Supplementary Information for "A live, impaired-fidelity coronavirus vaccine protects in an aged, immunocompromised mouse model" by R.L. Graham, M.M. Becker, L.D. Eckerle, M. Bolles, M.R. Denison, and R.S. Baric



Supplementary Figure 1. Replication advantage of MAwt vs. MA-ExoN. Results from a competition assay using initial proportions of 1:1, 1:10, and 1:100 of MAwt and MA-ExoN favoring either MA-ExoN (**a**) or MAwt (**b**) are shown. Graphs show percentages of MAwt genomes vs. MA-ExoN genomes over five serial passages. Blue bars: MAwt; red bars: MA-ExoN. (**c**) Real-time RT-PCR was used to quantify viral genome RNA from MA-ExoN and MAwt infections. Results are expressed as GAPDH-normalized ratios of MA-ExoN/MAwt.

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Supplementary Figure 2. Mutation accumulation in ORF1a in infected SCID mice at 30 d p.i. Multiple plaque isolates from each mouse lung (see Fig. 4) were sequenced from nts 493–8603. Individual SCID mouse genome sequences are represented by black horizontal lines. Dashed lines separate the nsp sequences in ORF1a. Mutations are indicated by lollipop shapes. Colors are as follows: blue: synonymous; red: nonsynonymous. Common mutations identified between clones are shaded in yellow.



Supplementary Figure 3. Mutation accumulation in ORF1b in infected SCID mice at 30 d p.i. Multiple plaque isolates from each mouse lung (see Fig. 4) were sequenced from nts 12,915–16,520. Individual SCID mouse genome sequences are represented by black horizontal lines. Dashed lines separate the nsp sequences in ORF1b. Mutations are indicated by lollipop shapes. Colors are as follows: blue: synonymous; red: nonsynonymous. Common mutations identified between clones are shaded in yellow.

Mouse/Virus				
Combination	Day 1	Day 2	Day 3	Day 4
STAT ExoN/MAwt	0.1774892	0.01731602	0.004329	0.004329
ExoN STAT/129	0.930736	0.1255412	0.536796	0.662338
MAwt STAT/129	0.082251	0.1774892	0.008658	0.004329
129 ExoN/MAwt	0.1255412	0.082251	0.01731602	0.030303
RAG ExoN/MAwt	0.0079365	0.420634	0.031746	1
ExoN RAG/B6	0.030303	0.930736	0.246754	0.246754
MAwt RAG/B6	0.082251	0.1774892	1	0.536796
B6 ExoN/MAwt	0.588744	0.01515152	0.0021645	0.0930736
SCID ExoN/MAwt	0.181018	0.986466	0.000996702	5.05 × 10⁻⁵
ExoN SCID/BALB	0.581148	0.00262108	1.04 × 10 ⁻⁵	0.0755026
MAwt SCID/BALB	0.068171	1.16 × 10 ⁻⁷	4.08 × 10 ⁻⁶	4.08 × 10 ⁻⁶
BALB ExoN/MAwt	0.846998	8.51 × 10 ⁻⁵	1.55 × 10⁻⁴	1.55 × 10⁻⁴

Supplementary Table 1. *In Vivo* Mann-Whitney *U* Test Results for Weight Loss Differences, Days 1–4 Post-Infection

Significant values (P < 0.05) are displayed in bold font.

SCID Clone	Genome Position	Nucleotide Change	Region	Synonymous (S) or Nonsynonymous (N)	AA Change	Present in Clones*
			Whole genor	me		
MA-ExoN 1.1	1980	T-C	nsp2	S		1.1, 1.2
	2300	T-C	nsp2	Ν	I499T	1.1
	2304	T-C	nsp2	S		1.1, 1.2
	3634	G-A	nsp3	Ν	A306T	1.1, 1.2
	4127	T-C	nsp3	Ν	M470T	1.1, 1.2
	6211	A-G	nsp3	Ν	N1165D	1.1
	7951	G-A	nsp3	Ν	V1745I	1.1, 1.2
	11231	T-C	nsp6	Ν	L110P	
	11405	T-C	nsp6	Ν	V168A	
	13042	T-C	nsp10	Ν	Y30H	1.1, 1.2, 1.3
	14469	A-T	nsp12	N	S367C	1.1, 1.2, 1.3
	14738	T-C	nsp12	S		1.1, 1.2
	15308	T-C	nsp12	S		1.1, 1.2
	16999	C-A	nsp13	Ν	S278Y	1.1, 1.2, 1.3, 2.1
	18238-18239	AT-CC	nsp14	N (ExoN inactivation)	D90A	,
	18244-18245	AG-CC	nsp14	N (ExoN inactivation)	E92A	
	18734	T-C	nsp14	S		
	20431	T-C	nsp15	N	V294A	
	23053	A-C	Spike	N	K521T	
	23638	C-T	Spike	Ν	T716I	
	23678	T-C	Spike	S		
	27304-27323	deletion	ORF7a	I runcates to 17 aa		
	27334	A-G	ORF7a	Part of truncated portion		
	27724	G-A	ORF7b	Creates stop after 28 aa		
	28584		Nucleocapsid	S	אדרכם	
	20949	G-A		N	RZIIN	
WA-EXUN 2.1	321		nsp1	5 9		
	809	U-1 T-C	nsp1	S N	\/2∆	21
	1924	ЧС 6-С	nsp2	N	4374P	2.1
	2506	G-A	nsp2	N	D568N	21
	2599	G-A	nsp2	N	V599I	2.1
	2673	T-C	nsp2	S		2.1
	3054	G-T	nsp3	Ν	E112D	2.1
	3235	A-G	nsp3	Ν	1173V	2.1
	3704	T-C	nsp3	Ν	V329A	2.1
	4076	T-C	nsp3	Ν	D453V	2.1
	4314	T-C	nsp3	S		2.1
	4542	T-G (het)	nsp3	Ν	1608M	2.1
	4610	C-T	nsp3	N	A631V	2.1
	5094	G-A	nsp3	S		2.1
	9499	C-T	nsp4	N	P339S	
	11405	T-C	nsp6	N	V168A	
	11550	C-T	nsp6	S	Fa / a	
	13621	A-G	nsp12	N	E84G	2.1
	14842	A-G	nsp12		N4915	2.1
	10999	C-A	nsp13	IN	52/8Y	1.1, 1.2, 1.3, 2.1
	17185 17693	T-C T-C	nsp13 nsp13	N S	V340A	

Supplementary Table 2. SCID 30-Day Mutations: Whole-Genome, ORF1a, and ORF1b

18238-18239 1824-18245 AT-CC A-G 21579 nsp15 T-C 22378 N (ExoN inactivation) N (ExoN inactivation) D90A E92A 189V 22778 T-G (net) Spike 23321 T-C C Spike Pike RBD S 223983 A-G 225983 A-G C ORF3a N D239G 225983 A-G ORF7a N S33P 225983 A-G ORF7a N S33P 225983 A-G OVITR N/a G193S 7519 T-C Nsp2 N S33P 225983 A-G OVITR N/a G193S 7619 T-C Nsp2 N N33D 3.1 1711 T-C nsp3 N Y184V 2.23,3.1 2248 A-T nsp3 N V1382A 3.1 1711 T-C nsp3 N V1382A 3.1 16659 A-G nsp5 N H149V 3.1 6887 T-C nsp4 N A1419		18083	A-G	nsp14	S		
Image: space of the system of the s		18238-18239	AT-CC	nsp14	N (ExoN inactivation)	D90A	
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10437 0-1 11903 3 10548 A-G nsp5 S 12831 T-C nsp9 S 14046 G-A nsp12 N A226T 3.1 14471 T-A nsp12 N S367R 2.2, 2.3, 3.1 14891 T-C nsp12 N A772V 3.1 16685 C-T nsp14 N F182L J980 18238-18239 AT-CC nsp14 N (ExoN inactivation) D90A 18244-18245 AG-CC nsp14 N (ExoN inactivation) E92A 18233 T-C nsp15 N P111S 20918 T-A nsp16 S 5 21925 G-A Spike S 6145D 22669 T-C Spike RBD N F360L 22664 C-T Membrane N A84V 27084 T-C ORF6 N L4P 27107 G-A		10134		nsp5		L9/R	
10040 1405 1405 1493 3 3 14046 G-A nsp12 N A226T 3.1 14471 T-C nsp12 N S367R 2.2, 2.3, 3.1 14481 T-C nsp12 N A226T 3.1 14891 T-C nsp12 N A772V 3.1 16710 T-C nsp14 N (ExoN inactivation) D90A 18238-18239 AT-CC nsp14 N (ExoN inactivation) E92A 18234-18245 AG-CC nsp14 N (ExoN inactivation) E92A 18244-18245 AG-CC nsp14 N (ExoN inactivation) E92A 18533 T-C nsp16 S P111S 20918 T-A nsp16 S 1445D 21620 T-A Spike N G145D 22669 T-C Spike RBD N F360L 22641 G-T Envelope S 2644 T-C ORF6		10437		nsp5	3 9		
12031 1-C 1893 3 A226T 3.1 14446 G-A nsp12 N A226T 3.1 14471 T-A nsp12 N S367R 2.2,2,3,3.1 14891 T-C nsp12 N A772V 3.1 15685 C-T nsp13 N F182L 3.1 16710 T-C nsp13 N F182L 3.1 18238-18239 AT-CC nsp14 N (ExoN inactivation) D90A 18244-18245 AG-CC nsp14 N (ExoN inactivation) D90A 19881 C-T nsp15 N P111S 20918 T-A nsp16 S 21225 21925 G-A Spike N G145D 22913 T-C Spike RBD S 26341 2204 T-C ORF6 N L4P 27084 T-C ORF6 N A12T 27355 C-T OR		12831	A-G T_C	nsp0	3		
14471 T-A Insp12 N S267R 2.2,3,3.1 14891 T-C nsp12 S A772V 3.1 15685 C-T nsp12 N F182L S 16710 T-C nsp12 N A772V 3.1 18238-18239 AT-CC nsp14 N (ExoN inactivation) D90A 18244-18245 AG-CC nsp14 N (ExoN inactivation) E92A 18533 T-C nsp14 S P111S 20918 T-A nsp16 S P111S 20918 T-A nsp16 S P111S 21620 T-A Spike N G145D 22569 T-C Spike RBD N F360L 22913 T-C Spike RBD S 26648 26648 C-T Membrane N A84V 27084 T-C ORF6 N L4P 27107 G-A ORF7a N		12031	G-A	nsp3	S N	A226T	3.1
Internet Inspire Inspire <thinspire< th=""> <t< th=""><th></th><th>14471</th><th>Ο-Α Τ-Δ</th><th>nsp12</th><th>N</th><th>S367R</th><th>222331</th></t<></thinspire<>		14471	Ο-Α Τ-Δ	nsp12	N	S367R	222331
Instruct Instruct N A772V 3.1 16710 T-C nsp13 N F182L 3.1 18238-18239 AT-CC nsp14 N (ExoN inactivation) D90A 18238-18239 AT-CC nsp14 N (ExoN inactivation) E92A 18533 T-C nsp15 N P111S 18533 T-C nsp16 S 20918 T-A nsp16 S 21925 G-A Spike N 22639 T-C Spike RBD N 26341 G-T Envelope S 26648 C-T Membrane N A84V 27055 C-T ORF6 N L4P 27453 A-G ORF7a N T28I 27453 A-G ORF7a N T61A 28097 T-C Ncleocapsid S 1.1 213138 A-G (het) nsp3 S 1.1 <		14891	T-C	nsp12	S	000/11	3 1
16710 T-C nsp13 N F182L D90A 18238-18239 AT-CC nsp14 N (ExoN inactivation) D90A E92A 18244-18245 AG-CC nsp14 N (ExoN inactivation) E92A 18533 T-C nsp14 S E92A 19881 C-T nsp15 N P111S 20918 T-A nsp16 S 1 21620 T-A Spike S 6145D 22569 T-C Spike RBD N F360L 22913 T-C Spike RBD S 26648 226341 G-T Envelope S 26648 270784 T-C ORF6 N L4P 27107 G-A ORF7a N T28I 27453 A-G ORF7a N T61A 28097 T-C Nucleocapsid S 1.1, 1.2, 1.3, 3.1, 3.3 3138 A-G (het) nsp3 S 1.1, 1.2, 1.3 </th <th></th> <th>15685</th> <th>C-T</th> <th>nsp12</th> <th>N</th> <th>A772V</th> <th>3.1</th>		15685	C-T	nsp12	N	A772V	3.1
18238-18239 AT-CC nsp14 N (ExoN inactivation) D90A 18244-18245 AG-CC nsp14 N (ExoN inactivation) E92A 18533 T-C nsp14 N (ExoN inactivation) E92A 18831 C-T nsp14 S P111S 20918 T-A nsp16 S S 21620 T-A Spike N G145D 22569 T-C Spike RBD N F360L 22213 T-C Spike RBD S S 26648 C-T Membrane N A84V 27084 T-C ORF6 N L4P 27107 G-A ORF6 N A12T 27355 C-T ORF7a N T61A 28097 T-C ORF8b S 1.1, 1.2, 1.3 28266 T-C Nucleocapsid S 1.1, 1.2, 1.3, 3.1, 3.3 3138 A-G (het) nsp3 S 1.1 1.1, 1.2, 1.3		16710	T-C	nsp13	N	F182L	0.1
18244-18245 AG-CC nsp14 N (ExoN inactivation) E92A 18533 T-C nsp14 S P111S 19881 C-T nsp15 N P111S 20918 T-A nsp16 S S 21620 T-A Spike S S 21925 G-A Spike N G145D 22669 T-C Spike RBD N F360L 22913 T-C Spike RBD S S 26648 C-T Membrane N A84V 27084 T-C ORF6 N L4P 27107 G-A ORF6 N A12T 27355 C-T ORF7a N T61A 28097 T-C ORF8b S 1.1, 1.2, 1.3 3138 A-G (het) nsp2 N N490K 1.1, 1.2, 1.3 9690 C-A nsp4 S 1.1, 1.2, 1.3 1.1 1.3, 3.1, 3.3		18238-18239	AT-CC	nsp14	N (ExoN inactivation)	D90A	
18533 T-C nsp14 S P111S 19881 C-T nsp15 N P111S 20918 T-A nsp16 S 2 21620 T-A Spike S 2 22569 T-C Spike RBD N F360L 22913 T-C Spike RBD S 2 26341 G-T Envelope S 2 26648 C-T Membrane N A84V 27084 T-C ORF6 N L4P 27107 G-A ORF7a N T28I 27453 A-G ORF7a N T61A 28097 T-C ORF8b S 2 28266 T-C Nucleocapsid S 1.1, 1.2, 1.3, 3.1, 3.3, 1.1 3138 A-G (het) nsp3 S 1.1, 1.2, 1.3, 3.1, 1.1 4394 C-T nsp4 S 1.1, 1.2, 1.3 9690 C-A nsp4		18244-18245	AG-CC	nsp14	N (ExoN inactivation)	E92A	
19881 C-T nsp15 N P111S 20918 T-A nsp16 S S 21620 T-A Spike S G145D 22569 T-C Spike RBD N F360L 22913 T-C Spike RBD S S 26648 C-T Envelope S S 26648 C-T ORF6 N L4P 27107 G-A ORF6 N L4P 27107 G-A ORF6 N L4P 27107 G-A ORF7a N T28I 27453 A-G ORF7a N T61A 28097 T-C ORF8b S 1.1, 1.2, 1.3, 3.1, 3.3 3138 A-G (het) nsp3 S 1.1 4394 C-T nsp4 S 1.1, 1.2, 1.3 9690 C-A nsp4 S 1.1, 1.2, 1.3 9690 C-A nsp4 S <td< th=""><th></th><th>18533</th><th>T-C</th><th>nsp14</th><th>` S</th><th></th><th></th></td<>		18533	T-C	nsp14	` S		
20918 T-A nsp16 S G145D 21620 T-A Spike S G145D 21925 G-A Spike N G145D 22669 T-C Spike RBD N F360L 22913 T-C Spike RBD S 2 26648 C-T Membrane N A84V 27084 T-C ORF6 N L4P 27107 G-A ORF6 N A12T 27355 C-T ORF7a N T28I 27453 A-G ORF7a N T61A 28097 T-C ORF8b S 1.1, 1.2, 1.3, 3.1, 3.3 3138 A-G (het) nsp2 N N490K 1.1, 1.2, 1.3, 3.1, 3.3 3138 A-G (het) nsp3 S 1.1 1.1, 1.2, 1.3 9690 C-A nsp4 S 1.1, 1.2, 1.3 1.1, 1.2, 1.3 9690 C-A nsp4 S 1.1, 1.2, 1.3 </th <th></th> <th>19881</th> <th>C-T</th> <th>nsp15</th> <th>Ν</th> <th>P111S</th> <th></th>		19881	C-T	nsp15	Ν	P111S	
21620 T-A Spike S 21925 G-A Spike N G145D 22569 T-C Spike RBD N F360L 22913 T-C Spike RBD S		20918	T-A	nsp16	S		
21925 G-A Spike N G145D 22569 T-C Spike RBD N F360L 22913 T-C Spike RBD S 26341 G-T Envelope S 26648 C-T Membrane N A84V 27084 T-C ORF6 N L4P 27107 G-A ORF6 N A12T 27355 C-T ORF7a N T28I 27453 A-G ORF7a N T61A 28097 T-C ORF8b S 1.1, 1.2, 1.3, 3.1, 3.3 3138 A-G (het) nsp2 N N490K 1.1, 1.2, 1.3, 3.1, 3.3 3138 A-G (het) nsp3 S 1.1 1.3, 3.1, 3.3 4394 C-T nsp4 S 1.1, 1.2, 1.3 1.1, 1.2, 1.3 9690 C-A nsp4 S 1.1, 1.2, 1.3 1.1, 1.2, 1.3		21620	T-A	Spike	S		
22569 T-C Spike RBD N F360L 22913 T-C Spike RBD S		21925	G-A	Spike	N	G145D	
22913 T-C Spike RBD S A84V 26341 G-T Envelope S A84V 26648 C-T Membrane N A84V 27084 T-C ORF6 N L4P 27107 G-A ORF6 N A12T 27355 C-T ORF7a N T28I 27453 A-G ORF7a N T61A 28097 T-C ORF8b S 1.1, 1.2, 1.3, 3.1, 3.3 MAwt 1.1 2274 C-A nsp2 N N490K 1.1, 1.2, 1.3, 3.1, 3.3 MAwt 1.1 2274 C-A nsp3 S 1.1 3138 A-G (het) nsp3 S 1.1 4394 C-T nsp3 N T559I 1.1, 1.2, 1.3 9690 C-A nsp4 S 1.1, 1.2, 1.3 18718 C-T nsp14 N T250M		22569	T-C	Spike RBD	N	F360L	
26341 G-T Envelope S A84V 26648 C-T Membrane N A84V 27084 T-C ORF6 N L4P 27107 G-A ORF6 N A12T 27355 C-T ORF7a N T28I 27453 A-G ORF7a N T61A 28097 T-C ORF8b S - 28266 T-C Nucleocapsid S - MAwt 1.1 2274 C-A nsp2 N N490K 1.1, 1.2, 1.3, 3.1, 3.3 3138 A-G (het) nsp3 S 1.1 1.3, 3.1, 3.3 1.1 4394 C-T nsp3 N T559I 1.1, 1.2, 1.3 9690 C-A nsp4 S - 1.1, 1.2, 1.3 18718 C-T nsp14 N T250M -		22913	T-C	Spike RBD	S		
26648 C-T Membrane N A84V 27084 T-C ORF6 N L4P 27107 G-A ORF6 N A12T 27355 C-T ORF7a N T28I 27453 A-G ORF7a N T61A 28097 T-C ORF8b S - 28266 T-C Nucleocapsid S - MAwt 1.1 2274 C-A nsp2 N N490K 1.1, 1.2, 1.3, 3.1, 3.3 3138 A-G (het) nsp3 S - 1.1 4394 C-T nsp3 N T559I 1.1, 1.2, 1.3 9690 C-A nsp4 S - 1.1, 1.2, 1.3		26341	G-T	Envelope	S		
27084 T-C ORF6 N L4P 27107 G-A ORF6 N A12T 27355 C-T ORF7a N T28I 27453 A-G ORF7a N T61A 28097 T-C ORF8b S - 28266 T-C Nucleocapsid S - MAwt 1.1 2274 C-A nsp2 N N490K 1.1, 1.2, 1.3, 3.1, 3.3 3138 A-G (het) nsp3 S 1.1 1.3, 3.1, 3.3 3138 A-G (het) nsp3 S 1.1 4394 C-T nsp3 N T559I 1.1, 1.2, 1.3 9690 C-A nsp4 S - 1.1, 1.2, 1.3 18718 C-T nsp14 N T250M -		26648	C-T	Membrane	N	A84V	
27107 G-A ORF6 N A12T 27355 C-T ORF7a N T28I 27453 A-G ORF7a N T61A 28097 T-C ORF8b S 161A 28266 T-C Nucleocapsid S 1.1, 1.2, 1.3, 3.1, 3.3 MAwt 1.1 2274 C-A nsp2 N N490K 1.1, 1.2, 1.3, 3.1, 3.3 3138 A-G (het) nsp3 S 1.1 1.3, 3.1, 3.3 4394 C-T nsp3 N T559I 1.1, 1.2, 1.3 9690 C-A nsp4 S 1.1, 1.2, 1.3 18718 C-T nsp14 N T250M		27084	T-C	ORF6	N	L4P	
27355 C-1 ORF7a N 1281 27453 A-G ORF7a N T61A 28097 T-C ORF8b S T61A 28266 T-C Nucleocapsid S 1.1, 1.2, 1.3, 3.1, 3.3 MAwt 1.1 2274 C-A nsp2 N N490K 1.1, 1.2, 1.3, 3.1, 3.3 3138 A-G (het) nsp3 S 1.1 1.1, 1.2, 1.3 4394 C-T nsp3 N T559I 1.1, 1.2, 1.3 9690 C-A nsp4 S T250M 1.1, 1.2, 1.3		27107	G-A	ORF6	N	A12T	
27453 A-G ORF7a N 161A 28097 T-C ORF8b S 161A 28266 T-C Nucleocapsid S 161A MAwt 1.1 2274 C-A nsp2 N N490K 1.1, 1.2, 1.3, 3.1, 3.3 3138 A-G (het) nsp3 S 1.1 4394 C-T nsp3 N T559I 1.1, 1.2, 1.3 9690 C-A nsp4 S 1.1, 1.2, 1.3 1.1		27355	C-T	ORF7a	N	T28I	
28097 1-C ORF8D S 28266 T-C Nucleocapsid S MAwt 1.1 2274 C-A nsp2 N N490K 1.1, 1.2, 1.3, 3.1, 3.3 3138 A-G (het) nsp3 S 1.1 1.1 1.1 4394 C-T nsp3 N T559I 1.1, 1.2, 1.3 1.1 9690 C-A nsp4 S T559I 1.1, 1.2, 1.3 1.1 18718 C-T nsp14 N T250M T250M 1.1		2/453	A-G	ORF/a	N	161A	
Z6200 1-C Nucleocapsid S N MAwt 1.1 2274 C-A nsp2 N N490K 1.1, 1.2, 1.3, 3.1, 3.3 3138 A-G (het) nsp3 S 1.1 1.1 4394 C-T nsp3 N T559I 1.1, 1.2, 1.3 9690 C-A nsp4 S T250M		28097		UKF8D	5		
INTAWL 1.1 2274 C-A nsp2 N N490K 1.1, 1.2, 3138 A-G (het) nsp3 S 1.3, 3.1, 3.3 3138 C-T nsp3 N T559I 1.1, 1.2, 1.3 9690 C-A nsp4 S T250M 18718 C-T nsp14 N T250M		28200		Nucleocapsid	5	NIADOLA	1 4 4 0
3138 A-G (het) nsp3 S 1.3, 3.1, 3.3 4394 C-T nsp3 N T559I 1.1, 1.2, 1.3 9690 C-A nsp4 S T250M 1.1, 1.2, 1.3 18718 C-T nsp14 N T250M	iviAwt 1.1	2274	C-A	nsp2	N	N490K	1.1, 1.2,
4394 C-T nsp3 N T559I 1.1, 1.2, 1.3 9690 C-A nsp4 S 1 18718 C-T nsp14 N T250M		3129	$\Lambda (c)$	nen?	c		1.3, 3.1, 3.3 1 1
9690 C-A nsp4 S 15591 1.1, 1.2, 1.3 18718 C-T nsp14 N T250M		1301 1301		nspo nspo	S NI	TEEOI	1.1 111010
18718 C-T nsp14 N T250M		9690	C-A	nen4	S	10081	1.1, 1. 2 , 1.J
		18718	C-T	nsp14	Ň	T250M	

	20528	A-G	nsp15	S		
MAwt 2.1	2819	A-G	nsp3	N	K34R	2.1
	3921	G-A	nsp3	S		2.1, 2.2, 2.3
	4192	T-A	nsp3	N	C492S	2.1, 2.2, 2.3
	5584	C-T	nsp3	S		2.1
	9866	C-T	nsp4	N	T461I	
	20528	A-G	nsp15	S		
MAwt 3.1	2274	C-A	nsp2	N	N490K	1.1, 1.2,
						1.3, 3.1, 3.3
	20528	A-G	nsp15	S		
		(ORF1a (nts 493-	-8603)		
MA-ExoN 1.1	1980	T-C	nsp2	S		1.1, 1.2
	2300	T-C	nsp2	N	1499T	1.1
	2304	T-C	nsp2	S		1.1, 1.2
	3634	G-A	nsp3	N	A306T	1.1, 1.2
	4127	T-C	nsp3	N	M470T	1.1, 1.2
	6211	A-G	nsp3	N	N1165D	1.1
	7951	G-A	nsp3	N	V1745I	1.1, 1.2
MA-ExoN 1.2	1402	C-T	nsp2	N	P200S	1.2
	1980	T-C	nsp2	S		1.1, 1.2
	2304	T-C	nsp2	S		1.1, 1.2
	3634	G-A	nsp3	N	M470T	1.1, 1.2
	4127	T-C	nsp3	N	A306T	1.1, 1.2
	7404	T-A	nsp3	S		1.2
	7951	G-A	nsp3	N	V1745I	1.1, 1.2
MA-ExoN 1.3	872	A-G	nsp2	N	D23G	1.3
	3759	C-T	nsp3	S		1.3
	4896	T-C	nsp3	S		1.3
	5006	T-C	nsp3	N	V763A	1.3
	7452	A-G	nsp3	S		1.3
	8114	G-A	nsp3	N	G1799D	1.3
MA-ExoN 2.1	809	T-C	nsp2	N	V2A	2.1
	1924	G-C	nsp2	N	A374P	2.1
	2506	G-A	nsp2	N	D568N	2.1
	2599	G-A	nsp2	N	V599I	2.1
	2673	T-C	nsp2	S		2.1
	3054	G-1	nsp3	N	E112D	2.1
	3235	A-G	nsp3	N	11/3V	2.1
	3704	1-C	nsp3	N	V329A	2.1
	4076		nsp3	N	D453V	2.1
	4314		nsp3	5	100014	2.1
	4542	I-G (net)	nsp3	N	1608101	2.1
	4610		nsp3	N	A631V	2.1
	5094	G-A	nsp3	5		2.1
MA-EXON 2.2	855		nsp2	S	10417	2.2, 2.3
	865	A-G (net)	nsp2	N	1210	2.2
	1699		nsp2	N C	5299P	2.2
	2487		nsp2	5		2.2
	2595		nsp2	5		2.2
	2041		nsp3	D D D D D D D D D D D D D D D D D D D	1/2004	2.2
	3057		nsp3	IN NI	V 38UA	
	4444		nsp3		Нолст	2.2, 2.3, 3.1
	4014	A-G (net)	nsp3	5		2.2
	4704	A-net	nsp3	l S		2.2, 2.3

	5034	T-C	nsp3	S		2.2, 2.3
	5067	T-C	nsp3	S		2.2, 2.3
	5631	T-C (het)	nsp3	S		2.2
MA-ExoN 2.3	855	T-C	nsp2	S		2.2, 2.3
	3731	A-G	nsp3	N	N338S	2.3
	4444	T-C	nsp3	N	Y576H	2.2, 2.3, 3.1
	4704	A-G	nsp3	S		2.2, 2.3
	4839	T-A	nsp3	S		2.3
	5034	T-C	nsp3	S		2.2, 2.3
	5067	T-C	nsp3	S		2.2, 2.3
	5697	T-C	nsp3	S		2.3
	7379	A-T	nsp3	S		2.3
MA-ExoN 3.1	1516	A-G	nsp2	N	N238D	3.1
	1711	T-C	nsp2	N	S303P	3.1
	2848	A-T	nsp3	N	T44S	3.1
	4444	I-C	nsp3	N	Y576H	2.2, 2.3, 3.1
	6559	A-G	nsp3	N	11281V	3.1
	6803	I-C	nsp3	N	V1362A	3.1
	6887		nsp3	N	M13901	3.1
	6971		nsp3	N	A1419V	3.1
MA-ExoN 3.2	648	I-C (het)	nsp1	S	E 4 61	3.2
	832	I-C (het)	nsp2	N	F10L	3.2
	1108	A-G (net)	nsp2	N	K102E	3.2
	4106	A-C	nsp3	IN N	K4631	3.2, 3.3
	4536	G-A	nsp3	IN N		3.2, 3.3
	5353 5550	A-G (net)	nsp3	IN S	K879E	3.2
	000U	1-C (net)	nsp3	5	T1024A	J.∠ 2.2.2.2
	0010 7001	A-G (net)	nspo non2	IN NI	11034A	3.2, 3.3
	7001		nsp3		L14203	3.2
	8166		nsp3	S S		3233
	83/3	$A_{-}G$ (bet)	nsp3	5		3.2, 3.3
	8361	T ₋ C (het)	nsp3	5		3.2
MA ExoN 3.3	4106		nen3	3	KA63T	3233
	4100	G_A	nsp3	N	M606I	3233
	4 000 5025	T_C (bet)	nsp3	S	WOOOI	33
	5818	Δ_{-G} (het)	nsp3	N	T1034A	3233
	6254		nsp3	N	D1170G	3.2, 3.3
	6462	G-A	nsp3	S	DIIII00	33
	7602		nsp0	5		33
	8166	T-A	nsp3	S		3233
MAwt 1 1	2274	<u>С-А</u>	nsp2	N	NAOOK	1112
	2214	0-7	nəpz		114301	133133
	3138	A-G (het)	nsn3	S		1 1
	4394	C-T	nsp3	N	T559I	11 12 13
MAwt 1 2	2274	<u>С-А</u>	nsp2	N	N490K	1112
1017 (000 1.2		077	11302		14501	133133
	4394	C-T	nsp3	Ν	T559I	11 12 13
MAwt 1.3	2274	C-A	nsp2	N	N490K	11 1 2
		07	hope			133133
	4394	C-T	nsp3	Ν	T559I	1.1. 1.2. 1.3
MAwt 2 1	2819	A-G	nsn3	N	K34R	21
	3921	G-A	nsn3	S		2.1. 2.2. 2.3
	4192	T-A	nsp3	Ň	C492S	2.1, 2.2, 2.3
	· · • • • • • • • • • • • • • • • • • •					,,

	5584	C-T	nsp3	S		2.1
MAwt 2.2	3921	G-A	nsp3	S		2.1, 2.2, 2.3
			·			
	4192	T-A	nsp3	N	C492S	2.1, 2.2, 2.3
MAwt 2.3	3921	G-A	nsp3	S		2.1, 2.2, 2.3
	4192	T-A	nsp3	N	C492S	2.1, 2.2, 2.3
MAwt 3.1	2274	C-A	nsp2	N	N490K	1.1, 1.2,
						1.3, 3.1, 3.3
MAwt 3.2	None					
MAwt 3.3	2274	C-A	nsp2	N	N490K	1.1, 1.2,
						1.3, 3.1, 3.3
	ORF1	<u>b (nts 12,915–</u>	16,520; nt 1699	9 was verified separately)		
MA-ExoN 1.1	13042	T-C	nsp10	N	Y30H	1.1, 1.2, 1.3
	14469	A-T	nsp12	N	S367C	1.1, 1.2, 1.3
	14738	T-C	nsp12	S		1.1, 1.2
	15308	T-C	nsp12	S		1.1, 1.2
	16999	C-A	nsp13	N	S278Y	1.1, 1.2,
						1.3, 2.1
MA-ExoN 1.2	12935	C-T (het)	nsp9	N	A107V	1.2
	13042	T-C	nsp10	N	Y30H	1.1, 1.2, 1.3
	14469	A-T	nsp12	Ν	S367C	1.1. 1.2. 1.3
	14738	T-C	nsp12	S		1.1.1.2
	15308	T-C	nsp12	S		1112
	16999	C-A	nsp12	N	S278Y	1112
	10000	0 / (nopio		02101	1321
MA-EvoN 13	130/2	T_C	nen10	N	V30H	111213
	13541		nsp10	C C	13011	1.1, 1.2, 1.3
	14460		nsp12	S N	S267C	1.0
	14409		nop12		33070	1.1, 1.2, 1.3
	10420	A-G	nsp12	5	0070V	1.0
	10999	C-A	risp 15	IN	32/01	1.1, 1.2,
MA-ExoN 2.1	13621	A-G	nsn12	N	F84G	21
	14842	A-G	nsp12	N	N491S	2.1
	16999	C-A	nsp12	N	S278Y	1112
	10000	07	1130 10		02701	1321
MA-ExoN 2.2	13104	T-C	nsn10	S		2223
	13798	A-G (het)	nsp12	N	K143R	22
	14471	Т-А	nsp12	N	S367R	22 23 31
	14915	T-C (het)	nsp12	S	000/11	2.2, 2.0, 0.1
	16334	T-C (het)	nsp12	S		2.2
MA ExoN 2.2	13104		nsp10	<u>0</u>		2.2
WA-EXUN 2.5	1//71	Τ-C Τ_Δ	nsp10	S N	S367P	2.2, 2.3
	14471		nsp12	IN NI	0007T	2.2, 2.3, 3.1
WA-EXON 3.1	14040	G-A	nsp12	IN NI	A2201	3.1 2.2.2.2.4
	14471	I-A T-C	nsp12		530/R	2.2, 2.3, 3.1
	14091		nsp12	J N	A 7701/	3.1 2.4
	10000			IN N		3.1
MA-EXON 3.2	13380	I-A (het)	nsp12	N	D3E	3.2
	15236	I-C (het)	nsp12	S		3.2
	16177	I-C	nsp13	N	V4A	3.2
MA-ExoN 3.3	14452	T-C	nsp12	N	L361S	3.3
	15698	A-T	nsp12	S		3.3
MAwt 1.1	None					

MAwt 1.2	None			
MAwt 1.3	None			
MAwt 2.1	None			
MAwt 2.2	None			
MAwt 2.3	None			
MAwt 3.1	None			
MAwt 3.2	None			
MAwt 3.3	None			

*Data entered in "Present in Clones" column only if more than one plaque isolate per mouse was sequenced at that nucleotide position.

Virus	SNP	Region	AA	Young	Old	SCID
		-	Change	BALB/c	BALB/c	Clones
MA-ExoN	C1142Y	nsp2	T113I	1/10	0/10	
	A3053R	nsp3	E112G	0/10	1/10	
	T11405Y	nsp6	V168A	0/10	1/10	2/9
	C16999M*	nsp13	S278Y	10/10	10/10	4/9
	G22822R	Spike	R444K	1/10	2/10	
	C23638Y	Spike	T716I	2/10	6/10	1/9
MAwt	T4192A	nsp3	C492S	10/10	10/10	3/9
	T11006C	nsp6	F35S	10/10	10/10	2/9
	C29536Y	3'UTR	n/a	1/10	0/10	

Supplementary Table 3. SNP Results from Short-Term BALB/c Infections

*Upon Sanger sequencing of this allele, mutation frequency was consistently maintained at approximately 40% both *in vitro* and *in vivo*.

Supplementary Table 4. PCR and Sequencing Primers and Amplicon Sets

Primer	Nt position	Sequence*
SURB1F ¹	1–24	ATATTAGGTTTTTACCTACCCAGG
S1F ^A	493–513	TTAAGCACCAATCACGGCCAC
S2aF	1056–1075	CACTTTCAAAGGGGAATGCC
S3F	1577–1596	TTACTGGTGACAATGTGGAG
S4F ^{2,B}	2149–2171	GAATGGATTGAGGCGAAACTTAG
S5F	2743-2764	GGAGAAGATACTGTTTGGGAAG
S6F	3324_3344	TGTTGACATCGTTAAGGAGGC
975 ^C	3861_3880	GAAGCCTGTCGATGTGAAGC
58F ³	4431-4450	CARCOLOTOTOCATOTOCARO
501 S0E	4431-4450	CTICCATCCTCCTCATCTTAC
59F	4909-5009	
	5008-5027	GTTTGGCACATTAACCAGGC
STIAF S10F ^{4,E}	0100-0185	
012F	7210 7240	
513F	7219-7240	
514F	/824-/843	TGATGGCAAGTCCAAATGCG
S15F	8381-8400	
S16F	8935-8954	
S1/aF	9552-9571	
S18F	10084–10103	GACACAGIAIACIGICCAAG
S19F^	10611–10630	TGCTGCTGTTATCAATGGTG
S20F°	11168–11187	GCTGGGTGATGCGTATCATG
S21F	11721–11741	TAAGTTGTTGGGTATTGGAGG
S22aF	12389–12408	CTACAGCAGCCAAACTCATG
S23F	12915–12934	TATGGTGCTGGGCAGTTTAG
S24F'	13450–13469	GTACTGATGTCGTCTACAGG
S25F	14021–14040	CGATTTCGGTGATTTCGTAC
S26F	14548–14569	CTACATGCTTTTCAGTAGCTGC
S27F ^G	15101–15120	GTCAATAGCCGCCACTAGAG
S28F ⁸	15646–15665	CTGATGATGCCGTTGTGTGC
S29aF ^Y	16243–16262	GTTGCAAGTGCTGCTATGAC
S30F	16775–16794	TGACTATGGTGATGCTGTTG
S31aF	17399–17418	GCTGACTAAAGGCACACTAG
S32F ⁹	17931–17951	AGTCTAGAAATACCACGTCGC
S33aF	18569–18588	GATTGGACCTGAAAGAACGT
S34F	19132–19151	ACGTTGATCGTTACCCAGCC
S35F	19706–19726	TGTTGCATTTGAGCTTTGGGC
S36F ¹⁰	20261–20280	TGGAGATTTCAGTCATGGAC
S37F	20801–20820	TGCTGGCTCTGATAAAGGAG
S38aF	21420–21439	GGTAGGCTTATCATTAGAGA
S39F	21924–21944	GGTACACAGACACATACTATG
S40F ¹¹	22491–22510	TTCCCTTCTGTCTATGCATG
S41F	23081–23100	TGGACTCACTGGTACTGGTG
S42aF	23724–23743	CTAAATCGTGCACTCTCAGG
S43F	24263–24282	AACTGCATTGGGCAAGCTGC
S44F ¹²	24851–24870	TGATCCTCTGCAACCTGAGC
S45F	25411–25430	TGGCGTTGCATTTCTTGCTG
S46F	25978–25997	TAAAGACCCACCGAATGTGC
S47F	26590-26609	GTGCTTGCTGCTGTCTACAG
S48F ¹³	27132-27153	GGACTTTCAGGATTGCTATTTG
S49F	27729–27749	CACTCGAAATCCAGGATCTAG
S50F	28273-28292	TCTTGGTTCACAGCTCTCAC
S51F	28840-28860	CAACAACAAGGCCAAACTGTC
S52F	29410-29429	GGCAGATGGGCTATGTAAAC
<u>\$1</u> R	<u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u>_</u> <u></u>	
\$2R	011_031	CGATGTAATCAAGTTGTTCCC
02N 02D	1210 1227	
33K	1310-1337	COACATGIAGIAGGICCIIC

S4R	1877–1896	GATAACACCAGCAGCCTGTG
S5R ^{1,A}	2421-2440	GCTCCTTGCCACGTATACAC
S6R	3063-3082	CCTCACACTCTGCATCGTCC
S7R	3619–3638	GGTGCAAGTAAGATGTCCTG
S8R	4111-4131	GAGCATCTCAGTAGTGCCACC
S9R ^{2,B}	4654-4673	GATGACGAAGTGAGGTATCC
S10R	5301-5322	GTTAGCAGCATCACCAGCACGG
S11R ^C	5819-5838	CGACACAGGCTTGATGGTTG
S12R	6401–6420	GACATTGCCTACAACTTCGG
S13R ^{3,D}	6983-7002	CAATTCTCTAACGCCATTAC
S14R	7514-7533	CTTGCAGAAGCCACGGCCTC
S15aR	8061-8080	CACCATCTAAAGCTACACCC
S16aR ^E	8584-8603	GTGTAACCATCATGGATTGA
S17aR ⁴	9144-9163	CGCATGTACCATGTCTACAG
S18R	9781-9800	GTAAGTGGCAACAGTGTCTC
S19aR	10265-10284	CTTGGGTGTCTTAGGGTTAG
S20R	10884_10903	
S21R ^{5,X}	11512-11532	GATACACTGTAAGGTGTTGCC
S22R	12076-12095	GCCTGCTCATAGGCCTCCTG
S23R	12654-12673	GTGTGGTACCAGCCGCACAG
S24R	13184–13204	GATGGTCAATGTGGCATCTAC
S25R ⁶	13704–13723	CGCTGACGTGATATATGTGG
S26R	14276–14295	GAAGGATACACCTATCATCC
S27R	14811–14830	CAGCCACCATCGTAACAATC
S28aR ^F	15326–15345	ACTCGTTAGCTAACCTGTAG
S29R ⁷	15947-15966	CATCAATAGCCAGTGACACG
S30R ^G	16501–16520	GCCAGCATTAGTCCAATCAC
S31R	17068–17087	CGTATACACTATGCGAGCAG
S32R ^Y	17664-17683	CAAGCAGGATTGCGTGTAAG
S33R ⁸	18248–18268	GCATCTCTAGTTGCATGACAG
S34R	18833–18852	CAACAGACCAATCAACGCGC
S35R	19439–19458	CATCCAAGTACTGTCGGTAC
S36aR	19862–19881	GTTTCTTGGCAATGTCAGTC
S37aR ⁹	20420–20439	GATCAATCACAGAACACACA
S38R	21103–21123	CAGCATTCCAAGAATGCTCTG
S39R	21812–21833	CACCGACTGTGACTTGTTGTTC
S40R	22341-22360	ACAGAGCATTTGAGTTCAGC
S41aR ¹⁰	22765–22784	AGTAGCATCAATGTTCCTAG
S42aR	23343-23362	GTAGAATATATGCGCCAAGC
S43R	23912–23931	CAGCATCAGCGAGTGTCACC
S44aR	24432–24451	TGAAGGCTTTGAAGTCTGCC
S45R ¹¹	24987-25006	GCGACCTCATTGAGGCGGTC
S46R	25552-25571	CCATACCTGCAGCGACAAGC
S47aR	26054–26073	GTCGTCGTCGGCTCATCATA
S48R	26590–26609	CTGTAGACAGCAGCAAGCAC
S49R ¹²	27285–27304	ACAATCAATGTCAGGAAGAG
S50aR	27739–27758	AAGGTTCTTCTAGATCCTGG
S51aR	28330–28349	GTGTTGATTGGAACGCCCTG
S52aR	28869–28888	TAGATGCCTCAGCAGCAGAT
S53aR	29553–29572	CTTTCAAGTCCTCCCTAATG
S54aR ¹³	29682–29701	TCACATGGGGATAGCACTAC

Amplicon-generating primers (1–13, A–G, X, Y) are indicated in superscript next to the relevant primers. Amplicons were sequenced with all primers that fall between the amplicon-generating primers. *All sequences are listed 5'–3'.