

## Supplementary Information for

### Drug repositioning of mesalamine via supramolecular nanoassembly for the treatment of drug-induced acute liver failure

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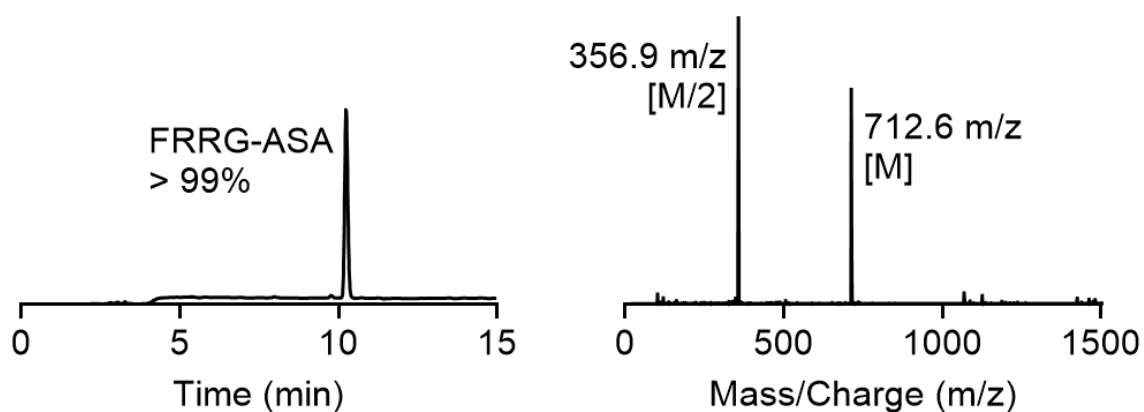
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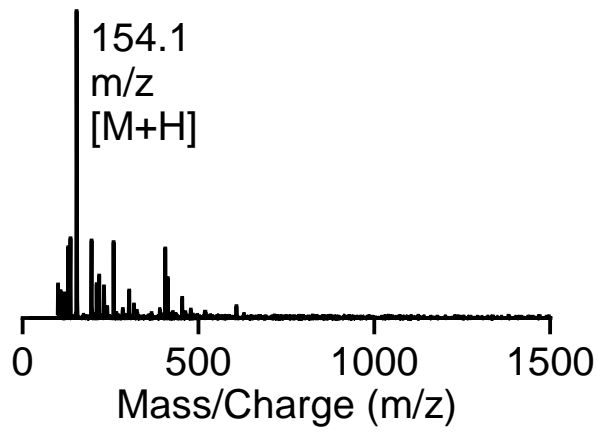
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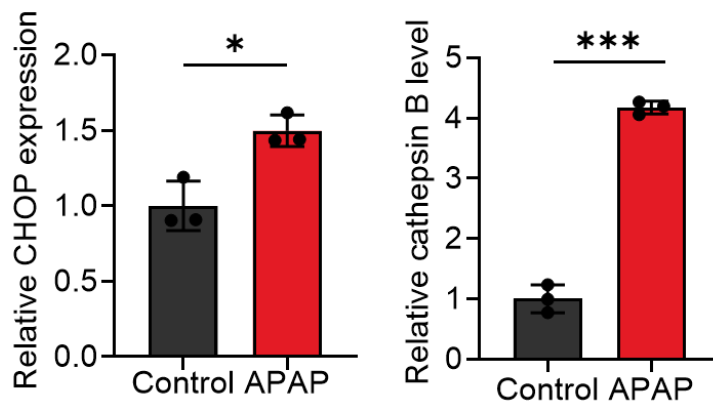
**Figure S1.** The purity and molecular weight of mesalamine prodrug, as confirmed by LC/MS.

	Incubation time in Saline					
	0 h	1 h	3 h	6 h	9 h	24 h
Size (nm)	125.3 ± 5.198	125.3 ± 16.18	121.1 ± 9.326	115.0 ± 2.052	121.6 ± 0.153	123.4 ± 3.808
PDI	0.263 ± 0.012	0.304 ± 0.121	0.317 ± 0.028	0.293 ± 0.051	0.258 ± 0.088	0.16 ± 0.02

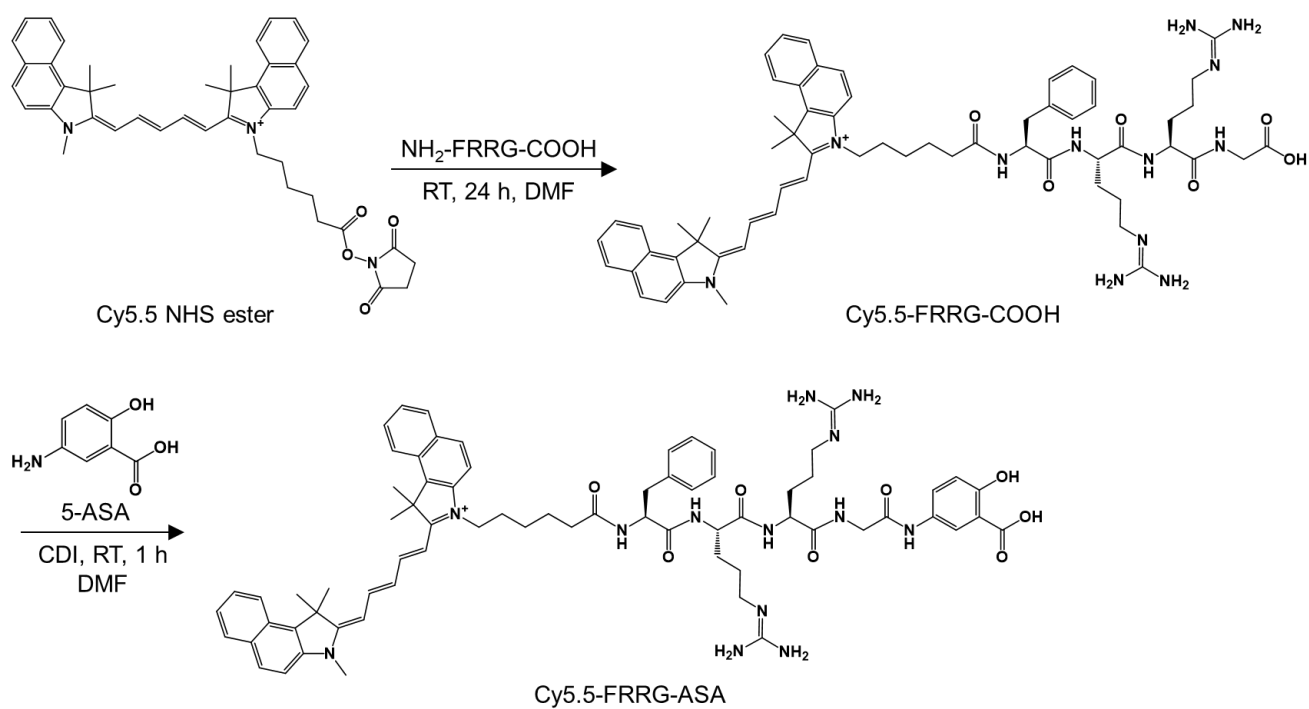
**Figure S2.** Detail information on hydrodynamic size and polydispersity index (PDI) of SPNs upon incubation in saline for 24 h.



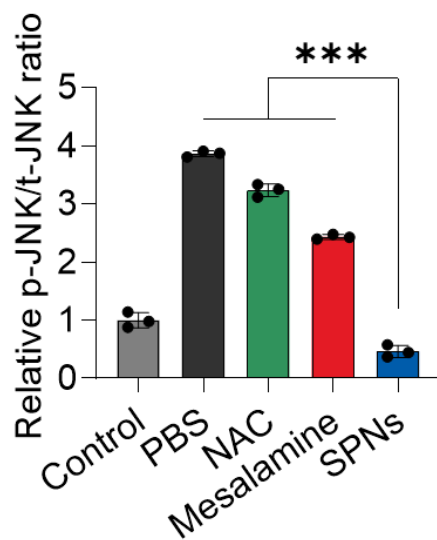
**Figure S3.** Mass analysis of emerged peak in the HPLC spectrum after incubation of SPNs cathepsin B in pH 5.5 MES buffer.



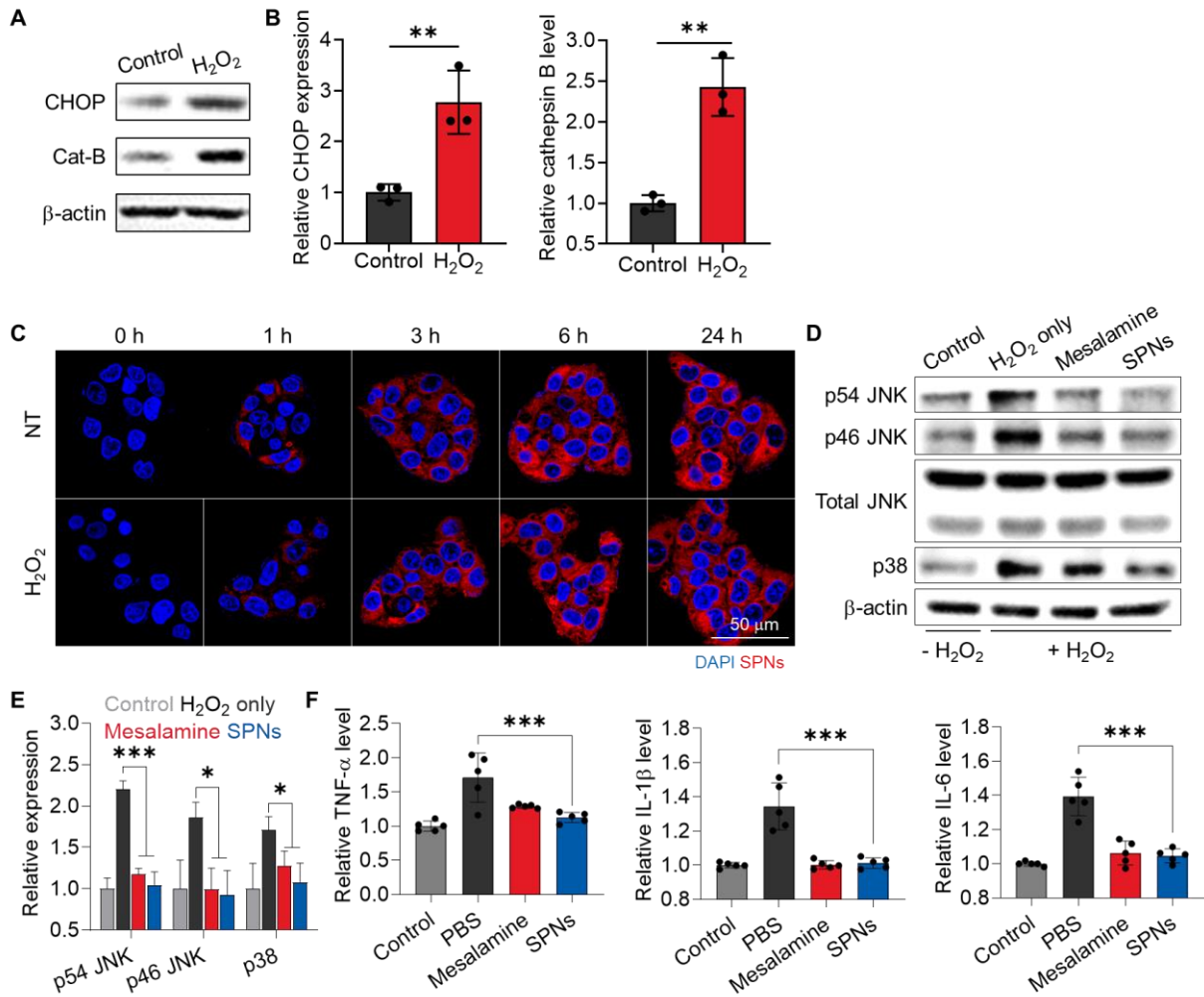
**Figure S4.** Quantitative analysis of CHOP and Cat-B in LO-2 cells before and after treatment with APAP.



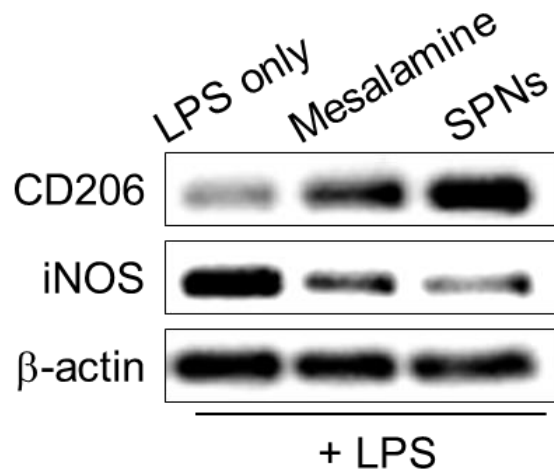
**Figure S5.** Synthetic diagram of Cy5.5-labeled mesalamine prodrug.



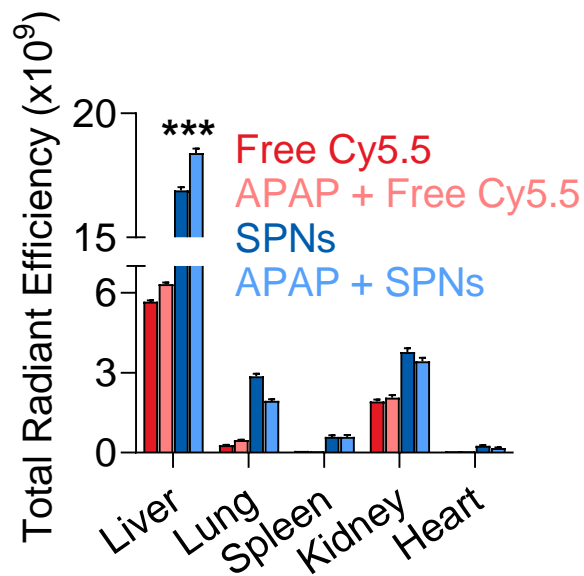
**Figure S6.** The relative ratio of phosphorylated JNK to total JNK levels in APAP-treated LO-2 cells and those cells treated with NAC, SPNs or mesalamine for 6 h.



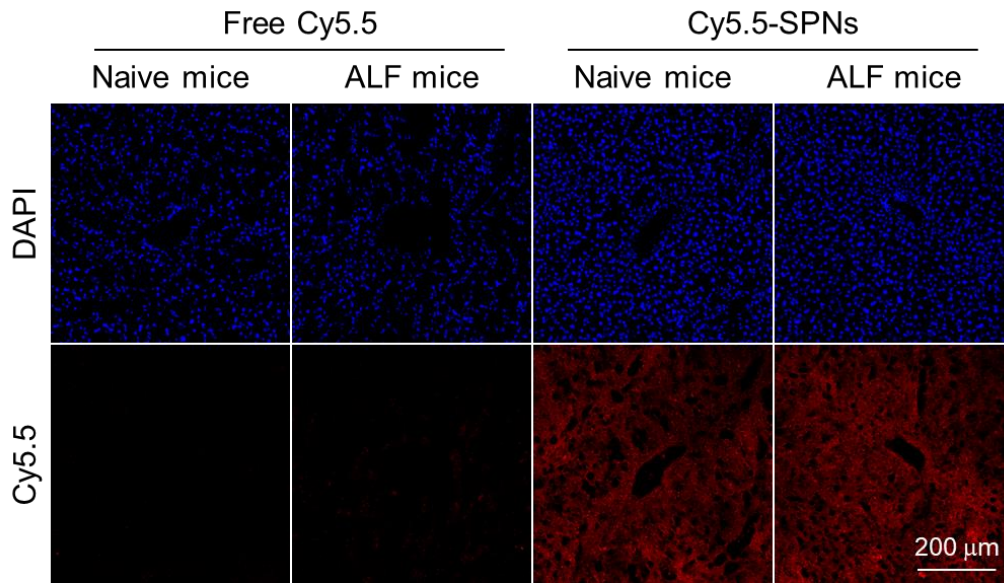
**Figure S7.** (A, B) Expression of CHOP and Cat-B in HepG2 cells before and after treatment with H<sub>2</sub>O<sub>2</sub>. (C) Representative confocal microscopy images of naive and H<sub>2</sub>O<sub>2</sub>-treated HepG2 cells after treatment with Cy5.5-SPNs. (D, E) Expression levels of phosphorylated JNKs and p38 in H<sub>2</sub>O<sub>2</sub>-treated HepG2 cells and those cells treated with SPNs or mesalamine for 6 h. (F) Levels of cytokines in H<sub>2</sub>O<sub>2</sub>-treated HepG2 cells and those cells treated with SPNs or mesalamine for 6 h.



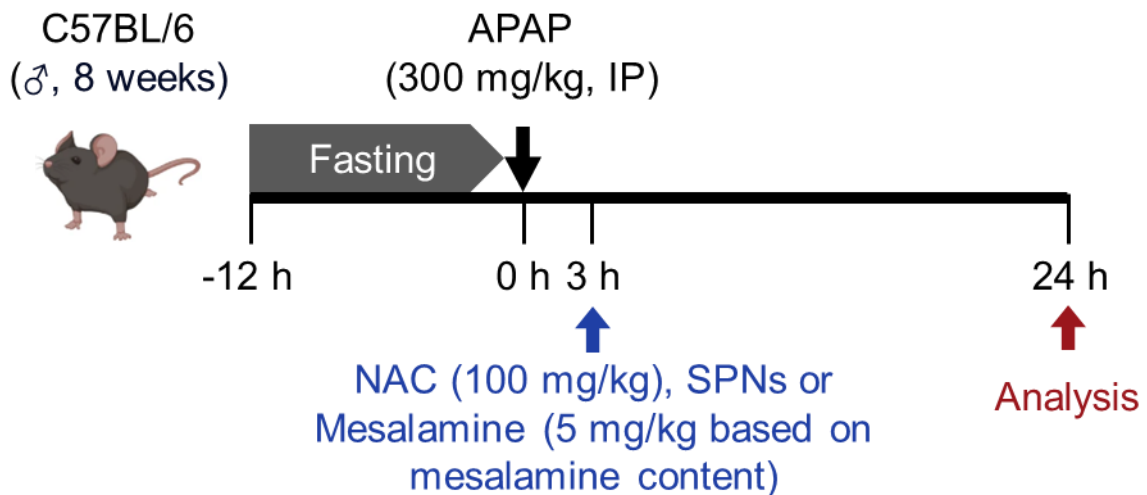
**Figure S8.** Expression levels of CD206 and iNOS in LPS-stimulated RAW 264.7 cells before and after treatment with mesalamine or SPNs.



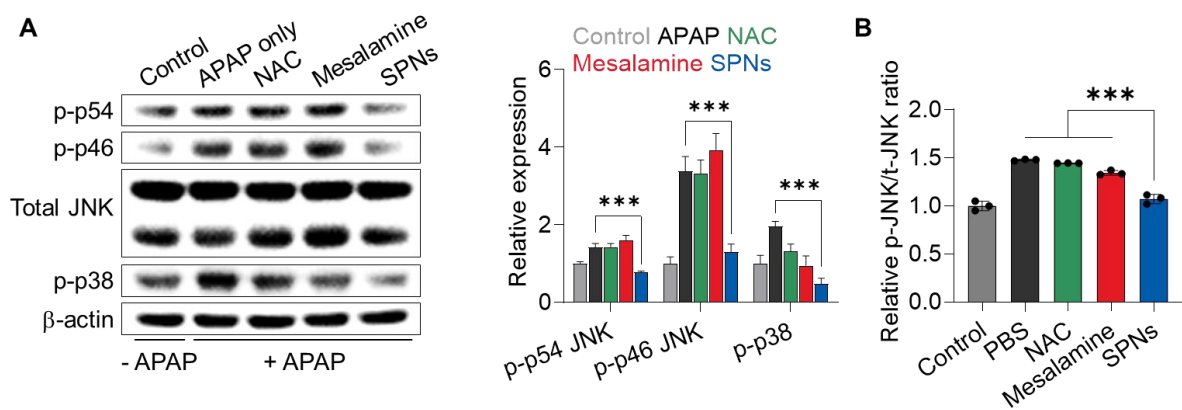
**Figure S9.** Quantitative analysis of fluorescence intensity of free Cy5.5 and SPNs in major organs from ALF mice following 9 h of treatment.



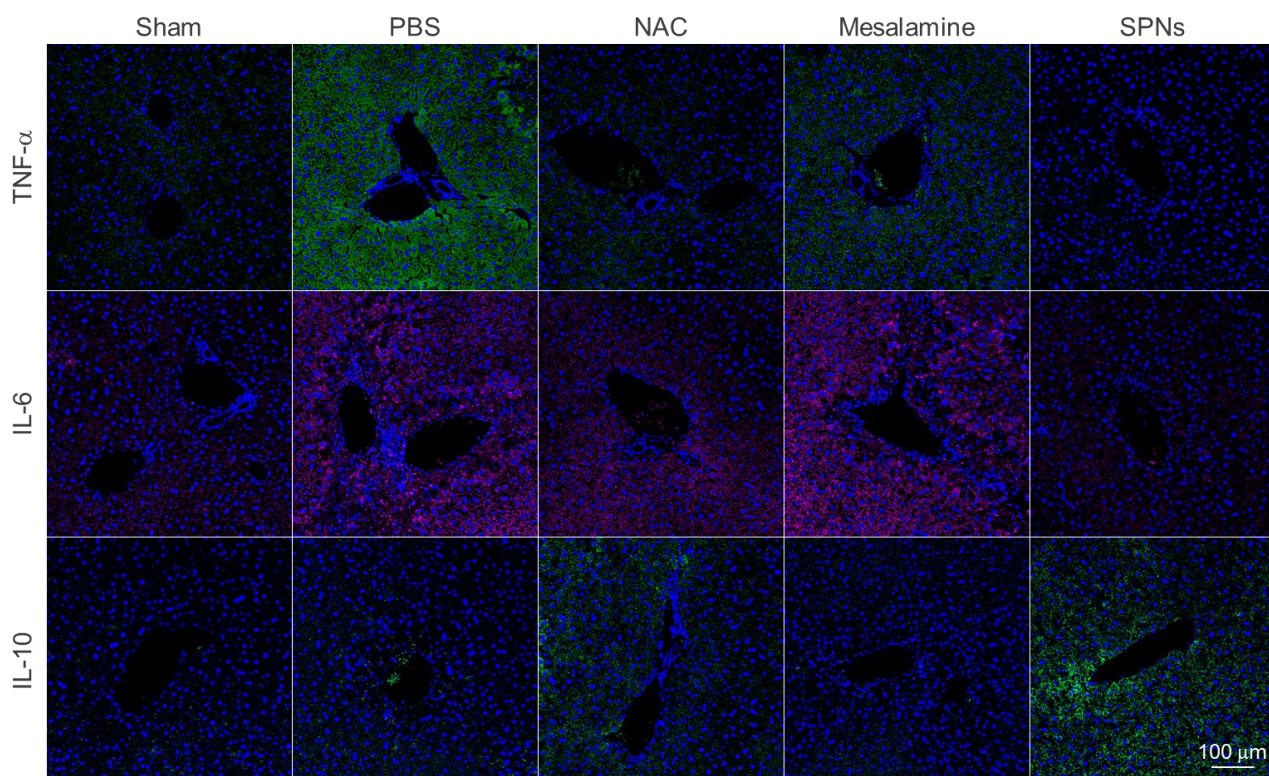
**Figure S10.** Channel images showing representative confocal microscopy images of liver tissues after 9 h of intravenous injection of free Cy5.5 or Cy5.5-SPNs.



**Figure S11.** Treatment schedule to assess the therapeutic efficacy of SPNs in ALF mice.



**Figure S12.** (A) Expression levels of total and phosphorylated JNKs and (B) the relative ratio of phosphorylated JNK to total JNK levels in the liver tissues of ALF mice at 24 h post-treatment with PBS, NAC, mesalamine or SPNs.

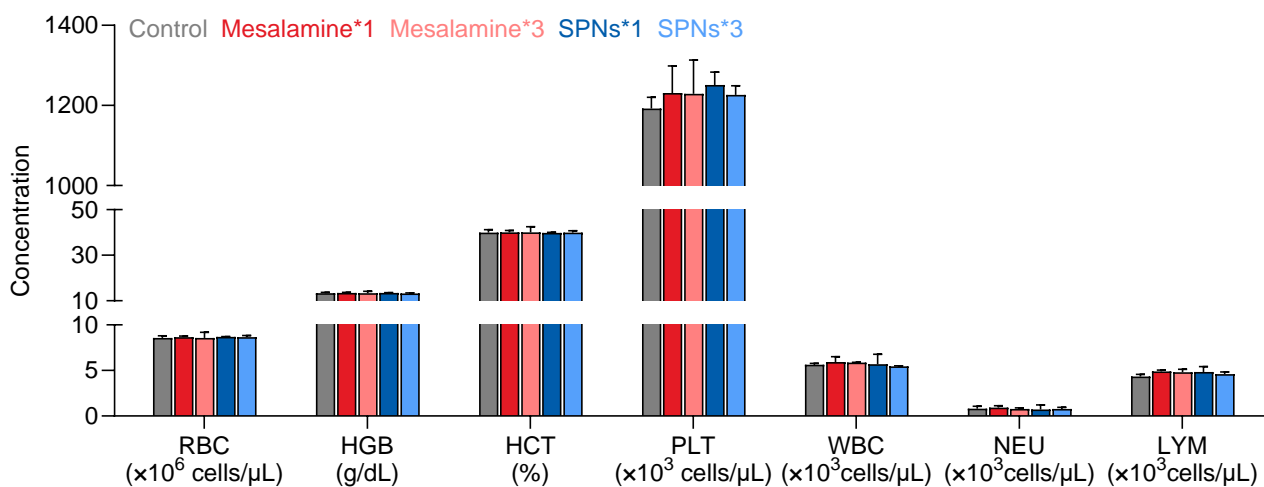


**Figure S13.** Histological analysis showing pro- and anti-inflammatory cytokines in liver tissues of ALF mice treated with NAC, mesalamine and SPNs.

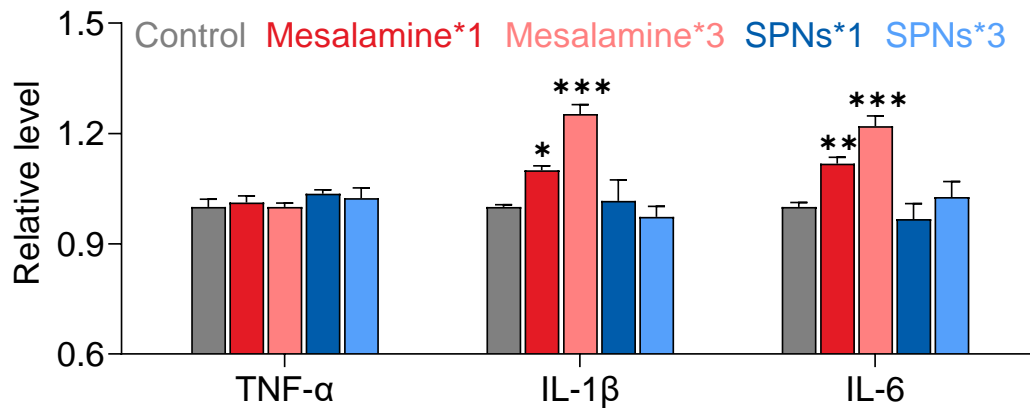


	AST (IU/L)	ALT (IU/L)	BUN (mg/dL)	Creatinine (mg/dL)	LDH (IU/L)	CK (IU/L)
Control	38.67 ± 3.95	26.53 ± 3.80	24.64 ± 4.11	0.32 ± 0.01	130.67 ± 6.06	128.93 ± 9.91
Mesalamine*1	49.2 ± 1.56	35.60 ± 3.14	29.93 ± 2.00	0.50 ± 0.01	187.13 ± 19.02	158.93 ± 4.80
Mesalamine*3	49.80 ± 1.97	34.87 ± 3.14	27.65 ± 1.38	0.50 ± 0.01	197.47 ± 13.60	213.13 ± 14.25
SPNs*1	39.47 ± 1.97	29.2 ± 0.80	27.03 ± 1.06	0.27 ± 0.09	141.87 ± 20.46	131.20 ± 18.61
SPNs*3	37.73 ± 0.46	27.47 ± 0.23	23.29 ± 1.02	0.27 ± 0.09	131.20 ± 6.44	125.73 ± 7.57

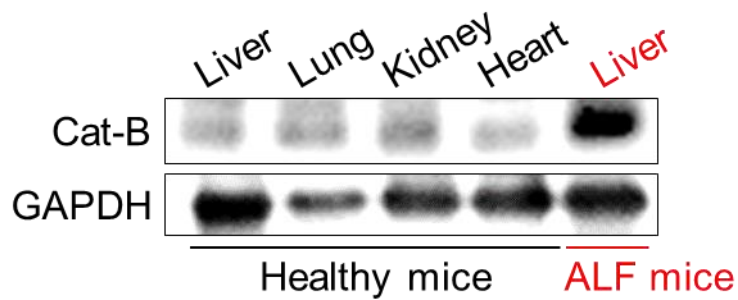
**Figure S14.** Detail information on hematological parameters.



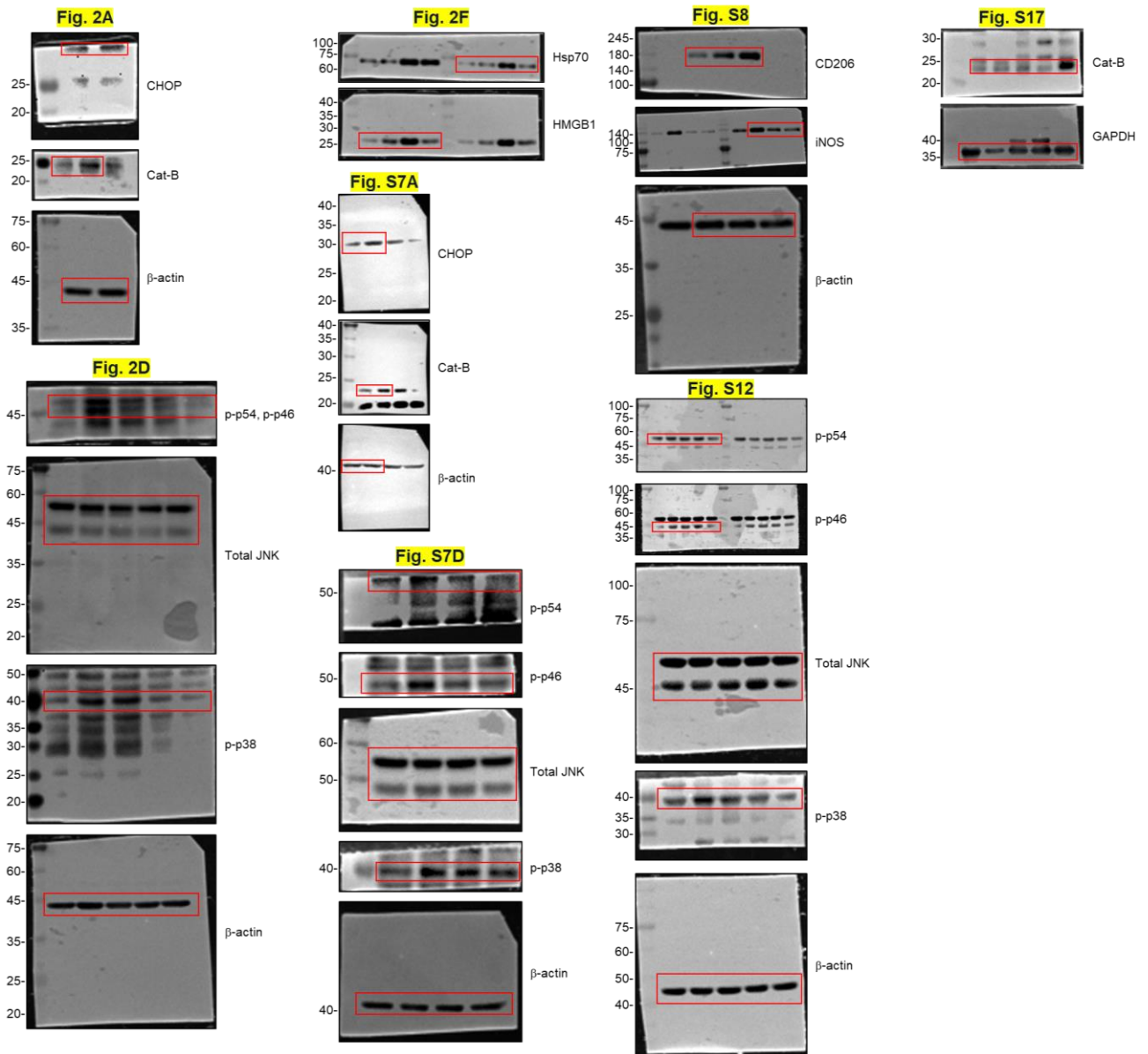
**Figure S15.** Levels of routine blood components of mice treated with single and multiple doses of mesalamine or SPNs.



**Figure S16.** Levels of inflammatory cytokines in the kidney tissues of mice treated with single and multiple doses of mesalamine or SPNs.



**Figure S17.** Expression levels of cathepsin B (Cat-B) in healthy organs and in liver tissues exposed to APAP, collected from naive and ALF mice, respectively.



**Figure S18.** Uncropped original images of Western blot results.