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Supplemental information

Identification of a therapeutic interfering particle—A single-dose SARS-CoV-2 antiviral intervention with a high barrier to resistance

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TABLE S1: List and sequences of oligonucleotides used in the study. Related to STAR methods

1	N gene qpcr	fw: aaattttggggaccaggaac rev: tggcacctgtgtaggtcaac
2	E gene qpcr	fw: acaggtacgttaatagttaatagcg rev: atattgcagcagtacgcacac
3	NSP 14 qpcr	fw: tggggytttacrggtaacct rev: aacrcgcttaacaaagcactc
4	mCherry qpcr	fw: gaacggccacgagttcgaga rev: cttggagccgtacatgaactgagg
5	Luciferase qpcr	fw: ttatgccggtgttgggcgc rev: ttttggaaacaaacactacggtaggct
6	TIP	t7 fw: taatacgactcactatagggattaaaggtt rev: ttttttttttttttttgtcattctcctaagaagc
7	mCherry	t7fw:taatacgactcactataatggtgagcaagggcgaggag rev: ttacttgtacagctcgtccatgccgc
8	ORF1a internal rev	tggtgcaagtagaacttcgt
9	Luciferase	t7fw:taatacgactcactataggatggaagacgccaaaaacata rev:ttaggggggggggggagggagcctcctgcaggttaaccttactcgagtttggactt
10	GAPDH qpcr	fw: ttcgacagtcagccgcatctt rev: caggcgcccaatacgaccaaa
12	IFNL1 qpcr	fw: cgccttggaagagtcactca rev: gaagccttaggtcccaattc
13	IL6 qpcr	fw:aacctgaaccttccaaagatgg rev:tctggcttgctcctcactact
14	TNF qpcr	fw:atgagcacggaaagcatgatcc rev:gagggctgaatagagaggggc
15	CCL5 qpcr	fw: aggtctccgtggctgccctcg rev:ggagcacttgccactggtgtg
16	CCL2 qpcr	fw: acctccagcatgaaagtctc rev: aagtgacgggggcattgat
17	ISG20 qpcr	fw: tgagggagagatcaccgatt rev: tagcggctcatgtcctcttt
18	ISG54 qpcr	fw:ggtcttttcagcgtttattggg rev: tgccgtaggctgctctcca
19	CXCL10 qpcr	fw: gtggcattcaaggaatacctc rev: gccttagattctggattcagca
20	M with 3 stopcodons control RNA	t7 m: fw:taatacgactcactatagggatggcagattcctaataataaaacggtactattaccgttg rev with ires overlap: gttaggggggggggggagggattactgtacaagcaaagcaatatt ires fw with s overlap: aatgaaaatggaaccattacagatccctcccccccccctaacg m overlap: atattgctttgcttgtacagtaatccctcccccccccctaac mcherry rev: ttacttgtacagctcgtccatgccgc
21	S with 3 stop codons control RNA	fw:taatacgactcactataggatgtttgtttttaataataacttgttttattgccactagt s rev with ires overlap: cgttaggggggggggggagggatctgtaatggttccattttca ires fw with aatgaaaatggaaccattacagatccctcccccccccctaacg mcherry rev: ttacttgtacagctcgtccatgccgc
22	5’ UTR Control RNA	t7 fw: taatacgactcactatagggattaaaggtt mcherry rev: ttacttgtacagctcgtccatgccgc
23	3’ UTR Control RNA	fw: taatacgactcactataggtccctcccccccccctaac rev: ttttttttttttttttgtcattctcctaagaagc
24	b-actin hamster qpcr	fw: actgccgcatcctcttcct rev: tcgttgccaatggtgatgac
25	TIP1 sequence	attaaaggtttataccttcccaggtaacaaaccaaccaactttcgatctcttgtagatctgttctctaaacgaactttaaaatctgtgtggctg tcactcggctgcatgcttagtgcactcacgcagtataattaataactaattactgtcgttgacaggacacgagtaactcgtctatcttctgc

		aggctgcttacggtttcgtccgtgttgcagccgatcatcagcacatctaggtttcgtccgggtgtgaccgaaaggtaagatggagagccttgtccctggtttcaacgagaaaacacacgtccaactcagtttgcctgttttacaggttcgcgacgtgctcgtacgtggctttggagactccgtggaggaggtcttatcagaggcacgtcaacatcttaaagatggcacttgtggcttagtagaagttgaaaaaggcgttttgcctccctcccccccccctaacgttactggccgaagccgcttggaataaggccggtgtgcgtttgtctatatgttattttccaccatattgccgtcttttggcaatgtgagggcccggaaacctggccctgtcttcttgacgagcattcctaggggtctttcccctctcgccaaaggaatgcaaggtctgttgaatgtcgtgaaggaagcagttcctctggaagcttcttgaagacaaacaacgtctgtagcgaccctttgcaggcagcggaacccccccacctggcgacaggtgcctctgcggccaaaagccacgtgtataagatacacctgcaaaggcggcacaaccccagtgccacgttgtgagttggatagttgtggaaagagtcaaatggctctcctcaagcgtattcaacaaggggctgaaggatgcccagaaggtaccccattgtatgggatctgatctggggcctcggtacacatgctttacatgtgtttagtcgaggttaaaaaacgtctaggccccccgaaccacggggacgtggttttcctttgaagaacacgatgataatatggtgagcaagggcgaggaggataacatggccatcatcaaggagttcatgcgcttcaaggtgcacatggagggctccgtgaacggccacgagttcgagatcgagggcgagggcgagggccgcccctacgagggcacccagaccgccaagctgaaggtgaccaagggtggccccctgcccttcgcctgggacatcctgtcccctcagttcatgtacggctccaaggcctacgtgaagcaccccgccgacatccccgactacttgaagctgtccttccccgagggcttcaagtgggagcgcgtgatgaacttcgaggacggcggcgtggtgaccgtgacccaggactcctccctgcaggacggcgagttcatctacaaggtgaagctgcgcggcaccaacttcccctccgacggccccgtaatgcagaagaagaccatgggctgggaggcctcctccgagcggatgtaccccgaggacggcgccctgaagggcgagatcaagcagaggctgaagctgaaggacggcggccactacgacgctgaggtcaagaccacctacaaggccaagaagcccgtgcagctgcccggcgcctacaacgtcaacatcaagttggacatcacctcccacaacgaggactacaccatcgtggaacagtacgaacgcgccgagggccgccactccaccggcggcatggacgagctgtacaagtaagaccacacaaggcagatgggctatataaacgttttcgcttttccgtttacgatatatagtctactcttgtgcagaatgaattctcgtaactacatagcacaagtagatgtagttaactttaatctcacatagcaatctttaatcagtgtgtaacattagggaggacttgaaagagccaccacattttcaccgaggccacgcggagtacgatcgagtgtacagtgaacaatgctagggagagctgcctatatggaagagccctaatgtgtaaaattaattttagtagtgctatccccatgtgattttaatagcttcttaggagaatgacaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa
26	TIP2 sequence	attaaaggtttataccttcccaggtaacaaaccaaccaactttcgatctcttgtagatctgttctctaaacgaactttaaaatctgtgtggctgtcactcggctgcatgcttagtgcactcacgcagtataattaataactaattactgtcgttgacaggacacgagtaactcgtctatcttctgcaggctgcttacggtttcgtccgtgttgcagccgatcatcagcacatctaggtttcgtccgggtgtgaccgaaaggtaagatggagagccttgtccctggtttcaacgagaaaacacacgtccaactcagtttgcctgttttacaggttcgcgacgtgctcgtacgtggctttggagactccgtggaggaggtcttatcagaggcacgtcaacatcttaaagatggcacttgtggcttagtagaagttgaaaaaggcgttttgcctcaacttgaacagccctatgtgttcatcaaacgttcggatgctcgaactgcacctcatggtcatgttatggttgagctggtagcagaactcgaaggcattcagtacggtcgtagtggtgagacacttggtgtccttgtccctcatgtgggcgaaataccagtggcttaccgcaaggttcttcttcgtaagaacggtaataaaggagctggtggccatagttacggcgccgatctaaagtcatttgacttaggcgacgagcttggcactgatccttatgaagattttcaagaaaactggaacactaaacatagcagtggtgttacccgtgaactcatgcgtgagcttaacggaggggcatacactcgctatgtcgataacaacttctgtggccctgatggctaccctcttgagtgcattaaagaccttctagcacgtgctggtaaagcttcatgcactttgtccgaacaactggactttattgacactaagaggggtgtatactgctgccgtgaacatgagcatgaaattgcttggtacacggaacgttctgaaaagagctatgaattgcagacaccttttgaaattaaattggcaaagaaatttgacaccttcaatggggaatgtccaaattttgtatttcccttaaattccataatcaagactattcaaccaagggttgaaaagaaaaagcttgatggctttatgggtagaattcgatctgtctatccagttgcgtcaccaaatgaatgcaaccaaatgtgcctttcaactctcatgaagtgtgatcattgtggtgaaacttcatggcagacgggcgattttgttaaagccacttgcgaattttgtggcactgagaatttgactaaagaaggtgccactacttgtggttacttaccccaaaatgctgttgttaaaatttattgtccagcatgtcacaattcagaagtaggacctgagcatagtcttgccgaataccataatgaatctggcttgaaaaccattcttcgtaagggtggtcgcactattgcctttggaggctgtgtgttctcttatgttggttgccataacaagtgtgcctattgggttccagaattagatctctcgaggttaacgaattctgctatacgaagttatccctctccctcccccccccctaacgttactggccgaagccgcttggaataaggccggtgtgcgtttgtctatatgttattttccaccatattgccgtcttttggcaatgtgagggcccggaaacctggccctgtcttcttgacgagcattcctaggggtctttcccctctcgccaaaggaatgcaaggtctgttgaatgtcgtgaaggaagcagttcctctggaagcttcttgaagacaaacaacgtctgtagcgaccctttgcaggcagcggaaccccccacctggcgacaggtgcctctgcggccaaaagccacgtgtataagatacacctgcaaaggcggcacaaccccagtgccacgttgtgagttggatagttgtggaaagagtcaaatggctctcctcaagcgtattcaacaaggggctgaaggatgcccagaaggtaccccattgtatgggatctgatctggggcctcggtacacatgctttacatgtgtttagtcgaggttaaaaaacgtctaggccccccgaaccacggggacgtggttttcctttgaagaacacgatgataatatggtgagcaagggcgaggaggataacatggccatcatcaaggagttcatgcgcttcaaggtgcacatggagggctccgtgaacggccacgagttcgagatcgagggcgagggcgagggccgcccctacgagggcacccagaccgccaagctgaaggtgaccaagggtggccccctgcccttcgcctgggacatcctgtcccctcagttcatgtacggctccaaggcctacgtgaagcaccccgccgacatccccgactacttgaagctgtccttccccgagggcttcaagtgggagcgcgtgatgaacttcgaggacggcggcgtggtgaccgtgacccaggactcctccctgcaggacggcgagttcatctacaaggtgaagctgcgcggcaccaacttcccctccgacggccccgtaatgcagaagaagaccatgggctgggaggcctcctccgagcggatgtaccccgaggacggcgccctgaagggcgagatcaagcagaggctgaagctgaaggacggcggccactacgacgctgaggtcaagaccacctacaaggccaagaagcccgtgcagctgcccggcgcctacaacgtcaacatcaagttggacatcacctcccacaacgaggactacaccatcgtggaacagtacgaacgcgccgagggccgccactccaccggcggcatggacgagctgtacaagtaaatttgcccccagcgcttcagcgttcttcggaatgtcgcgcattggcatggaagtcacaccttcgggaacgtggttgacctacacaggtgccatcaaattggatgacaaagatccaaatttcaaagatcaagtcattttgctgaataagcatattgacgcatacaaaacattcccaccaacagagcctaaaaaggacaaaaagaagaaggctgatgaaactcaagccttaccgcagagacagaagaaacagcaaactgtgactcttcttcctgctgcagatttggatgatttctccaaacaattgcaacaatccatgagcagtgctgactcaactcaggcctaaactcatgcagaccacacaaggcagatgggctatataaacgttttcgcttttccgtttacgatatatagtctactcttgtgcagaatgaattctcgtaactacatagcacaagtagatgtagttaactttaatctcacatagcaatctttaatcagtgtgtaacattagggaggacttgaaagagccaccacattttcaccgaggccacgcggagtacgatcgagtgtacagtgaacaatgctagggagagctgcctatatggaagagccctaatgtgtaaaattaattttagtagtgctatccccatgtgattttaatagcttcttaggagaatgacaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa

Table S2: Parameters used for simulating within-host upper and lower respiratory tract infection. Related to Figure 1 and Figure S1. With exception of ρ and ψ, all parameters were obtained from (Ke et al., 2020), which resulted from calibration to clinical samples. Sensitivity analysis to the initial viral inoculum ($V_1(t = 0)$) was varied from 1 to 100, where 100 is at the limit of detection. *For entries where a set of nine values is listed in brackets, this corresponds to the nine individual patient simulations.

Parameter	**Description**	**Value**
$T_1(t = 0)$	Initial target cells in URT	4 x 10^6 cells
$T_2(t = 0)$	Initial target cells in LRT	4.8 x 10^8 cells
$I_1(t = 0)$	Initial infected cells in URT	0 cells
$V_1(t = 0)$	Initial virus in URT	1-100 virion swab^{-1}
c	Virus and TIP clearance rate	10 day^{-1}
k	Rate of progression to productive infection (1/k is eclipse period)	4 day^{-1}
Γ	Virus and TIP transport rate from URT to LRT	0.001 swab ml^{-1} day^{-1}
β_T	Infectivity (URT)	*[21.45 x 10^{-6}, 1.31 x 10^{-6}, 13.35 x 10^{-6}, 2.4 x 10^{-6}, 1.41 x 10^{-6}, 6.94 x 10^{-6}, 18.21 x 10^{-6}, 5.12 x 10^{-6}, 1.53 x 10^{-6}] swab^{-1} day^{-1}
δ_1	Death rate of infected cells (URT)	*[0.86, 1.82, 1.16, 3.55, 1.42, 0.76, 0.38, 3.53, 4.06] day^{-1}
π_T	Virus production (URT)	*[3.68, 15.53, 11.61, 11.53, 12.47, 5.89, 8.74, 4.5, 9.65] swab^{-1} day^{-1}
β_S	Infectivity (LRT)	*[0.17 x 10^{-7}, 0.8 x 10^{-7}, 2.63 x 10^{-7}, 1.35 x 10^{-7}, 1.06 x 10^{-7}, 0.17 x 10^{-7}, 9.19 x 10^{-7}, 4.9 x 10^{-7}, 0.29 x 10^{-7}] ml^{-1} day^{-1}
δ_2	Death rate of infected cells (LRT)	*[2.2, 2.18, 4.17, 1.6, 2.17, 3.33, 0.41, 2.04, 3.96] day^{-1}
π_S	Virus production (LRT)	*[10.89, 2.46, 1.67, 1.7, 1.08, 10.34, 0.15, 1.64, 8.15] ml^{-1} day^{-1}
t_T	Target cell extension timing	*[14.7, 15, 6.5, 15.7, 22, 17.3, 17.85, 8.3, 17.11] days

$\log_{10} T_N$	Number of new target cells that appear in LRT, log 10	*[8.21, 8.44, 7.92, 10.99, 8.21, 8.79, 9, 6.89, 9.47]
w	Adaptive immune response parameter	*[0.06, 0.18, 0, 2.4, 0, 0.15, 0.22, 1.89, 0.66] day^{-1}
ρ	Production rate of TIP genomes relative to SARS-CoV-2 genomes in cells containing both TIP and wildtype virus	1.5
ψ	Production rate of SARS-CoV-2 genomes in cells containing both TIP and wildtype virus, compared to the production rate of SARS-CoV-2 genomes containing only wildtype virus	0.02

Table S3. Parameters used for within-host model cross-validation. Related to Figure 1 and Figure S1G.

Patient ID	γ	β	δ	V_0
Singapore 2	3.998	6.64×10^{-6}	0.71	6605
Singapore 3	3.999	1.26×10^{-6}	0.43	6380
Singapore 4	3.999	5.81×10^{-6}	0.72	6514
Singapore 6	3.999	3.08×10^{-6}	0.47	6498
Singapore 8	3.997	1.96×10^{-5}	0.36	6850
Singapore 9	3.999	1.56×10^{-5}	0.28	6558
Singapore 11	3.999	8.46×10^{-6}	1.38	6860
Singapore 12	3.999	7.77×10^{-6}	0.78	6506
Singapore 14	3.997	3.52×10^{-7}	1.03	5337
Singapore 16	3.999	4.88×10^{-6}	0.54	6489
Singapore 17	3.998	1.32×10^{-6}	1.01	5891
Singapore 18	3.999	5.80×10^{-6}	0.38	6537
China C	4.002	7.95×10^{-6}	1.29	6596
China D	3.999	1.69×10^{-6}	0.76	6752
China E	3.999	5.87×10^{-6}	0.84	6517
China H	3.999	1.05×10^{-5}	1.45	7059
China I	3.999	6.15×10^{-7}	0.45	6251
China L	3.999	1.73×10^{-6}	0.77	6178
China O	3.999	4.57×10^{-5}	1.9	8541
China P	3.997	1.02×10^{-5}	1.03	6808
Germany 1	3.999	7.28×10^{-6}	0.98	6610
Germany 2	3.999	2.88×10^{-6}	1.51	6262
Germany 3	3.999	1.11×10^{-5}	1.32	5894
Germany 4	3.996	6.65×10^{-6}	1.6	6678
Germany 7	3.999	3.08×10^{-6}	1.11	6259
Germany 8	3.999	3.29×10^{-6}	1.08	6375
Germany 10	3.999	2.67×10^{-6}	0.61	6268
Germany 14	3.996	8.91×10^{-6}	1.61	6350
Korea 13	3.999	9.67×10^{-6}	1.15	7674
Korea 15	3.999	1.44×10^{-5}	1.16	5802