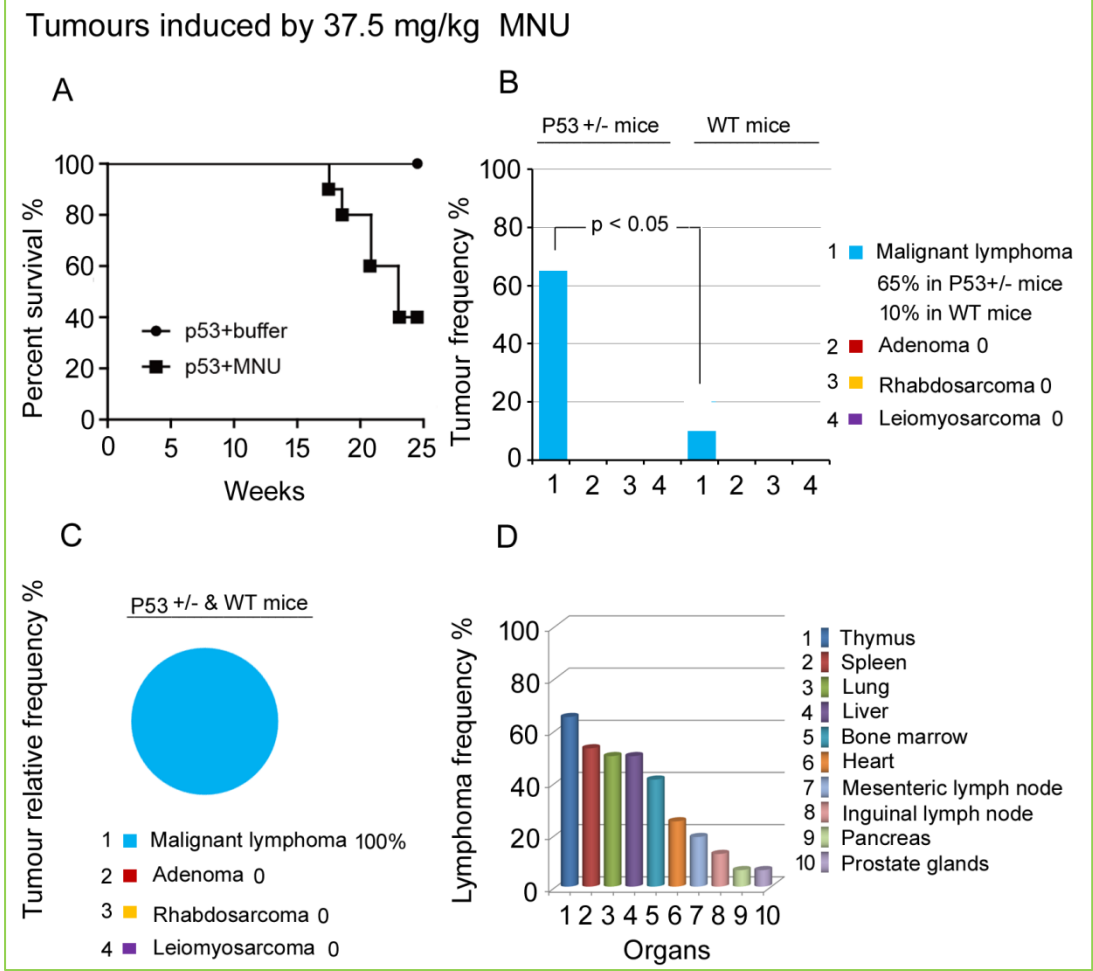


2

3 Supplementary Figure 1: Spontaneous lymphoma occurrence in *p53<sup>-/-</sup>* homozygous mice.  
 4 A. Survival curve of wild-type, *p53<sup>-/-</sup>* and *p53<sup>+/-</sup>* mice. All homozygous mice died before 32  
 5 weeks, while heterozygous and wild-type mice survived until 32 weeks. B. Spontaneous  
 6 tumor profile and frequency of *p53<sup>-/-</sup>*. Malignant lymphoma was the most prominent type  
 7 with an incidence of 93.3%. C. Relative frequency of malignant lymphoma, adenoma,  
 8 rhabdosarcoma, and leiomyosarcoma. D. The top 10 organs with a high incidence of  
 9 lymphoma. 30 *p53<sup>-/-</sup>* homozygous mice were used in this experiment.



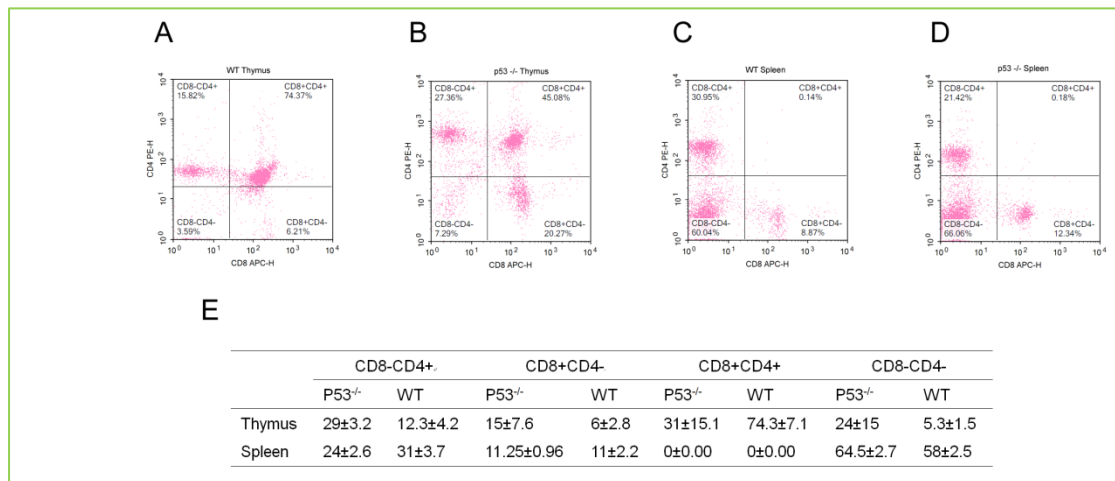
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12 Supplementary Figure 2: Lymphoma incidence in *p53* deficient heterozygote mice  
 13 induced by 37.5 mg/kg MNU. A. Survival curve of *p53*<sup>+/-</sup> mice administered 37.5 mg/kg  
 14 MNU. B. The tumor profile and its frequency of *p53*<sup>+/-</sup> and wild type mice administered with  
 15 MNU. Only lymphoma was observed in both mice. This figure indicates *p53*<sup>+/-</sup> mice were  
 16 more susceptible to MNU than wild type mice. C. The relative tumor frequency of  
 17 lymphoma, adenoma, rhabdosarcoma and leiomyosarcoma. D. The malignant lymphoma  
 18 frequency in various organs. 17 *p53*<sup>+/-</sup> and 20 wild type mice were used in this experiment.

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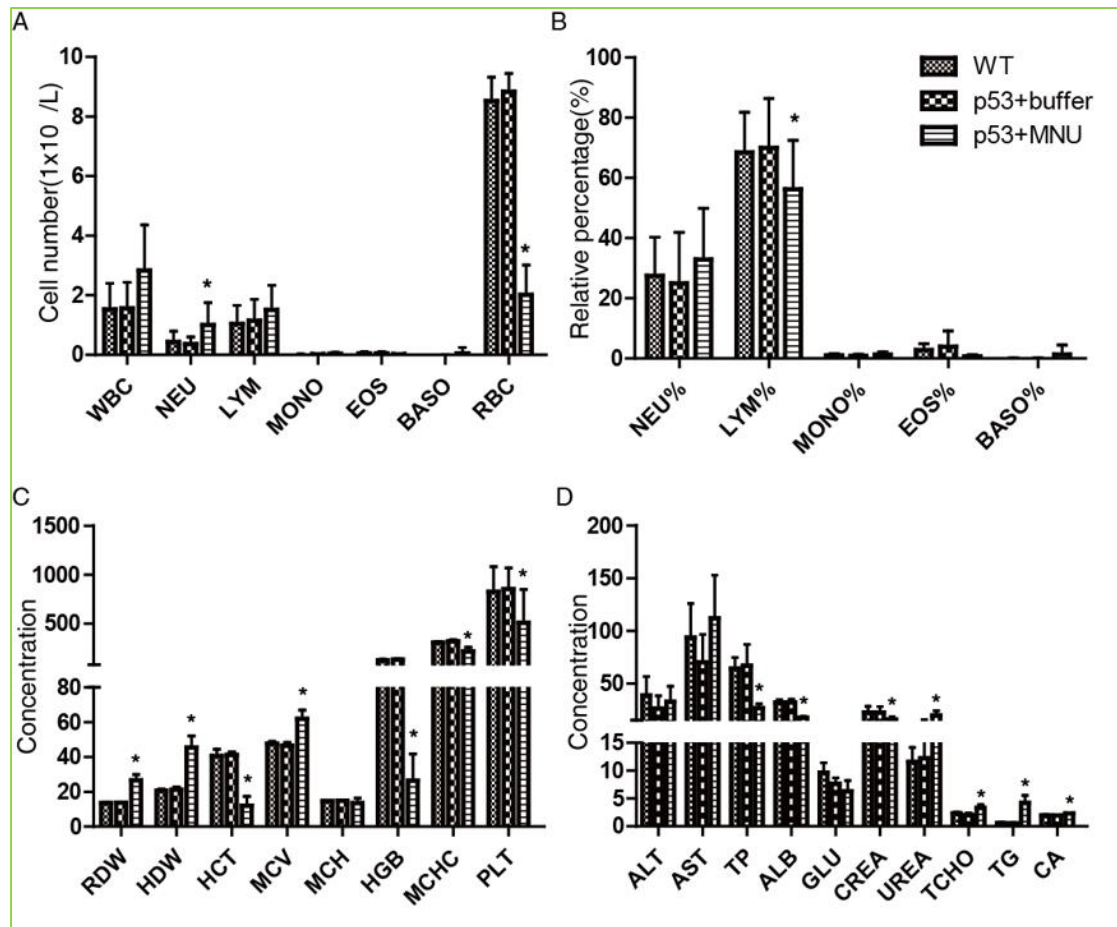


21

22 Supplementary Figure 3: CD4 and CD8 cells were isolated from the thymus and spleen of  
 23 healthy mice or *p53*<sup>-/-</sup> mice over six months old. Only enlarged thymus glands or spleens  
 24 of *p53*<sup>-/-</sup> mice were selected, for indication of its tumorigenic effect based on our previous  
 25 experiments. Data are representative of 3 - 4 independent mice.

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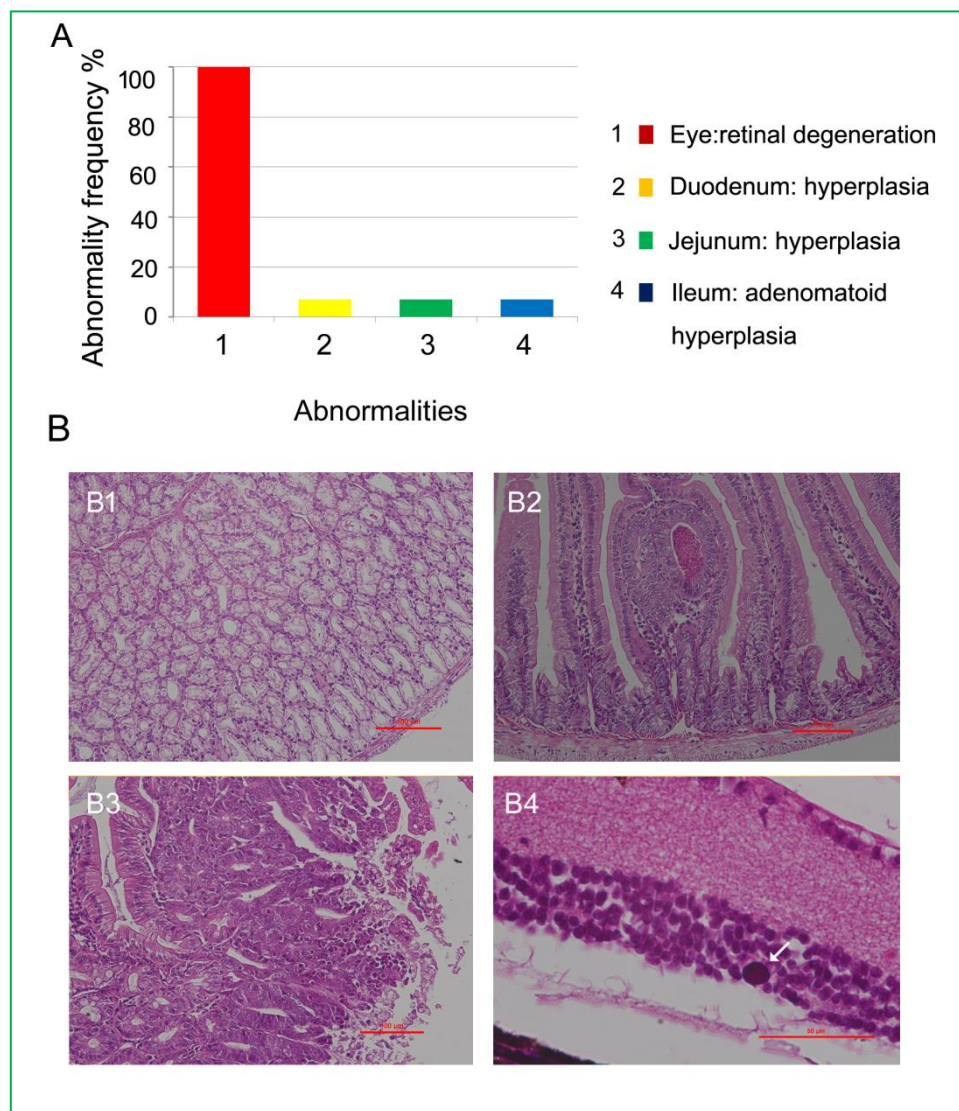


29

30 Supplementary Figure 4: Characteristics of the hematological and biochemical analysis of  
31 the animals administered 75 mg/kg MNU at the end of the experiment. A: Peripheral blood  
32 analysis of mice from different groups showing cell counts B: Percentage of all cell types.  
33 C: Other hematological indices. D: Serum biochemical parameters.

34 WBC: white blood cell count. NEU: neutrophil count. LYM: lymphocyte count. MONO:  
35 Monocyte count. EOS: Eosinophil count. BASO: Basophile count. RBC: Red blood cell.  
36 RDW: Red blood cell distribution width. HDW: Hemoglobin distribution width. HCT:  
37 Hematocrit. MCV: Mean corpuscular volume. MCH: Mean corpuscular hemoglobin. HGB:  
38 Hemoglobin. MCHC: Red blood cell hemoglobin concentration. PLT: Platelet count. ALT:  
39 Alanine aminotransferase. AST: Aspartate aminotransferase. TP: Total protein. ALB:  
40 Albumen. GLU: Glucose. CREA: Creatinine. UREA: Urea nitrogen. TCHO:  
41 Cholesterol. TG: Triglyceride. CA: Calcium.

42



44

45 Supplementary Figure 5: Frequency and histopathological features of 75 mg/kg MNU

46 induced other neoplastic and non-neoplastic microscopic findings in  $p53^{+/-}$  deficient mice.47 A. Frequency of 75 mg/kg MNU-induced non-neoplastic microscopic findings in  $p53^{+/-}$ 

48 deficient mice. B. Histopathological features of 75 mg/kg MNU induced other neoplastic

49 and non-neoplastic microscopic findings in  $p53^{+/-}$  deficient mice. B1. Photomicrograph of

50 glandular hyperplasia of the duodenum. B2. Photomicrograph of adenomatous

51 hyperplasia of the duodenum. B3. Photomicrograph of the jejunal adenoma. B4.

52 Photomicrograph of retinal degeneration with loss of the photoreceptor layer, outer

53 nuclear layer, and outer plexiform layer. Large basophilic bodies are present in the inner

54 nuclear layer (white arrows). B1-B3. Magnification was  $\times 100$ , bar = 100  $\mu\text{m}$ . B4.55 Magnification was  $\times 200$ , bar = 100  $\mu\text{m}$ .

57 Supplementary Table 1: Macroscopic findings of MNU and citrate buffer control animals.

Dose	75mg/kg MNU		37.5mg/kg MNU		Citrate buffer	
Numbers of animals	<i>p53</i> <sup>+/-</sup>	WT	<i>p53</i> <sup>+/-</sup>	WT	<i>p53</i> <sup>+/-</sup>	
Numbers of animals	14	20	17	10	19	
Numbers of animals with tumors*	14	2	11	0	0	
Thymus, enlarged	6	0	5	0	0	
Thymus, mass	1	0	0	0	0	
Spleen, enlarged	10	1	8	0	0	
Spleen, mass	2	0	2	0	0	
Inguinal lymph node, enlarged	0	0	3	0	0	
Mesenteric lymph node, enlarged	0	0	2	0	0	
Mandibular lymph node, enlarged	0	0	0	0	0	
Kidney, mass	0	0	2	0	0	
Liver, enlarged	2	0	3	0	0	
Liver, mass	0	0	3	0	0	
Lung, mass	1	0	0	0	0	

58 Note: \* number confirmed by microscopic findings.

59

Supplementary Table 2: The influence of genetic background on the tumor spectra and lymphoma frequency observed in *p53*-deficient mice <sup>a)</sup>

Lines	Genetic background of mice	Induced or spontaneously	<i>p53</i> -mutant alleles	Main tumor spectrum and lymphoma frequency	Age (weeks)	References
L01	D3	Spontaneously	<i>p53</i> <sup>+/-</sup>	Osteosarcoma, lymphoma (25%), fibrosarcoma	26-68	Jacks et al, 1994
L02	D3	Spontaneously	<i>p53</i> <sup>-/-</sup>	Lymphoma (71%), rhabdomyosarcoma, teratoma	26-68	Jacks et al, 1994
L03	BABL/c <sup>b)</sup>	Spontaneously	<i>p53</i> <sup>+/-</sup>	Mammary carcinoma, lymphoma (24%), hemangiosarcoma	> 72	Kuperwasser et al, 2000
L04	BABL/c <sup>b)</sup>	Spontaneously	<i>p53</i> <sup>-/-</sup>	Lymphoma (53%), hemangiosarcoma, soft-tissue sarcoma	> 72	Kuperwasser et al, 2000
L05	129/Sv	Spontaneously	<i>p53</i> <sup>-/-</sup>	Lymphoma (65%), testicular, hemangiosarcoma	5-24	Harvey et al, 1993
L06	129/Sv	Spontaneously	<i>p53</i> <sup>+/-</sup>	Osteosarcoma, lymphoma (22%)	>100	Donehower LA, 1995
L07	129/Sv	Spontaneously	<i>p53</i> <sup>-/-</sup>	Lymphoma (47%), malignant teratoma	>100	Donehower LA, 1995
L08	75% C57BL/6, 25% 129/Sv	Spontaneously	<i>p53</i> <sup>-/-</sup>	Lymphoma (69%), hemangiosarcoma, sarcoma	8-37	Donehower et al, 1992
L09	75% C57BL/6, 25% 129/Sv	Spontaneously	<i>p53</i> <sup>-/-</sup>	Lymphoma (75%), hemangiosarcoma, testicular tumors	Nd <sup>f)</sup>	Harvey et al, 1993
L10	75% C57BL/6, 25% 129/Sv	Spontaneously	<i>p53</i> <sup>+/-</sup>	Osteosarcoma, lymphoma (28%)	>100	Donehower LA, 1995
L11	75% C57BL/6, 25% 129/Sv	Spontaneously	<i>p53</i> <sup>-/-</sup>	Lymphoma (65%), hemangiosarcoma	>100	Donehower LA, 1995
L12	B6.129-Trp53 N5 <sup>c)</sup>	Induced <sup>d)</sup>	<i>p53</i> <sup>+/-</sup>	Lymphoma (85%), adenoma, adenocarcinoma	26	Morton et al, 2008
L13	100% C57BL/6J	Spontaneously	<i>p53</i> <sup>-/-</sup>	Lymphoma (90.5%), leiomyoma, rhabdosarcoma	12-32	This work
L14	100% C57BL/6J	Induced <sup>d)</sup>	<i>P53</i> <sup>+/-</sup>	Lymphoma (100%), adenoma	24-26	This work
L15	100% C57BL/6J	Induced <sup>e)</sup>	<i>P53</i> <sup>+/+</sup>	Lymphoma (10%)	24-26	This work
L16	100% C57BL/6J	Induced <sup>e)</sup>	<i>P53</i> <sup>+/-</sup>	Lymphoma (65%)	24-26	This work

a) Only the top three types of tumors were observed, and lymphoma frequencies were indicated.

b) C57BL/6x129/Sv *p53*-deficient mice were backcrossed for nine generations onto BALB/c mice.

c) 129/Sv *p53*-deficient mice were backcrossed for five generations onto the C57BL/6 strain, about 97% of C57BL/6 background;

d) Induced by 75mg/kg MNU;

e) Induced by 37.5 mg/kg MNU;

f) nd: not determined;