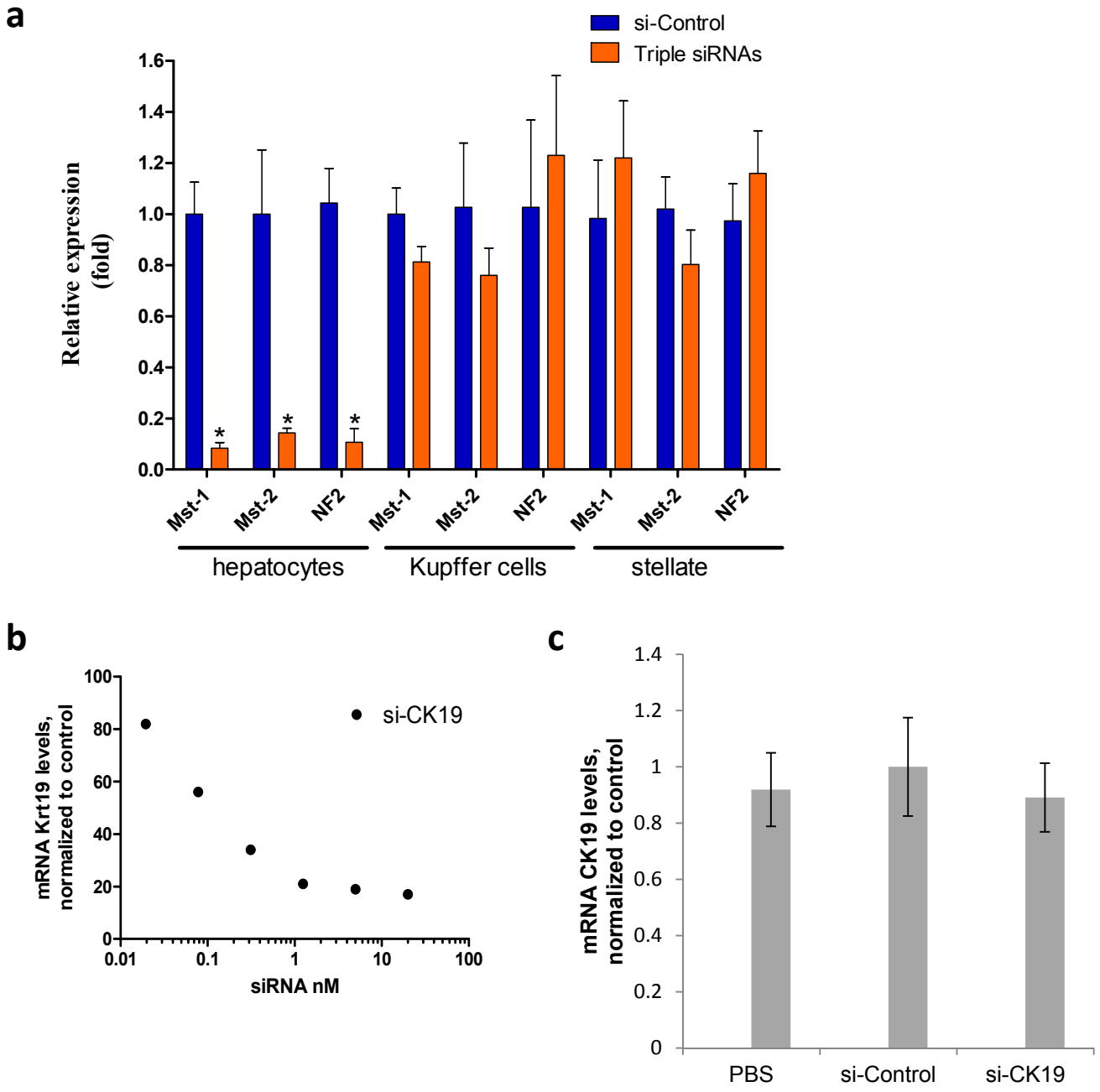
Supplementary Figure 6. Optimization of triple siRNAs. C57BL/6 female mice were treated with dose matched LNP-formulated si-NF2 plus si-Control, or si-NF2 plus si-Mst1, or si-NF2 plus si-Mst2, or triple siRNAs, or si-Control or PBS. Livers were taken 15 days after treatment, and weight recorded. *, $p<0.05$ (N=5). b-d, To optimize the dose for each siRNA, the mRNA levels of b) Mst-2, c) Mst-1, d) NF2 in total liver were analyzed in 3 or 5 days post each siRNA injection. (N=3) e, C57BL/6 female mice were treated with various doses of LNP-formulated triple siRNAs and dose regiment. Livers were taken 15 days after treatment, and weight was recorded (N=3).

Fig 7S



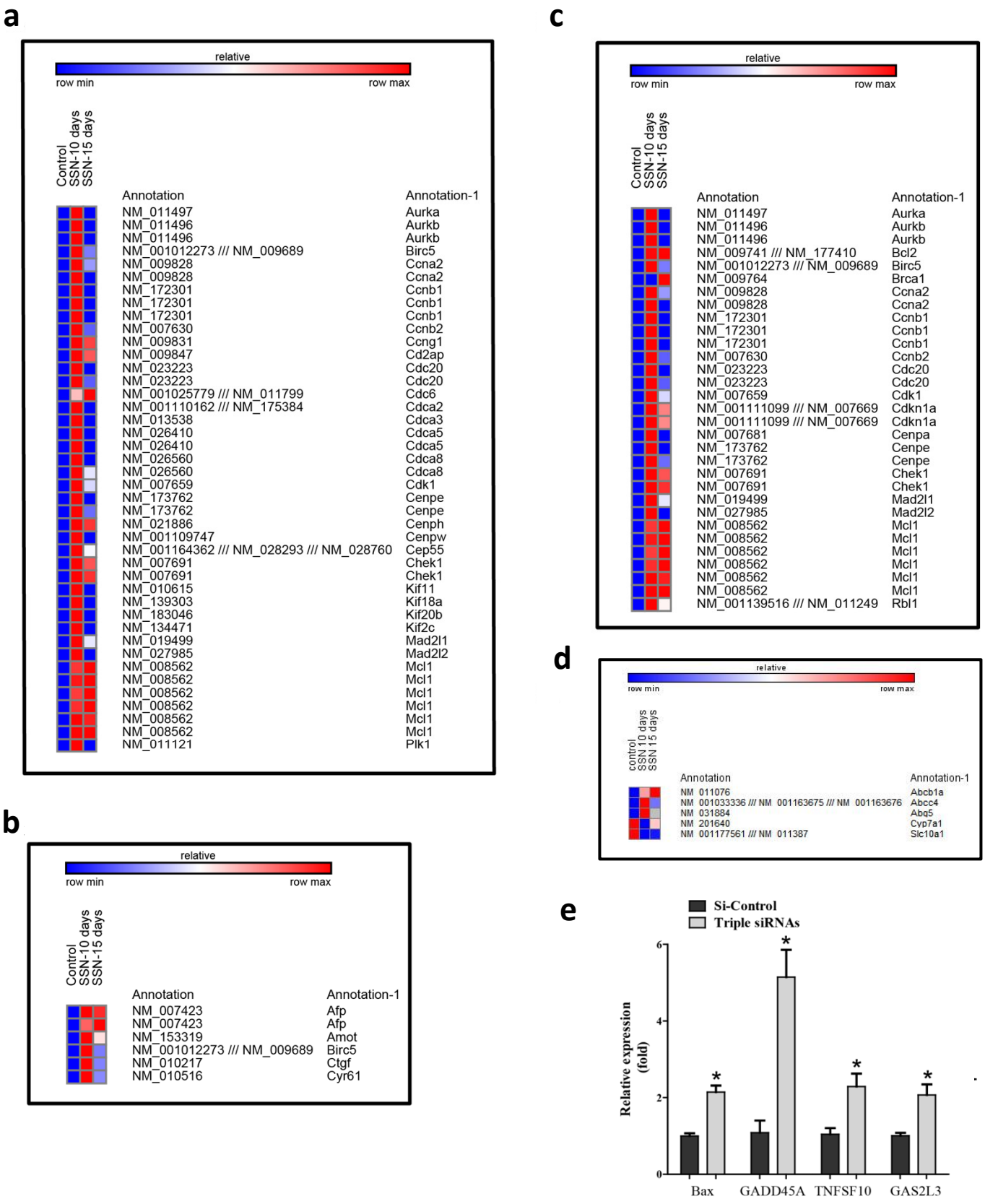
Supplementary Figure 7. Detection of apoptosis after the withdrawal of triple siRNAs treatment. C57BL/6 female mice were treated with PBS, or LNP-formulated si-control, or triple siRNAs. Livers were taken at 12 days after the last dose of siRNAs. a, Liver sections were stained for TUNEL and counterstained with DAPI , scale bars = 100μm. b, Liver lysate was made and western blot performed to detect cleaved Caspase 3 and 8. Band intensity was measured using ImageJ and compared to PBS as control group. n=3 or 5, *p<0.05.

Fig 8S



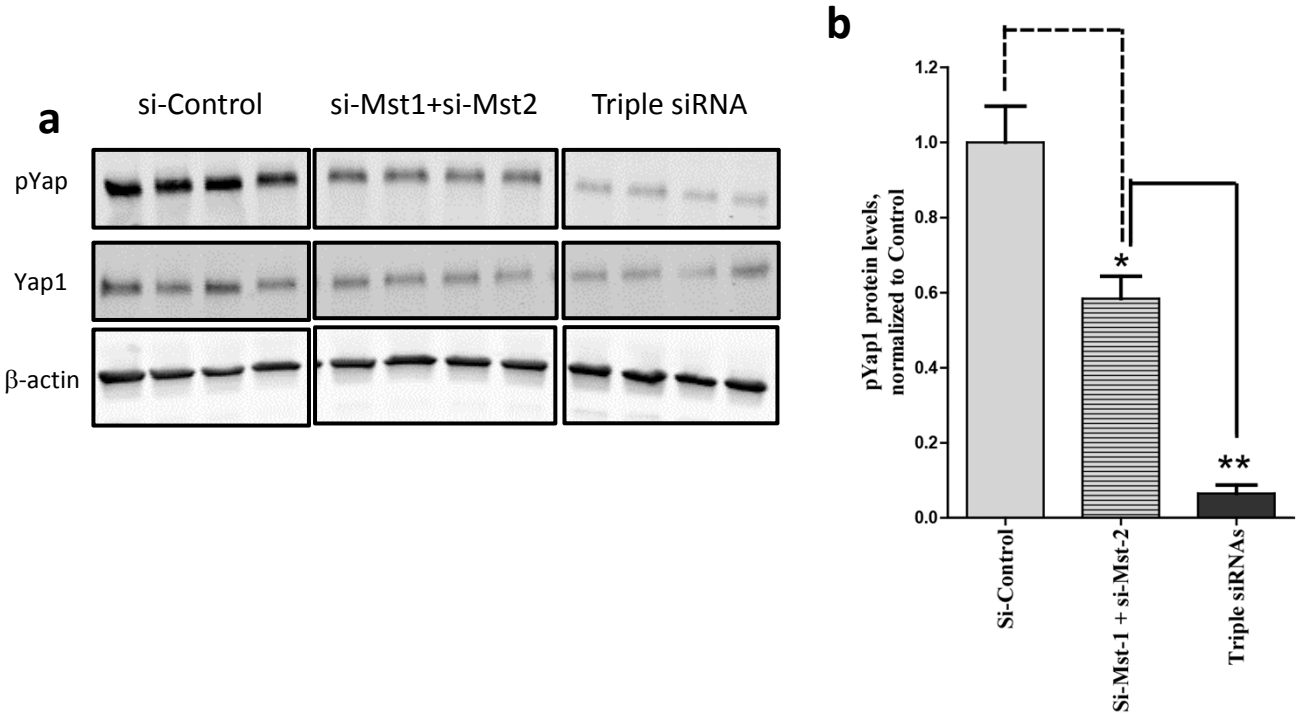
Supplementary Figure 8. Target specificity of siRNA mediated knockdown in liver. a, C57BL/6 female mice were treated with LNP-formulated triple siRNAs or dose matched si-control for a single injection. Three days after the injection, hepatocytes, Kupffer cells and stellate cells were isolated from animals. Expression of genes was analyzed by qPCR, mean ± n=3, *p<0.05. b, Dose-dependence of CK19 mRNA down-regulation specific siRNA, cells were transfected in triplicate and mRNA levels were analyzed in 24 hours. c, C57BL/6 mice were treated with LNP-formulated si-CK19 (0.5mg/kg), PBS or dose-matched si-Control. Three days after injection, the mRNA levels of CK19 in total liver were analyzed (N=5).

Fig 9S



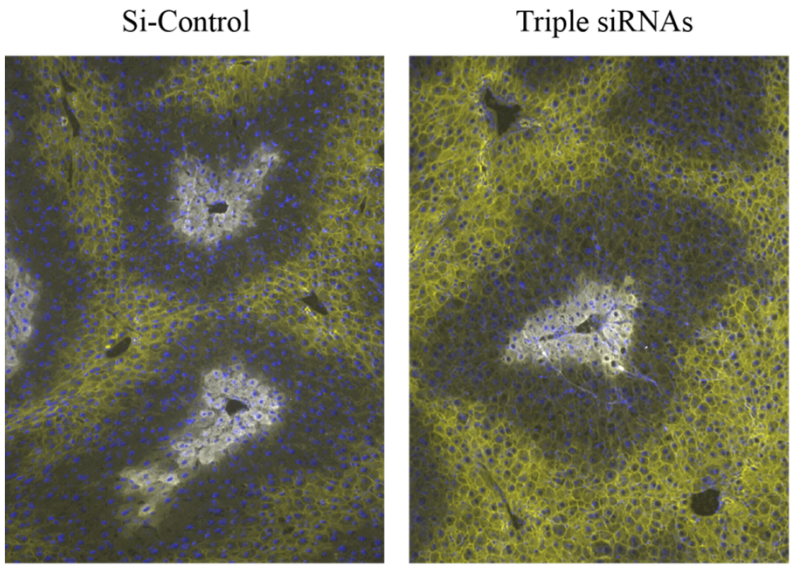
Supplementary Figure 9. Gene Expression pattern with triple siRNA treatment. C57BL/6 female mice were treated with LNP-formulated si-Luc or triple siRNAs. Total RNA from liver was purified at Day 10 and 15 after injection. Microarray was performed. a, Summary of cell cycle related genes. b, Summary of signature genes of Yap1. c, Summary of cell Cycle Checkpoint Genes. d, Summary of genes relevant to bile acids transport and metabolism. e, Total RNA from liver was purified at Day 15 after first injection of LNP-formulated siRNAs. Apoptosis related genes were determined by qPCR. *, $p<0.05$. (N=3).

Fig 10S



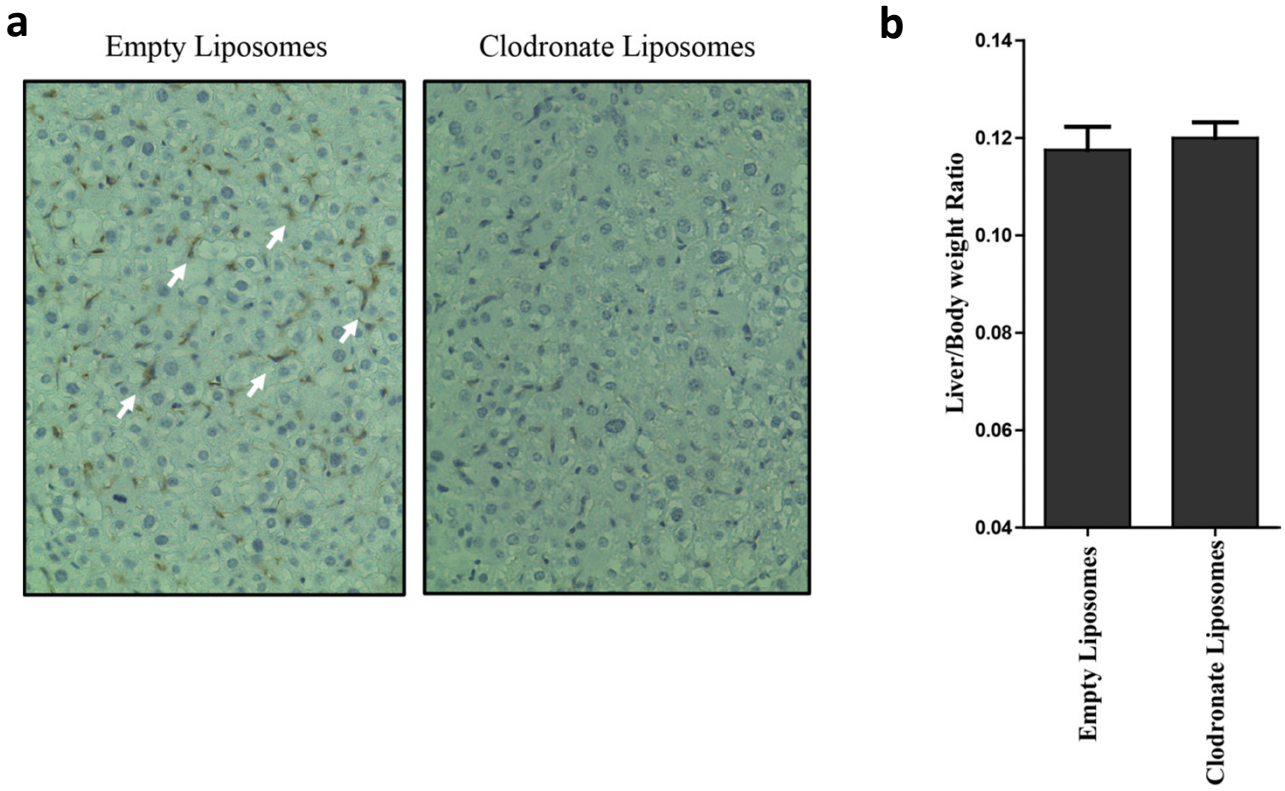
Supplementary Figure 10. The level of pYap1 after siRNA treatment. C57BL/6 female mice were treated with LNP-formulated si-Mst1 and si-Mst2, or triple siRNAs, or si-control. Livers were taken at Day 10 after injection. Liver lysate was made and western blot performed to detect phospho-Yap1 (pYap1). *, $p<0.05$; **, $p<0.01$ ($N\geq4$).

Fig 11S



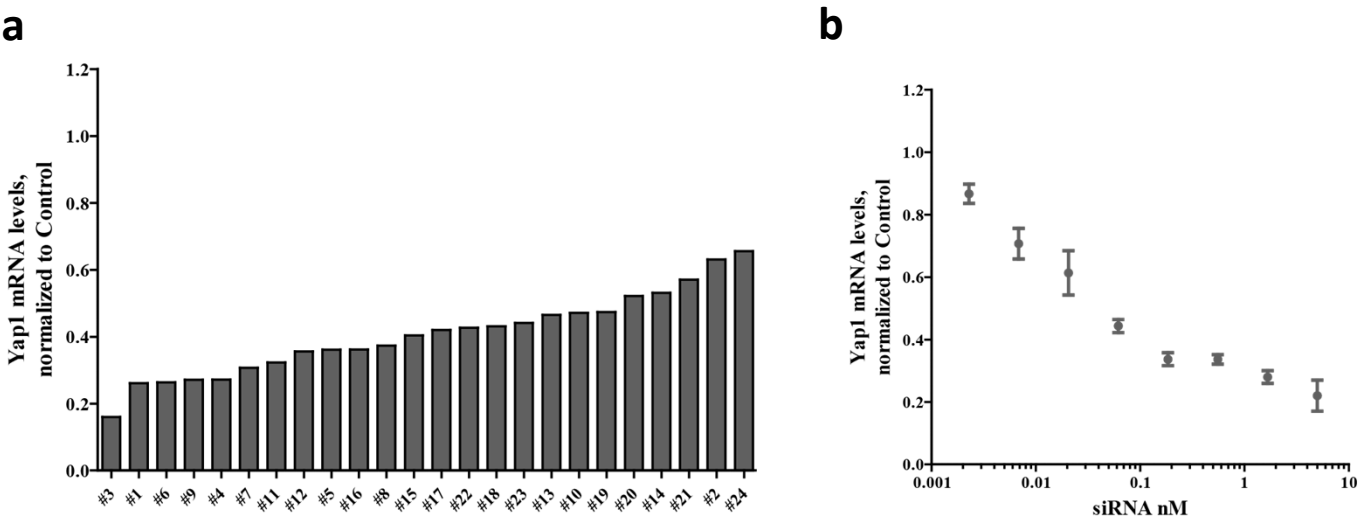
Supplementary Figure 11. Characterization of triple siRNAs induced liver growth. a, C57BL/6 female mice were treated with LNP-formulated triple siRNAs or dose matched si-control for 15 days. Liver sections were stained with E-cadherin (marker of periportal area, yellow), Hoechst (blue), and Glutamine Synthetase (marker of pericentral area, gray).

Fig 12S



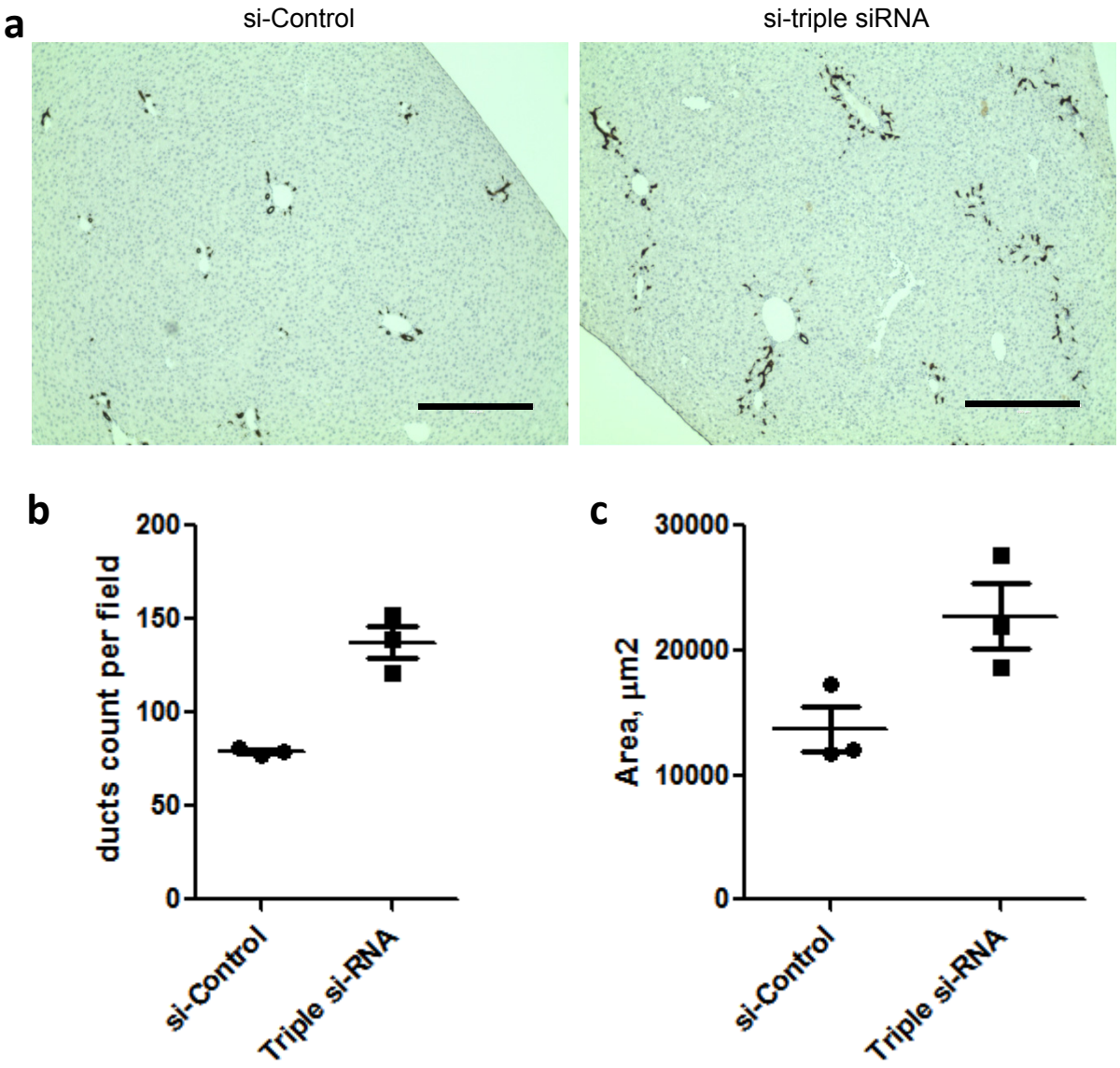
Supplementary Figure 12. The treatment by triple siRNAs induced liver growth independently of macrophage activation. C57BL/6 female mice were treated with empty liposomes or clodronate liposomes weekly with LNP-formulated triple siRNAs. Livers were taken at 15 days. a, Liver section taken for IHC staining for F4/80, a specific marker for macrophages. b, Liver weight was recorded (N=5).

Fig 13S



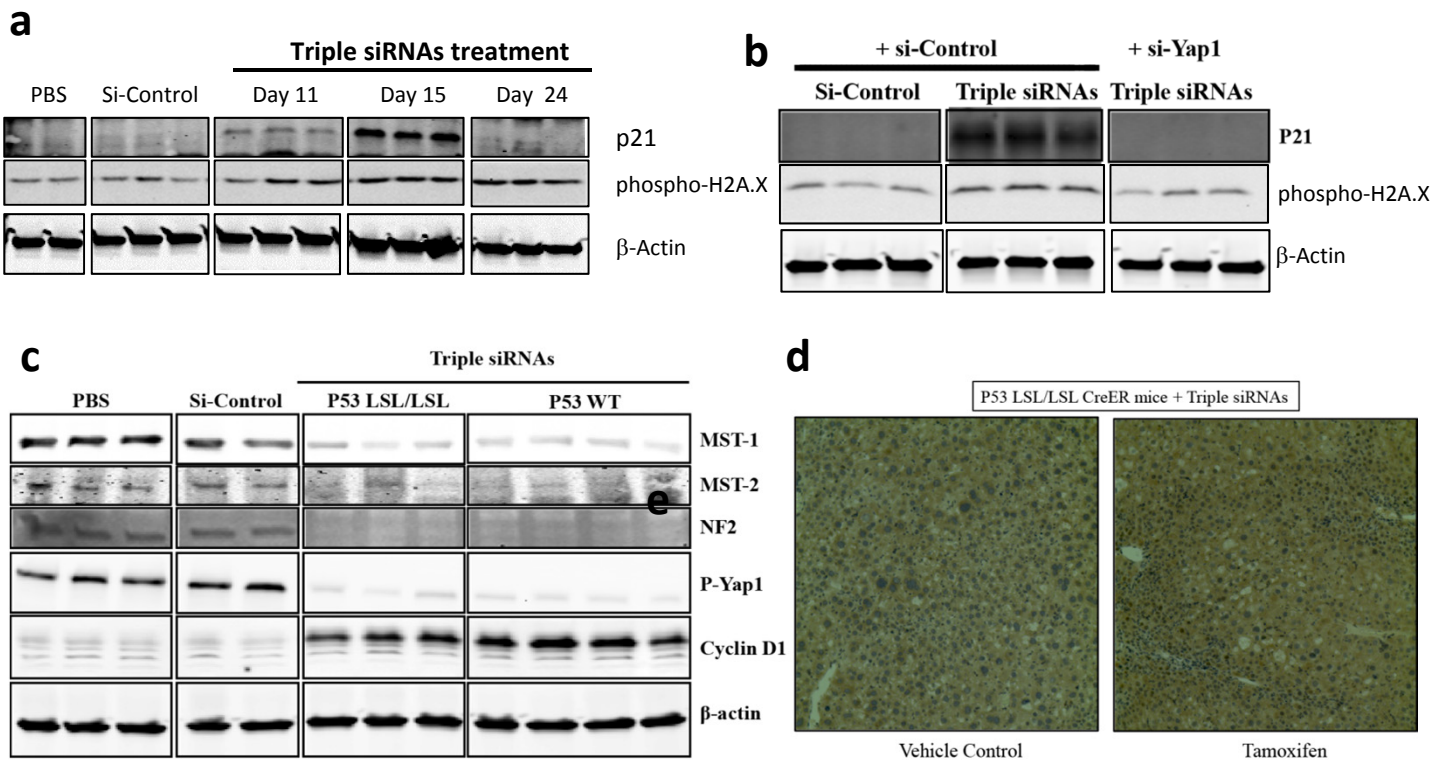
Supplementary Figure 13. Development of siRNAs against Yap1. The mRNA levels were analyzed 16-18 hours post transfection of siRNA in NIH3T3 cells. a, mRNA down-regulation by 5nM of specific siRNA against Yap1. b, Dose-dependence of Yap1 mRNA down-regulation by #3 siRNA from (a).

Fig 14S



Supplementary Figure 14. Triple siRNA treatment induces expansion of bile ducts. a, C57BL/6 female mice were treated with LNP-formulated si-control, or triple siRNAs. Livers were taken at 15 days after the first dose of siRNAs. Liver section were stained for CK19. Scale bar indicates 400 mm, b,c, Quantification of images, 3 random images were analyzed for each animal, b, number of bile ducts were quantified per visual field , c, total surface of bile ducts quantified by ImageJ, n=3.

Fig. 15S



Supplementary Figure 15. P53 plays an important role in gating liver size. a, C57BL/6 female mice were treated with PBS, or LNP-formulated si-control, or triple siRNAs. Livers were taken at 11, 15 or 24 days after first dose of siRNAs. Liver lysate was made and western blot performed to detect p21. b, C57BL/6 female mice were treated with dose matched LNP-formulated si-control, or triple siRNAs plus si-control, or triple siRNAs plus si-Yap1. Livers were taken at 15 days after the first dose of siRNAs. Liver lysate was made and western blot performed to detect p21. c-d, $p53^{LSL/LSL}$ male mice or wildtype control mice were treated with LNP-formulated triple siRNAs. Livers were taken at 22 days after treatment. c, Liver lysate was made and western was blot performed. d, $p53^{LSL/LSL}$ CreER Mice were treated with Tamoxifen or vehicle control for 3 times followed by LNP-formulated triple siRNAs treatment. Livers were taken at 22 days after first dose. Liver section taken for IHC staining for P53.