

**Cell, Volume 182**

**Supplemental Information**

**Pathogenesis of SARS-CoV-2  
in Transgenic Mice Expressing Human  
Angiotensin-Converting Enzyme 2**

**Ren-Di Jiang, Mei-Qin Liu, Ying Chen, Chao Shan, Yi-Wu Zhou, Xu-Rui Shen, Qian Li, Lei Zhang, Yan Zhu, Hao-Rui Si, Qi Wang, Juan Min, Xi Wang, Wei Zhang, Bei Li, Hua-Jun Zhang, Ralph S. Baric, Peng Zhou, Xing-Lou Yang, and Zheng-Li Shi**

**Table S1. Experimental strategy and preliminary results from the mice used in current study, Related to Figure 1.**

Group	Sex	Body Weight*								End point	Symptoms
		Day 0	1 DPI	2 DPI	3 DPI	4 DPI	5 DPI	6 DPI	7 DPI		
Mock-1	♂	32.48	31.32	32.08	32.26	31.94	31.64	32	31.83		No visible symptoms
Mock-2	♂	28.88	27.19	27.98	28.3	27.89	27.34	28.63	28.43	Sacrificed	
Mock-3	♀	18	17.99	18.94	18.79	19.14	19.05	19.6	19.36		
Mock-4	♀	20.79	20.55	20.71	21	20.89	20.53	21.04	21.22		
G-D1-M1	♂	28.64	26.7							Sacrificed	No visible symptoms
G-D1-M2	♂	30.65	30.6							Sacrificed	
G-D1-M3	♂	30.59	30.2							Sacrificed	
G-D1-M4	♂	33.15	33.4							Sacrificed	
G-D1-M5	♀	21.28	21.5							Sacrificed	
G-D1-M6	♀	22.67	22.32							Sacrificed	
G-D3-M1	♂	27.67	27.17	26.83	25.81					Sacrificed	No visible symptoms
G-D3-M2	♂	29.18	28.88	29.94	29.3					Sacrificed	
G-D3-M3	♂	31.28	31.13	31.22	29.96					Sacrificed	
G-D3-M4	♂	34.46	32.79	33.52	32.01					Sacrificed	
G-D3-M5	♀	20.36	19.99	20.48						Dead	
G-D3-M6	♀	18.87	19.25	19.12						Dead	
G-D5-M1	♂	23.3	23.93	24.28	24.63	25.15	25.47			Sacrificed	No visible symptoms
G-D5-M2	♂	28.23	25.27	22.36	25	26.84	26.82			Sacrificed	Weight loss and dyspnea 1- 2 DPI, later recovered
G-D5-M3	♂	22.36	23.05	24.12	22.51	17.39				Dead	Dead 4 DPI
G-D5-M4	♂	29.7	30.15	30.84	31.34	25.94	23.55			Dead	Weight loss and dyspnea, shrinkage, torpor 4 DPI, dead 5 DPI
G-D5-M5	♀	19.44	18.81	18.75	19.79	19.24	19.19			Sacrificed	No visible symptoms
G-D5-M6	♀	22.21	21.64	22.13	22.47	22.46	22.02			Sacrificed	No visible symptoms
G-D7-M1	♂	26.03	25.05	25.02	25.5	22.98	19.4			Dying, Sacrificed	Weight loss 4 DPI, shrinkage, dyspnea, torpor, neurological symptoms
G-D7-M2	♂	29.3	28.37	29.19	29.51	30.43	28.24	23.56	22.49	Dying, Sacrificed	Weight loss 6 DPI, shrinkage, dyspnea, torpor, neurological symptoms
G-D7-M3	♂	31.76	30.16	31.32	31.51	31.39	31.45	30.82	30.35	Sacrificed	No visible symptoms
G-D7-M4	♂	29.11	29.49	29.73	29.68	29.53	29.46	29.91	28.96	Sacrificed	
G-D7-M5	♀	21.82	21.92	21.95	22.41	22.24	22.63	22.9	22.6	Sacrificed	
G-D7-M6	♀	19.6	18.94	19.53	20.4	20.4	21.1	21	20.98	Sacrificed	

\*Body-weight/g. Blue, retained for re-infected protection testing. Green, failed infection. Yellow, significant weight loss. Red, dead, or dying. Purple, anaesthesia error resulting in death.

**Table S2. Routine blood parameters and biochemistry of mice infected with SARS-CoV-2, Related to Figure 1 and S1.**

Tests	Control(n=4)	Days post-infection				
		Day1(n=5)	Day3 (n=3)	Day 5(n=4)	Day 7(n=4)	Deceased (n=3)†
RBC(M/ $\mu$ L)	6.41 $\pm$ 0.42(5.75-7.53)	8.46 $\pm$ 0.72(6.18-9.74)	6.20 $\pm$ 0.68(5.04-7.4)	7.11 $\pm$ 0.17(6.68-7.43)	6.49 $\pm$ 0.24(5.86-7.03)	6.84 $\pm$ 2.12(2.69-9.63)
HGB(g/dL)	9.35 $\pm$ 0.55(8.4-10.7)	12.32 $\pm$ 1.07(8.8-14.4)	8.87 $\pm$ 0.84(7.5-10.4)	10.33 $\pm$ 0.27(9.7-10.9)	9.35 $\pm$ 0.38(8.3-10.1)	9.93 $\pm$ 3.14(3.8-14.2)
RET(K/ $\mu$ L)	249 $\pm$ 23.53(185-296)	437 $\pm$ 47.71(318-611)	723 $\pm$ 329(355-1378)	481 $\pm$ 149 (221-907)	547 $\pm$ 72.5(366-668)*	389 $\pm$ 203(68.1-763.7)
RET (%)	3.88 $\pm$ 0.28(3.21-4.59)	5.32 $\pm$ 0.76(4.24-8.29) *	13.08 $\pm$ 7.17(4.79-27.35)	6.72 $\pm$ 1.96(3.02-12.2)	8.56 $\pm$ 1.35(5.21-11.25)*	4.85 $\pm$ 1.6(2.53-7.93)
PLT(K/ $\mu$ L)	958.5 $\pm$ 84.01(763-1144)	931.4 $\pm$ 54.82(721-1036)	926 $\pm$ 114.29(765-1147)	892.75 $\pm$ 26.10(815-926)	1011 $\pm$ 117(788-1309)	1406 $\pm$ 229(972-1751)
MPV(fL)	7.9 $\pm$ 0.11(7.7-8.2)	8.08 $\pm$ 0.55(5.9-8.8)	8.6 $\pm$ 0.15(8.4-8.9) *	8.85 $\pm$ 0.35(8.4-9.9)*	8.2 $\pm$ 0.08(8-8.4)	8.5 $\pm$ 0.31(8.1-9.1)
WBC(K/ $\mu$ L)	2.48 $\pm$ 0.36(1.8-3.48)	3.44 $\pm$ 0.20(3.02-4.07) *	6.02 $\pm$ 0.78(4.48-7.04)**	3.91 $\pm$ 0.30(3.34-4.6)*	4.36 $\pm$ 0.84(2.3-6.38)	2.62 $\pm$ 0.47(1.67-3.15)
NEUT(K/ $\mu$ L)	0.26 $\pm$ 0.03(0.2-0.35)	0.85 $\pm$ 0.16(0.51-1.41) *	0.77 $\pm$ 0.14(0.55-1.02)**	0.57 $\pm$ 0.09(0.4-0.77)*	0.57 $\pm$ 0.18(0.23-1.06)	1.63 $\pm$ 0.36(0.93-2.12) **
LYMPH(K/ $\mu$ L)	2.16 $\pm$ 0.37(1.53-3.22)	2.42 $\pm$ 0.20(1.98-2.93)	4.93 $\pm$ 0.73(3.48-5.72)*	3.15 $\pm$ 0.28(2.56-3.67)	3.57 $\pm$ 0.62(1.96-4.92)	0.82 $\pm$ 0.07(0.68-0.93) *
MONO(K/ $\mu$ L)	0.03 $\pm$ 0.01(0.02-0.04)	0.12 $\pm$ 0.03(0.06-0.22) *	0.23 $\pm$ 0.05(0.14-0.32)**	0.16 $\pm$ 0.04(0.07-0.24)*	0.14 $\pm$ 0.05(0.06-0.28)	0.14 $\pm$ 0.07(0.05-0.28)
NEUT (%)	11.1 $\pm$ 1.90(5.8-14.8)	24.56 $\pm$ 4.21(14.8-38.8)*	13.2 $\pm$ 2.47(8.4-16.6)	14.5 $\pm$ 2.27(9.4-19.6)	12.4 $\pm$ 1.87(8.6-16.6)	61.37 $\pm$ 3.35(55.7-67.3) ***
LYMPH (%)	86.4 $\pm$ 2.23(81.9-92.5)	70.62 $\pm$ 4.73(54.5-72)*	81.6 $\pm$ 3.04(77.7-87.6)	80.5 $\pm$ 2.4(74-84.2)	82.7 $\pm$ 2.07(77.1-86.4)	32.87 $\pm$ 3.93(28.4-40.7) ***
MONO (%)	1.08 $\pm$ 0.10(0.8-1.3)	3.4 $\pm$ 0.75(2.0-6.1) *	3.9 $\pm$ 0.92(2.1-5.1)*	4 $\pm$ 1.01(2.1-5.8)*	3.05 $\pm$ 0.53(1.9-4.4)*	5.03 $\pm$ 2.08(2.9-9.2)
	Control(n=3)	Day1(n=4)	Day3(n=3)	Day 5(n=5)	Day 7(n=4)	Deceased (n=2)
BUN (mg/dL)	17 $\pm$ 0.41(16-18)	17 $\pm$ 0.41(16-18)	17 $\pm$ 0.57(16-18)	43.4 $\pm$ 27.66(14-154)	15.75 $\pm$ 0.25(15-16)	36.5 $\pm$ 19.5(17-56)
ALT (U/L)	65.67 $\pm$ 5.66(60-77)	66.25 $\pm$ 2.25 (60-70)	72.33 $\pm$ 9.94 (60-92)	123.66 $\pm$ 56(60-350)	74 $\pm$ 8.86(60-99)	80.5 $\pm$ 11.5(69-92)
AST (U/L)	25.66 $\pm$ 4.33(18-33)	55 $\pm$ 15.72(29-100)	45 $\pm$ 6(33-51)	200 $\pm$ 117(56-433)	36.75 $\pm$ 3.12(31-45)	103 $\pm$ 5(98-108) **
CK( U/L)	141 $\pm$ 47.06(60-223)	627 $\pm$ 228(262-1216)	522 $\pm$ 109(322-699) *	508 $\pm$ 163(183-678)	320 $\pm$ 142(172-749)	1040 $\pm$ 365(675-1405) *

Significant difference of SARS-CoV-2-inoculated mice vs. mock-infected mice were performed by two-tailed Student's t-tests, \*\*\* $P < 0.001$ , \*\* $P < 0.01$ , \* $P < 0.05$ . †, three deceased mice 6 DPI (one was from the infected group and the other two were from the survival test group). At each time point, 3-5 mice each were inoculated with SARS-CoV-2, then analysed and the results were presented as the mean  $\pm$  SEM. Results from mock-infected mice were presented as the mean  $\pm$  SEM.

**Table S3. Genome comparison of the re-isolated virus with the original viral genome, Related to Figure 3 and S4.**

Sample	Genome (Start, end)	Gene Mutation (nt, aa)
Reference	1-29891	-
Lung	10-29863	nsp13, C14554T, L372F Spike, C23525T, H644Y
Brain	10-29860	Spike, C23525T, H644Y

**Table S4. Neutralisation antibody titre of re-infected mouse serum, Related to Figure 4 and 5.**

Group	Mice No.	Neutralisation antibody titre		
		14 days post-infection	21 days post-infection (re-infection day)	26 days post-infection
Naïve infection	3/3	NT	ND	ND
	1	<1:10	<1:10	<1:10
Challenge	2	<1:10	1:40	1:40
	3	<1:10	<1:10	<1:10

NT, not tested. ND, not detected

**Table S5. Viral RNA detection in mice after reinfection, Related to Figure 5.**

Group	Number (M/F)*	Number of viral RNA positive									
		Lung	Brain	Serum	Eye	Heart	Liver	Spleen	Kidney	Intestines	Testis/Ovary
Naïve infection	(1/2)	3/3	2/3	0/3	1/3	3/3	3/3	2/3	3/3	2/3	1/3
Challenge	(1/2)	3/3	0/3	0/3	0/3	1/3	2/3	1/3	2/3	0/3	1/3

\*, M, male, F, female