

Supplementary information

Genetically modified mouse models to help fight COVID-19

In the format provided by the authors and unedited

General notes

- The information presented in the first two columns of the Table 1 (included in the main article) is copied here for the convenience to the reader.

Model #	Name
1	B6.mAce2 ^{KO} -hACE2 ^{KI}
2	B6.mAce2 ^{KO} -hACE2-P2A-EGFP ^{KI}
3	NSG.mAce2 ^{KO} -hACE2 ^{KI}
4	NSG.mAce2 ^{KO} -hACE2-P2A-EGFP ^{KI}
5	BALB/c.mAce2 ^{KO} -hACE2 ^{KI}
6	BALB/c.mAce2 ^{KO} -hACE2-P2A-EGFP ^{KI}
7	B6.mAce2 ^{KI-31K,82M,353K}
8	NSG.mAce2 ^{KI-31K,82M,353K}
9	BALB/c.mAce2 ^{KI-31K,82M,353K}
10	B6.mAce2 ^{KO} -hACE2-P2A-hTMPRSS2 ^{KI}
11	NSG.mAce2 ^{KO} -hACE2-P2A-hTMPRSS2 ^{KI}
12	BALB/c.mAce2 ^{KO} -hACE2-P2A-hTMPRSS2 ^{KI}
13	B6.mAce2 ^{KO} -hACE2-IRES-hTMPRSS2 ^{KI}
14	NSG.mAce2 ^{KO} -hACE2-IRES-hTMPRSS2 ^{KI}
15	BALB/c.mAce2 ^{KO} -hACE2-IRES-hTMPRSS2 ^{KI}
16	ROSA26 ^(ACTB-Lox-hACE2-P2A-tdT-Lox-EGFP)
17	ROSA26 ^(ACTB-Lox-hACE2-IRES-tdT-Lox-EGFP)
18	ROSA26 ^(ACTB-Lox-tdT-Lox-hACE2-P2A-EGFP)
19	ROSA26 ^(ACTB-Lox-tdT-Lox-hACE2-IRES-EGFP)
20	Ai63-TIGRE-TRE-hACE2-P2A-tdT
21	Ai63-TIGRE-TRE-hACE2-IRES-tdT
22	B6.mAce2 ^{ckKO} -hACE2 ^{ckKI}
23	NSG.mAce2 ^{ckKO} -hACE2 ^{ckKI}
24	BALB/c.mAce2 ^{ckKO} -hACE2 ^{ckKI}
25	B6.mAce2 ^{ckKO} -hACE2-P2A-hTMPRSS2 ^{ckKI}
26	NSG.mAce2 ^{ckKO} -hACE2-P2A-hTMPRSS2 ^{ckKI}
27	BALB/c.mAce2 ^{ckKO} -hACE2-P2A-hTMPRSS2 ^{ckKI}
28	B6.mAce2 ^{ckKO} -hACE2-IRES-hTMPRSS2 ^{ckKI}
29	NSG.mAce2 ^{ckKO} -hACE2-IRES-hTMPRSS2 ^{ckKI}
30	BALB/c.mAce2 ^{ckKO} -hACE2-IRES-hTMPRSS2 ^{ckKI}

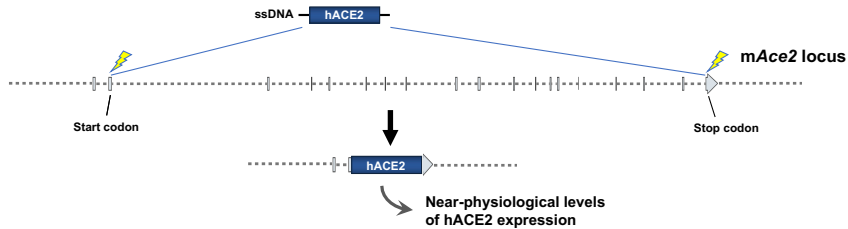
- The rationale for creating these models, and their advantages/disadvantages are described in the main article, wherever possible. Additional information relevant to specific models is included as 'notes' at the beginning the description for each model.
- For convenience, we have included schematics and parts of the figures that are presented in the main article.
- The nucleotide sequences of all the designs and the constructs were derived from the sequences available from ensemble.org web portal. Specifically, all sequences used for guide design are from the C57BL/6 mouse strain, even though some proposed models are meant to be created in other strains (NSG/NOG and BALB/c). We strongly recommend that researchers double-check the accuracy of the sequences and designs before proceeding with generating the model(s).
- Various elements in the schematics, and the nucleotide sequences, are displayed with matching colors.

Models #2 #4 and #6

- 2) *B6.mAce2^{KO}-hACE2-P2A-EGFP^{KI}*
- 4) *NSG.mAce2^{KO}-hACE2-P2A-EGFP^{KI}*
- 6) *BALB/c.mAce2^{KO}-hACE2-P2A-EGFP^{KI}*

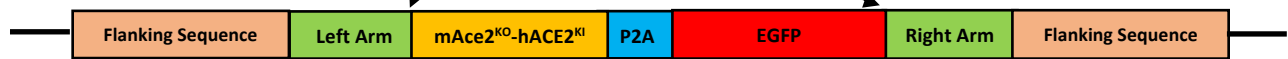
Notes:

- a. The goal is to swap the insertion cassette into the *mAce2* genomic locus between the start and stop codons. All the mouse introns between the coding exons will be deleted.
- b. The mouse sequence was derived from the transcript, https://uswest.ensembl.org/Mus_musculus/Transcript/Exons?db=core;g=ENSMUSG00000015405;r=X:164139332-164188420;t=ENSMUST00000112271. Exon 1 is noncoding.



Sequence near the insertion site (the cleavage location expected for the chosen guide RNA is marked as '/').

cggggaagatgtccagctcc/tcctgg:::ccttt/agcaaagcactgtcatcttctg



Left gRNA Sequence - GAAAGATGTCCAGCTCCTCC [TGG]

Right gRNA Sequence - ATGACAAGTGCTTTGCTAAA [AGG]

Sequence of the *mAce2^{KO}-hACE2-P2A-EGFP^{KI}* ssDNA donor:

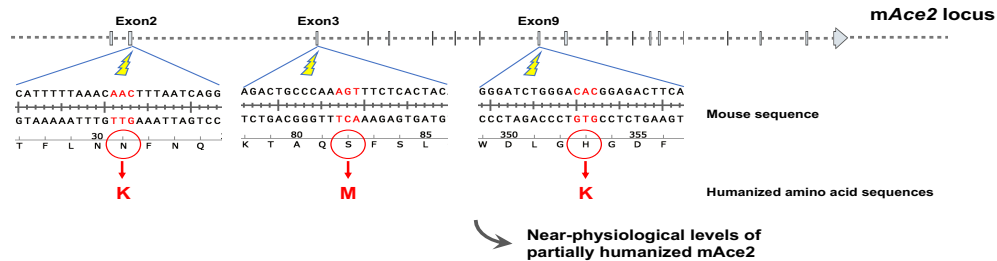
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TTTCTAGGATTAATGAATAACATGTCTTTATTTAGTTTACTTAAAAAATCATTCTAAAATATCTGTTTACATATCTGTCTCTCCAGGATTAACCTTCATAT
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AAAACTCATGAAGAGATTTTACTCTAGGGAAGTTGCTCAGTGGATGGGATCTTGGCGCACGGGGAAAGATGTCAGCTCaTCTGGCTCCTTCTCAGCC
TTGTGCTGTAACTGTCTCAGTCCACCTTGAAGAACAGCCCAAGCATTTTTGGACAAGTTTAAACCAGAACCCAAAGACCTGTTCTATCAAAGTTC
ACTTGTCTTGTGAATTATAACCACTAATTACTGAAGAGAATGTCCAAAACATGAATAATGCTGGGGACAAATGGTCTGCCTTTTTAAAGGAAAGCAGTCC
ACACTTGCCCAAAATGTATCCACTACAAGAAATTCAGAATCTCACAGTCAAGTTCAGCTGCAGGCTCTTCAGCAAAATGGGTCTTCAGTGTCTCAGAAG
ACAAGAGCAAAACGGTTGAACAAATCTAAATACAATGAGCACCATCTACAGTACTGGGAAAGTTTGTAAACCAGATAATCCACAAGAAATGCTATTACT
TGAAACAGGTTGAATGAATAATGGCAACAGTTAGACTACAATGAGAGGCTCTGGGCTTGGGAAAGCTGGAGATCTGAGGTCGGCAAGCAGCTGA
GGCCATATATGAAGAGTATGTGGTCTTGAATAATGAGATGGCAAGAGCAAAATCATTATGAGGACTATGGGGATTATTGGAGAGGAGACTATGAAGTAA
ATGGGGTAGATGGCTATGACTACAGCCGCGCCAGTTGATTGAAGATGTGGAACATACCTTTGAAGAGATTAACCCATATATGAACATCTCATGCTT
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AAATCTGTACTTTTGACAGTTCCTTTGGACAGAAACCAACATGATGTACTGTAGTCAATGGTGGACCAAGGCTGGGATGCCAGAGAATATTCAA
GGAGGCCGAGAAGTTCTTGTATCTGTTGGTCTTCTAATATGACTCAAGGATCTGGGAAAATTCATGCTAACGGACCCAGGAAATGTTTCAGAAAAGC
AGTCTGCCATCCACAGCTTGGGACCTGGGGAAGGGCGACTTCAGGATCCTTATGTGCACAAAGGTGACAAATGGACGACTTCTGACAGCTCATCATGA
GATGGGGCATATCCAGTATGATATGGCATATGCTGCACAACTTTCTGTCTAAGAAATGGAGCTAATGAAGGATTCCATGAAGCTGTTGGGGAATCAT
GTCACTTCTGACGCCACCTAAGCATTAAAAATCCATTGGTCTTCTGTCAACCCGATTTTCAAGAAGACAATGAAACAGAAATAAACTTCTGCTCAA
CAAGCACTCAGGATGTTGGGACTGTGCCATTTACTTACATGTTAGAGAAGTGGAGTGGATGGTCTTTAAAGGGGAAATTCCTCAAGACCAAGTGGATG
AAAAAGTGGTGGGAGATGAAGCGAGAGATAGTTGGGGTGGTGGAACTGTGCCCATGATGAAACATACTGTGACCCCGCATCTCTGTTCCATGTTTCT
AATGATTACTCATTTCATCGATATACAAAGACCTTTAACAATTCAGTTTCAAGAAAGCATTGTCAAAGCAGCTAAACATGAAGGCCCTGACACA
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TAATTTGAAACCAAGAAATCTCCTTAAATTTCTTTGTCAGTGCACCTAAAATGTGCTGATATCATTCCTAGAAGTGAAGTTGAAAAGGCCATCAGGATG
TCCCGGAGCCGTATCAATGATGCTTTCCGCTGTAATGACAACAGCCTAGAGTTTCTGGGATACAGCCAACACTTGGACCTCTAACCCAGCCCTGTT
TCCATATGGCTGATTGTTTTGGAGTTGTATGGGAGTGTATGGTGGTGGCATTGTCATCTTGAATCTTCACTGGGATCAGAGATCGGAAAGAAGAAAAT
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GGTGGTGGCCATCTGGTTCAGCTGGACGGCGAGTAAACGGCCACAAGTTTCAAGCTGTCCGGGAGGGCGAGGGCGATGCCACTACGGCAAGCTG
ACCTGAAGTTTCACTGCACACCCGCAAGCTGCCGCTGCCCTGGCCACCCTCGTGAACCCCTGACTACGGCGTGCAGTGTCTCAGCCGCTACCCC
GACCACATGAAGCAGCAGCACTTCTCAAGTCCGCCATGCCGAAGGCTACGCTCAGGAGCGCACCATCTTCTCAAGGACGACGGCAACTACAAGACC
CGCGCCGAGGTGAAGTTCGAGGGCGACACCTGGTGAACCCGATCGAGCTGAAGGGATCGACTTCAAGGAGGACGGCAACATCTGGGGACAAGCT
GGAGTCAACTACAACGCCACAACGCTATATCATGCCCAGCAAGCAGAAGAAGCCGATCAAGGTGAACCTCAAGATCCGCCACAACATCGAGGACG
GCAGCTCAGCTCGCCGACCACTACAGCAGAAACACCCCATCGGCGACGGCCCGCTGCTGCTGCCGCAACCACTACCTAGCAGCCGATCCCGCC
CTGAGCAAAAGCCCAAGCAGAGAAGCGGATCACATGGTCTGTGAGTTCGTGACCCGCGGGATCACTCTGGCATGGACGAGCTGTACAAGTA
ATAGAAAAGCACTTGTCTCTTCTTGTATGTAATGCTAACTTCATGATACACAATAATGAGAGTATACACATGTCAATAGTATCAAAAATATGATCT
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GTTTATTAATAGAGATGTTTATCTTAGCATA
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Models #7, #8 and #9

- 7) *B6.mAce2*^{KI-31K, 82M, 353K}
- 8) *NSG.mAce2*^{KI-31K, 82M, 353K}
- 9) *BALB/c.mAce2*^{KI-31K, 82M, 353K}

Notes:

- a. The goal is to create point mutations changing the coding sequence of *mAce2* to that of *hACE2*.
- b. There are three amino acid differences between *mACE2* and *hACE2* that are thought to be important for binding to the SARS-CoV-2 spike protein: N31K, S82M and H353K (Luan, et al., 2020. *Biochem. Biophys. Res. Commun.* **526**, 165–169).



mACE2^{KI-31K}

Additional note for the 31K mutation: Human and mouse ACE2 differ in this exonic region by three amino acids; 30, 31 and 34. Because they are close to each other, and because there is no gRNA site close to codon 31, we propose changing codons 30 (N to D) and 34 (Q to D) in addition to 31 (N to K) by using two flanking guide RNAs to remove the entire region and replace it with the complete humanized sequence.

Wild type Sequence (codons 30, 31 and 34 are shown in bold)

GGAAAGATGTCCAGCTCCTCCTGGCTCCTTCTCAGCCTTGTTGCTGTTACTACTGCTCAGTCCCTCACCGAGGAAAA
 TGCCAAGACATTTTTTAAACAACTTTAATCAGGAAGCTGAAGACCTGTCTTATCAAAGTTCACCTTGCTTCTTGAAT
 TATAATACTAACATTACTGAAGAAAATGCCCA

Left gRNA Sequence - TACTGCTCAGTCCCTCACCG [AGG]

Right gRNA Sequence - CAAGTGAACCTTTGATAAGAC [AGG]

31K Donor Sequence

GGAAAGATGTCCAGCTCCTCCTGGCTCCTTCTCAGCCTTGTTGCTGTTACTACTGCTCAGTCCCTCACCGAAGAAAA
 TGCCAAGACATTTTTTAA**g4CAAA**TTTAAT**g4c**GAAGCTGAAGA**g**CTGTCTTATCAAAGTTCACCTTGCTTCTTGAATTAT
 AATACTAACATTACTGAAGAAAATGCCCA

Note: Yellow highlighted, lower case letters are the silent mutations introduced to prevent Cas9 re-cleavage. The codons that are changed are highlighted in red.

mACE2^{KI-82M}

Wild type Sequence (codon 82 is shown in bold)

AGTGAGGCTGCAGCCAAATGGTCTGCCTTTTATGAAGAACAGTCTAAGACTGCCCAA**AGT**TTCTCACTACAAGAA
 ATCCAGACTCCGATCATCAAGCGTCAACTACAGGCCCTTCAGCAA

gRNA Sequence - TTCTTGATGAGAACTTT [GGG]

82M Donor Sequence

AGTGAGGCTGCAGCCAAATGGTCTGCCTTTTATGAAGAACAGTCTAAGACTGCCCAA**Atg**TTCTCACTACAAGAA
 TCCAGACTCCGATCATCAAGCGTCAACTACAGGCCCTTCAGCAA

mACE2^{KI-353K}

Wild type Sequence (codon 353 is shown in bold)

GCTGACTGAGCCAGCAGATGGCCGGAAAGTTGTCTGCCACCCACAGCTTGGGATCTGGGAC**CAC**GGAGACTTCAG
 GTAGTTGGGTTGTCACTTACAGTGCAGCTACTAAGTGAGAAACAG

gRNA Sequence - ACAGCTTGGGATCTGGGACA [CGG]

353K Donor Sequence

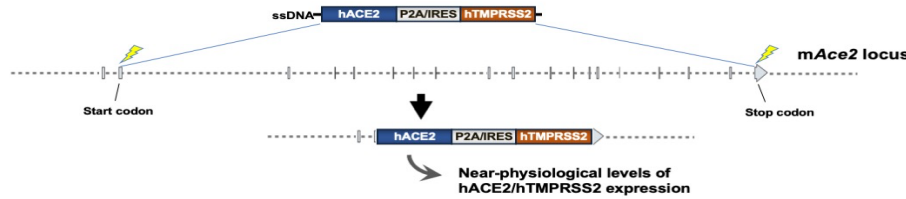
GCTGACTGAGCCAGCAGATGGCCGGAAAGTTGTCTGCCACCCACAGCTTGGGATCTGGGA**aAg**GGAGACTTCAGG
 TAGTTGGGTTGTCACTTACAGTGCAGCTACTAAGTGAGAAACAG

Models #10, #11 and #12

- 10) *B6.mAce2^{KO}-hACE2-P2A-hTMPRSS2^{KI}*
- 11) *NSG.mAce2^{KO}-hACE2-P2A-hTMPRSS2^{KI}*
- 12) *BALB/c.mAce2^{KO}-hACE2-P2A-hTMPRSS2^{KI}*

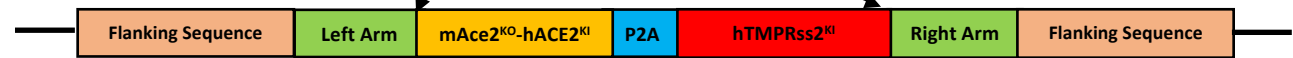
Notes:

- a. The goal is to swap a hACE2-P2A-hTMPRSS2 cassette into the *mAce2* locus between the start and stop codons in three different genetic backgrounds. All the mouse introns between the coding exons will be deleted.
- b. The mouse sequence was derived from the transcript; https://uswest.ensembl.org/Mus_musculus/Transcript/Exons?db=core;g=ENSMUSG0000015405;r=X:164139332-164188420;t=ENSMUST00000112271. Exon 1 is noncoding.



Sequence near the insertion site (the cleavage location expected for the chosen guide RNA is marked as '/').

cggggaaagatgtccagctcc/tcctgg:::ccttt/agcaaagcactgtcatcttctg



Left gRNA Sequence - GAAAGATGTCCAGCTCCTCC [TGG]

Right gRNA Sequence - ATGACAAGTGCTTTGCTAAA [AGG]

Sequence of the *mAce2^{KO}-hACE2-P2A-hTMPRSS2^{KI}* ssDNA donor:

TATAGTAAATCATAGTACACCCTCCTCCAGTGTATCTTTAAACAGCTTTAAAGGAACATATTAACATAAATGTCAGGTTTTGATTGGCCATAAAATGTTAGCAAA
GCTAAGGTTTTCTAGGATTAATGAATAACATGCTTTATTTAGTTTAACTTAAATAAATCACTTAAATAATATCTGTTTACATACTGCTCTCCAGGATTAACITCATAT
TGGTCCAGCAGCTTGTTACTGTTCTCTCTGTTCTTCTGCTTTTTTTCTCTCTCTCAGTGCCCAACCAAGTTCAAAGGCTGATGAGAGAGAAAACTCA
TGAAGAGATTTTACTAGGGAAAGTTGCTCAGTGGATGGGATCTTGGCGCACGGGGAAAGATGTCAGCTCaTGTGGCTCTCTCAGCCITGTTGCTGTAACCTGC
TGCTCAGTCCACCATTGAGGAACAGGCCAAGACATTTTGGACAAGTTTAAACCACGAAGCCGAAGACCTGTCTATCAAAGTTCACITGCTCTTGGAAATTATAAC
CAATATTACTGAAGAGAATGTCACAAACATGAATAATGCTGGGGACAAATGGTCTGCCTTTTTAAAGGAACAGTCCACACTGGCCAAATGTATCCACTACAGAAAT
TCAGAATCTCACAGTCAAGCTTCAGCTGCAGGCTCTCAGCAAAATGGGCTTCAGTGTCTCAGAAAGACAAGAGCAAACCGTTGAACCAAAATCTAAATACAAATGAG
CACCATCTACAGTACTGGAAAGTTTGAACCCAGATAATCCACAAAGAAATGCTTAACTTGAACCAAGTTCGAATGAAATAATGGCAAAAGTTCAGACTACAATGA
GAGGCTCTGGGCTTGGAAAGCTGGAGATCTGAGGTCGCAAGCACTGAGGCTGAGGCTTATATGAAGAGATGTGGTCTTGAATAATGAGATGGCAAGGCAAAATCATT
ATGAGGACTATGGGATTTTGGAGAGGAGACTATGAAGTAAATGGGGTAGATGGCTATGACTACAGCCGGGCCAGTTGATTGAAGATGTGGAACATACCTTTGAA
GAGATTAACCCATTATGAACATCTTCATGCCATGTGAGGGCAAGGTGATGAATGCCATCTCTCTATATCAGTCCAATTTGGATGGCTCCCTGCTCATTGTGCTG
GTGATATGGGGTAGATTTTGGACAATCTGTACTCTTTGACAGTTCCTTTGGACAGAAACCAATAGATGTTACTGTGCAATGGTGGACCAGGCCCTGGGATG
CACAGAGAATTTCAAGGAGGCCGAGAAGTCTTTGTATCTGTTGGTCTTCCTAATATGACTCAAGGATTTGGGAAAAATCCATGCTAACCGGACCAGGAAATGTT
AGAAAGCAGTCTGCCATCCACAGCTTGGGACCTGGGAAAGGGCGACTTCAGGATCTTATGTCACAAAGGTGACAATGGACGACTCTCTGACAGCTCATATGAG
ATGGGCGATATCCAGTATGATATGGCATATGCTGCACAACCTTTCTGCTGAAGAAATGGAGCTAAAGAAAGGATTCATGAAGCTGTGGGAAAAATCATGCTACTTCT
GCAGCCACCTAAGCATTTAAATCAATTTGGTCTCTGTCACCCGATTTTCAAGAAGACAATGAAACAGAAATAAACCTCTGCTCAAAACCAAGCTCAGCATTTGTT
GGGACTCTGCCATTTACTTACTATGTTAGAGAAGTGGAGGTGGATGGTCTTTAAAGGGAAATTTCCAAAGACCAAGTGGATGAAAAAGTGGTGGGAGATGAAGCGAGA
GATAGTGGGGTGGTGGAACTGTGCCCATGATGAACATACTGTGACCCCGCATCTGTGTCATGTTCTTAATGATTACTCATTCAITCGATATACACAAGGAC
CCTTTACCAATTCAGTTTCAAGAAGCACTTTGTCAAGCAGCTAAACATGAAGGCCCTCTGCACAAATGTGACATCTCAAACCTACAGAAGCTGGACAGAAACTGTT
CAATATGCTGAGGCTTGGAAAAATCAGAACCTGGACCCTAGCATTGGAAAAATGTTGAGGAGCAAAAGAACATGAATGTAAGGCCACTGTCTCAACTCTTTGAGCCCT
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TTGACTCCAAGCAAGCAAAATGACATTCGCTGATGAAGCTGCAGAAGCTGACTTTAACAAGCACTAGTGAACCCAGTGTGTCTGCCAACCCAGGATGA
TGCTGCAGCCAGAACAGCTCTGCTGGATTTCCGGGTGGGGGGCCACCGAGGAAAGGAAAGACTCAGAAAGTGTGAACCGCTGCCAAGGTGCTTCTCATTGAGAC
ACAGAGCTCAACAGCAGATATGCTATGACAACCTGATCACACAGCCATGATCTGTGCCGGTCTCTGAGGGGAACGTCGATTCTTGGCAGGGTGGACAGTGGAG
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GTATTCAGGACTGGATTTATCGACAATGAGGGCAGACGGCTCAAAAGGACTGTCATCTTCTGCTGATGTAATGCTAACTTCATAGTACACAAAATGAGAGTA
TACACATGCTATTAGCTATCAAAAAGTATGATCTGTTCAAGTAAACCTGTGCCAAAGCATCAAGCTTGAAGTGGACATCTTCACTGACATTGCTTCAAGTATTTATCT
GCCTAAGGATTTGACATCTCTCTGTTTATTAATAGAGATGTTTATCTTAGCATAAAAGAGGGAAATGTGCCCTTGGCCTCACAGCTATCCAGGGTATGATGTTGG

Additional note: Lower case letters in the beginning of hACE2 cDNA are the silent mutations introduced to prevent Cas9 re-cleavage.

Model #16: ROSA26^(ACTB-Lox-hACE2-P2A-tdT-Lox-EGFP)

Notes:

- The purpose is to create a constitutive expression model for hACE2 with reporter capability.
- The design strategy is to insert a 'hACE2-P2A' cassette upstream of the tdTomato sequence by re-engineering the mTmG locus of mouse strain; <https://www.jax.org/strain/007576> Muzumdar et al. 2007, A global double-fluorescent Cre reporter mouse *Genesis*;45(9):593-605. doi: 10.1002/dvg.20335). The source of the mTmG cassette sequence is from the Addgene plasmid 17787 (<https://www.addgene.org/17787/sequences/>).



Sequence near the start codon of the mT region (ATG shown in uppercase) and the cleavage location of the chosen guide RNA is marked as '/':

tatacgaagttatattaaggggttccggatc/cATGggttgctgttttctccaagaccatg



gRNA sequence: ATTAAGGGTTCGGATCCAT [GGG]. It cleaves 1bp upstream of the ATG.

Sequence of the ROSA26^(ACTB-Lox-hACE2-P2A-tdT-Lox-EGFP)KI ssDNA:

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GGCGCAGGGACTTCCTTTGTCCCAAATCTGTGCGGAGCCGAAATCTGGGAGGCGCCGCCGACCCCTCTAGCGGGCGCGGGGCGAAGCGGTGCGGC
GCCGGCAGGAAGGAAATGGGCGGGGAGGGCCCTTCGTGCGTCCGCGCGCCGCGCTCCCTTCTCCCTCTCCAGCCTCGGGGCTGTCGCGGGGGGACG
GCTGCCTTCGGGGGGACGGGGCAAGGGCGGGTTCGGCTTCTGGCGTGTGACCGGGCGCTCTAGAGCCTCTGCTAACCATGTTTCATGCCCTTCTCTTT
TTCTACAGCTCTGGCAACGTGCTGGTTATTGTGCTGTCTCATCATTTTGGCAAAGAATTGATTTGATACCAGCGGGCTCGACACTAGTGAACCTCTTC
GAGGGACCTAATAACTTCGTATAGCATACTATACGAAAGTTATATTAAGGGTTCGGGATCCATGCAAGCTCTCTCGGCTCTTCAGCCCTGTGTC
TGTAACCTGCTGCTCAGTCCACCAATTGAGGAACAGGCCAAGACATTTTGGACAAGTTTAAACCACGAAGCCGAAGACCTGTTCTATCAAAGTTCACCTGCT
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GGCAAAGTTGATGAATGCCTATCCTTCTATATACAGTCCAATTTGGATGCCCTCCCTGCTCATTGTGCTTGGTATATGTGGGGTATGATTTGGACAAATCTG
TACTCTTTGACAGTTCCTTTGGACAGAAACCAACATAGATGTTACTGATGCAATGGTGGACAGGCCCTGGGATGCACAGAGAATATTCAAGGAGGCC
GAGAAGTTCTTTGATCTGTGGTCTTCCATAATGACTCAAGGATTCGGGAAAATCCATGCTAACGGACCCAGGAAATGTTCAAGAACAGTCTGCC
ATCCCACAGCTGGGACCTGGGGAAGGGGACTTCAGGATCCTATGTGCACAAAGGTGACAAATGGACGACTTCTGACAGCTCATCATGAGATGGGG
CATATCCAGTATGATATGGCATATGCTGCACAACTTTTCTGCTAAGAAATGGAGTAAATGAAGGATTCATGAAGCTGTGGGGAAATCATGTCACCTT
CTGCAGCCACACTAAGCATTAAATCCATTTGCTTCTGTACCCGATTTCAAGAAGACAATGAAACAGAAATAAATCTCTGCTCAAAACAAGCACT
CACGATTTGGGACTCTGCCATTTACTTACATGTTAGAGAAGTGGAGGTGGATGGTCTTTAAAGGGGAAATTCCAAAGACCCAGTGGATGAAAAAGTG
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ATCTCAAACCTACAGAAAGCTGGACAGAACTGTTCAATATGCTGAGGCTTGGAAAATCAGAACCCCTGGACCCATGCAATGGAAAATGTTGTAGGAGCA
AAGAACATGAATGTAAGGCCACTGCTCAACTACTTTGAGCCCTTATTACCTGGCTGAAAGACCAGAACAAAGAATTCCTTTGGGGATGGAGTACCAG
TGGAGTCCATATGCAGACCAAGCATCAAAGTGAGGATAAGCCTAAAATCAGCTCTTGGAGATAAAGCATATGAATGGAACGACAATGAAATGTACCTG
TTCCGATCATCTGTTGCATATGCTATGAGGCAGTACTTTTAAAGTAAATAATCAGATGATCTTTTGGGGAGGAGGATGTGCGAGTGGCTAATTTGA
AACCAAGAAATCTCCTTTAATTTCTTTGTCAGTGCACCTAAAATGTGCTGATATCATTCCTAGAAGTGAAGTGAAGGAGCCATCAGGATGTCCCGGAG
CCGATATCAATGATGCTTTCCGCTGGAATGACAAACAGCCCTAGAGTTTCTGGGATACAGCCAAACACTTGGACCTCCTAACCCAGCCCTTTCATATGG
CTGATTTGTTTTGGAGTTGTATGGGAGTATGTTGGTGGCATTGTGATCTCTGATCTTCACTGGGATCAGAGATCGGAAGAAGAAAAATAAAGCAAGA
AGTGGAGAAAAATCCTTATGCTCCTATCGATATTAGCAAAGGAGAAAAATAATCCAGGATTCAAAACACTGATGATGTTACAGACCTCCTTTGGAAAGCGGA
GCTACTAACTTCAGCCTGCTGAAGCAGGCTGGAGACGTGGAGAGAACCCCTGGACCTGGTTGCTGTTTTCTCCAAGACCATGGTGGAGCAAGGGAGAGGA
GGTCAATCAAGAGTTCAATGCGCTTCAAGGTGCGCATGGAGGGCTCATGAACCGGCCAGGATTCGAGATCGAGGGGCGAGGGGCGGAGCCCGCCCTACG
AGGGCACCAGACCCGCAAGTGAAGGTGACCAAGGGCGGCCCTTCCCTTCGCTGGGACATCCTGTCCCCCACTGATCATGCTGCTCAAGGGC
TACGTGAAGCACCCTCCGACATCCCGATTACAAGAAGCTGTCTTCCCGAGGGCTTCAAGTGGGAGCGCGTGAATGAACCTTCAGGACCGGGCTCT
GGTGACCTGACCCAGGACTCCTCCCTGCAGGACGGCACGCTGATCTACAAGGTGAAGATGCGCGGCACCAACTTCCCCCGACGGCCCGTAAATGC
AGAAGAAGACCATGGGCTGGGAGGCTCCACCGAGCGCTGTACCCCGCGACGGCC
    
```


Model #17: ROSA26^(ACTB-Lox-hACE2-IRES-tdT-Lox-EGFP)

Notes: Same as model #16 except that IRES is used instead of P2A.



Sequence near the start codon of the mT region (ATG shown in uppercase) and the cleavage location of the chosen guide RNA is marked as '/':

tatacgaagttatattaagggttccggatc/cATGggttgctgttttctccaagaccatg



gRNA sequence: ATTAAGGGTTCGGATCCAT [GGG]. It cleaves 1bp upstream of the ATG.

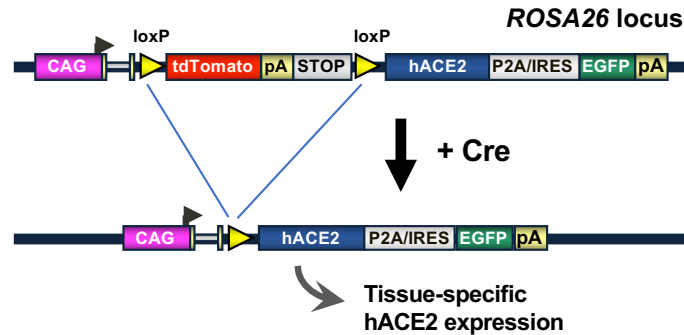
Sequence of the ROSA26^{(ACTB-Lox-hACE2-IRES-tdT-Lox-EGFP)KI} ssDNA:

```
GGCGCAGGGACTTCCTTTGTCCAAATCTGTGCGGAGCCGAAATCTGGGAGGCGCCGCCACCCCTCTAGCGGGCGCGGGGGC
AAGCGGTGCGGGCGCCGGCAGGAAGGAAATGGGCGGGGAGGGCCTTCGTGCGTCCGCCGCCGCCCTCCCTTCTCCCTCTCCAG
CCTCGGGGCTGTCCGCGGGGGACGGCTGCCTTCGGGGGGACGGGCGAGGGCGGGGTTCCGGCTTCTGGCGTGTGACCGGGCGG
TCTAGAGCCTCTGTAACCATGTTTCATGCCTTCTTTCTTTCTACAGCTCTGGGCAACGTGCTGGTTATTGTGCTGTCTCATCAT
TTTGGCAAAGAATTGATTTGATACCGGGGCTCGACACTAGTGAACCTTTCGAGGGACCTAATAACTTCGTATAGCATAACATTAT
ACGAAGTTATATTAAGGGTTCGGATCCATGTCAAGCTTTCCTGGCTCCTTCAGCCTTGTGTGCTGTAAGTCTGCTCAGTCCAC
CATTGAGGAACAGGCCAAGACATTTTGGACAAGTTTAAACCAGAACGCGAAGCCGAAAGACCTGTTCTATCAAAGTTCAGTCTTGG
ATTATAACACCAATATTACTGAAGAGAATGTCCAAAAATGAATAATGCTGGGGACAAATGGTCTGCCTTTTTAAAGGAACAGTCC
ACACTTGCCCAAATGTATCCACTACAAGAAATTCAGAATTCACAGTCAAGCTTCAGCTGCAGGCTTTCAGCAAATGGGCTTTC
AGTGTCTCAGAAGACAAGGCAACCGTTGAACACAATTTAAATACAATGAGCACCATCTACAGTACTGGAAAAGTTTGTAAACC
CAGATAATCCACAAGAAATGCTTACTTGAACCAAGTTTGAATGAAATAATGGCAAACAGTTAGACTACAATGAGAGGCTCTGG
GCTTGGGAAAGCTGGAGATCTGAGGTCGGCAAGCAGCTGAGGCCATTATATGAAGAGTATGTGGTCTTGAATAATGAGATGGCAA
GAGCAAATCATTATGAGGACTATGGGGATTATTGGAGAGGAGACTATGAAGTAAATGGGGTAGATGGTATGACTACAGCCGGCGG
CCAGTTGATTGAAGATGTGGAACATACCTTTGAAGAGATTAACCATATATGAACATCTTCATGCCTATGTGAGGGCAAAGTTGA
TGAATGCCTATCCTTCTATATCAGTCCAATTGGATGCCTCCCTGCTCATTGTGTTGGTATATGTGGGGTAGATTTTGGACAAATC
TGTACTCTTTGACAGTTCCTTTGGACAGAAACCAACATAGATGTTACTGATGCAATGGTGGACAGGCCCTGGGATGCACAGAGA
ATATTCAAGGAGGCCGAGAAGTCTTTGTATCTGTTGGTCTTCCTAATATGACTCAAGGATTTCTGGGAAAATTCATGTAAACGGA
CCCAGAAATGTTTCAGAAAGCAGTCTGCCATCCCACAGCTTGGGAGCTGGGGAAGGGCGACTTCAGGATCCTTATGTGCACAAAG
GTGACAAATGGACGACTTCTGACAGCTCATCATGAGATGGGGCATATCCAGTATGATGGCATATGCTGCACAACCTTTTCTGCT
AAGAAATGGAGCTAATGAAGGATTCATGAAGCTGTTGGGGAATCATGTCACTTTCTGCAGCCACACCTAAGCATTAAATCCA
TTGGTCTTCTGTCACCCGATTTCAAGAAGACAATGAACAGAAATAAATTCCTGCTCAAACAAGCACTCAGGATTTGGGACTC
TGCCATTTACTATGTTAGAGAAGTGGAGGTGGTGTCTTTAAAGGGGAAATCCCAAAGACCAGTGGATGAAAAAGTGGTGG
GAGATGAAGCGAGAGATAGTTGGGGTGGTGAACCTGTGCCCATGATGAAACATACTGTGACCCCGCATCTCTGTTCCATGTTTC
TAATGATTAATCATTTCGATATTACACAAGGACCCTTACCAATTCAGTTCGAAGAAGCACTTTGTCAAGCAGCTAAACATGA
AGGCCCTTGCACAAATGTGACATCTCAAACCTCAAGACTTGCAGAACTGGACAGAAACTGTTCAATATGCTGAGGCTTGGAAATCAGAAC
CCTGGACCCTAGCATTGGAAAATGTTGTAGGAGCAAAGAACATGAATGTAAGGCCACTGCTCAACTACTTTGAGCCCTTATTTACC
TGGTGAAAAGACCAGAACAGAATCTTTTGTGGGATGGAGTACCGACTGGAGTCCATATGCAGACCAAAGCATCAAAGTGAGGA
TAAGCCTAAAATCAGCTCTTGGAGATAAAGCATATGAATGGAACGACAATGAAATGTACCTGTTCCGATCATCTGTTGCATATGCT
ATGAGGCAGTACTTTTTAAAAGTAAAAAATCAGATGATTCCTTTTGGGGAGGAGGATGTGCGAGTGGCTAATTTGAAACCAAGAAT
CTCCTTTAATTTCTTTGTCACTGCACCTAAAAATGTGTCTGATATCATTCCTAGAACTGAAGTTGAAAAGGCCATCAGGATGTCCCG
GAGCCGATCAATGATGCTTCCGCTGAATGACAACAGCCTAGAGTTTCTGGGGATACAGCCAACACTTGGACCTCCTAACCAGC
CCCCGTTTCCATATGGCTGATTGTTTTGGAGTTGTATGGGAGTGATAGTGGTGGCATTGTCATCCTGATCTTCACTGGGATCA
GAGATCGGAAGAAGAAAAATAAAGCAAGAAGTGGAGAAAAATCCTTATGCCTCCATCGATATTAGCAAAGGAGAAAAATAATCCAGG
ATTCCAAAACACTGATGATGTTCAAGACTCCTTTAGCCCCCTCCTCCCTCCCCCCCCCTAACGTTACTGGCCGAAGCCGCTTGGAA
AAGCCGGTGTGCGTTTGTCTATATGTTATTTCCACCATATTGCCGCTCTTTGGCAATGTGAGGGCCCGGAAACCTGGCCCTGTC
TCTGTGACGAGCATTCTAGGGGCTTTCCCTCTCGCCAAAGGAATGCAAGGCTGTTGAATGTCGTGAAGGAAGCAGTTCCTCT
GGAAGCTTCTTGAAGACAACAACGCTGTGAGCGACCTTTGCAGGCAGCGGAACCCCCACCTGGCGACAGGTGCTCTGCGGC
CAAAAGCCACGTGATAAGATACACCTGCAAAGCGGCACAACCCCACTGCGCCAGTGTGAGTGGATAGTGTGGAAAGATCA
AATGGCTTCTCCTAAGGATTCAACAAGGGGCTGAAGGATCCCCAGAAAGTACCCATTGTATGGGATGTGATGGGCTTCG
GTGCACATGCTTACATGTGTTAGTCAGGTTAAAAAACGCTAGGCCCCCCGAACCAGGGGACGTGGTTTTCTTTGAAAAA
CACGATGATAAGGTTGCTGTTTCCAAAGACCATGGTGAAGGAGGAGGAGGTCATCAAAGAGTTTATCGGCTTCAAGGTCCG
CATGGAGGGCTCCATGAACGGCCAGTTCGAGATCGAGGGCGAGGGCGAGGGCCGCCCTACGAGGGCACCCAGACGGCCAA
GCTGAAGGTGACAAAGGGCGCCCTGCTGCTGCGCTGGGACATCTGCTCCCGCAGTTCATGTACGGCTCAAAGGCGTACGTG
AAGCACCCTGCGACATCCCGATTACAAGAAGCTGCTCTCCCGAGGGCTTCAAGTGGGAGCGCGTGATGAACTTCGAGGACG
GCGGTCTGGTGACCGTGACCCAGGACTCCTCCTGCAAGGACGGCACGCTGATCTACAAGGTGAAGATGCGCGGCACCAACTCC
CCCCAGCGCCCGTAATGCAGAAGAAGACATGGGCTGGGAGGCTCCACCGAGCGCTGTACCCCGCGACGGCG
```

Model #18: ROSA26^(ACTB-Lox-tdT-Lox-hACE2-P2A-EGFP)

Notes:

- The purpose is to create a CRE-activatable expression model for hACE2 with reporter capability.
- The design strategy is to insert a 'hACE2-P2A' cassette upstream of the EGFP sequence by re-engineering the mTmG locus of the mouse strain; <https://www.jax.org/strain/007576> (Muzumdar et al. 2007, A global double-fluorescent Cre reporter mouse *Genesis*;45(9):593-605. doi: 10.1002/dvg.20335). The source of the mTmG cassette sequence was from the Addgene plasmid 17787 (<https://www.addgene.org/17787/sequences/>).



Sequence near the start codon of the mG region (ATG shown in uppercase) and the cleavage location of the chosen guide RNA is marked as '/':

ttaagggttccggatcatcaccgcg/ATGggttgctgtttctccaagaccgcagcg

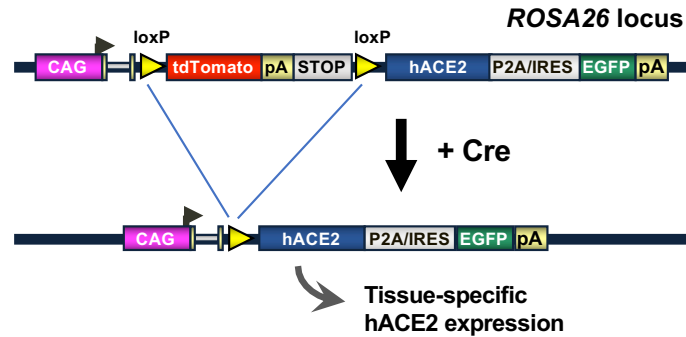


gRNA sequence: GAGAAACAGCAACCCATCCG [CGG]. It cleaves immediately upstream of the ATG sequence of the ROSA26^{(ACTB-Lox-tdT-Lox-hACE2-P2A-EGFP)^{KI}} ssDNA donor.

```
GGTTTGTCCAAACTCATCAATGTATCTTATCATGTCTGGATCTGACATGGTAAGTAAAGCTTGGGCTGCAGGTCGAGGGACCTAATAAAGTTCGTATAGCATACTTATA
CGAAGTATATTAAGGGTTCGGGATCACCAGCGGATGTC AAGCTCTTCTGGTCTCTCTCAGCCTTGTGCTGTAAGTCTGCTCAGTCCACCATTGAGGAAACAG
GCCAAGACATTTTGGACAAGTTAAACCAGGAAGCCGAAGACCTGTTCTATCAAAGTTCACITGCTTCTTGGAAATTATAACACCAATATTAAGTGAAGAGAATGTCCAA
AACATGAATAATGCTGGGGACAAATGGTCTGCCITTTTAAAGGAACAGTCCACACTTGCCTAAATGTATCCACTACAAGAAATTCAGAAATCTCAGAGTCAAGCTTCAG
CTGCAGGCTCTTCAGCAAAATGGGTCTTCAGTGTCTCAGAAAGCAAGAGCAAAACGGTTGAACACAATTTCAAATACAATGAGCACCATCTACAGTACTGGAAAAGTT
TGTAACCCAGATAATCCACAAGAATGCTTATTACTTGAACCAAGTTTGAATGAAAATAATGGCAAAACAGTTTAGACTACAATGAGAGGCTCTGGGCTTGGGAAAAGCTGG
AGATCTGAGGTCGGCAAGCAGCTGAGGCCATTATATGAAGAGTATGTGGTCTTGAAGAAATGAGATGGCAAGAGCAAAATCATTATGAGGACTATGGGGATTATTGGAG
AGGAGACTATGAAGTAAATGGGGTAGATGGCTATGACTACAGCCGGCCAGTTGATTGAAGATGGGAACATACCTTTGAAGAGATTAACCAATTATATGAACATC
TTATGCTTATGTGAGGGCAAGTTGATGAATGCCTATCCTTCTATATCATGCTCAAATTTGGATGCCTCCCTGCTCAATTTGCTTTGGTGTATGTGGGGTAGATTTTGA
CAAATCTGACTCTTTGACAGTTCCCTTTGGACAGAAACCAACATAGATGTTACTGATGCAATGGTGGACAGGCCCTGGGATGCACAGAGAAATTTCAAGGAGGCC
GAGAAGTCTTTGTATCTGTTGGTCTTCTTAATATGACTCAAGGATTTCTGGAAAATTTCCATGCTAACGGACCCAGGAAATGTTCAAGAAAGCAGTCTGCCATCCACA
GCTTGGGACCTGGGAAAGGGGACTTCAGGATCCTTATGTGCACAAAGTGACAAATGGACGACTTCTGACAGCTCATATGAGATGGGGCATATCCAGTATGATAT
GGCATATGCTGCACAACCTTTTCTGCTAAGAAATGGAGCTAATGAAGGATTCATGAAGCTGTTGGGAAATCATGTCACTTTCTGCAGCCACACCTAAGCAATTTAAA
ATCCATTGGTCTTCTGTCAACCCGATTTTCAAGAAAGACAATGAAACAGAAATAAACTTCTGCTCAAACAGCACTCACGATTGTTGGGACTCTGCCATTTACTTACATG
TTAGAGAAAGTGGAGGTGGATGGTCTTTAAAGGGGAAATTTCCAAAGACCAGTGGATGAAAAGTGGTGGGAGATGAAAGCAGAGATAGTTGGGGTGGTGGAACTG
TGCCCATGATGAACACTACTGTGACCCCGCATCTCTGTTCCATGTTTCTAATGATTAATCAATTCGATATACACAAGGACCCCTTACCAATTCAGITTTCAAGA
AGCAGCTTTGCAAGCAGCTAAACATGAAGGCCCTCTGCACAAATGTGACATCTCAAACCTACAGAAAGCTGGACAGAAACTGTTCAATATGCTGAGGCTTGGAAAATC
AGAACCCTGGACCTAGCATTTGAAAATGTTGTAGGAGCAAAGAATGAATGTAAGGCCACTGCTCAACTACTTTGAGCCCTTATTTACTGGCTGAAAAGCCAGA
ACAAGAAATCTTTTGGGATGGAGTACCGACTGGAGTCCATATGCAGACCAAGCAATCAAAGTGAAGGATAAGCCTAAAATCAGCTCTTGGAGATAAAGCATATGAA
TGGAACGACAAATGAAATGTACCTGTTCCGATCATCTGTGATATGCTATGAGGCAGTACTTTTAAAAGTAAAATAATCAGATGATTTCTTTGGGGAGGAGGATGTG
CGAGTGGCTAATTTGAAACCAAGAAATCTCCTTTAATTTCTTTGTCACTGCACCTAAAATGTGTCTGATATCATTCTAGAACTGAAGTTGAAAAGGCCATCAGGATGT
CCCGAGCCGTATCAATGATGCTTCCGCTGGAATGACAACAGCCTAGAGTTTCTGGGGATACAGCCAACTTGGACCTCTAACAGCCCTCTTTCCATATGCC
TGATTTGTTTGGAGTTGTGATGGGAGTGATAGTGGTGGCATTCCTGATCTTCACTGGGATCAGAGATCGGAAGAAGAAAATAAAGCAAGAAAGTGGAGAA
AATCCTTATGCCTCCATCGATATTAGCAAAGGAGAAAATAATCCAGGATTTCCAAAACACTGATGATGTTTCAGACCTTTTGGAAAGCGGAGCTACTACTTCAGCCTG
CTGAGCAGGCTGGAGACGTGGAGGAGAACCCTGGACCTATGGGTTGCTGTTTCTCCAAGACCCGACGGAAGGGAGAAGCCGCCGGGAGAGGCTGGGGAGGCG
GCTGTGGCTCTGCTCCAAAGCGAACGGACAGGAGAATGGCCACGTGAAGGTAGGATCCGTGAGCAAGGGCGAG
```

Model #19: ROSA26^(ACTB-Lox-tdT-Lox-hACE2-IRES-EGFP)

Notes: Same as model #18 except that IRES is used instead of P2A.



Sequence near the start codon of the mG region (ATG shown in uppercase) and the cleavage location of the chosen guide RNA is marked as '/':

ttaagggttccggatcatcaccgcg/ATGggttgctgtttctccaagaccgcagcg



gRNA sequence: GAGAAACAGCAACCCATCCG [CGG]. It cleaves immediately upstream of the ATG

Sequence of the ROSA26^{(ACTB-Lox-tdT-Lox-hACE2-IRES-EGFP)KI} ssDNA:

```
GGTTGTCCAAACTCATCAATGTATCTTATCATGTCTGGATCTGACATGGTAAGTAAAGCTTGGGCTGCAGGTCGAGGGACCTAATA
ACTTCGTATAGCATAACATTATAACGAAGTTATATTAAGGGTTCGGGATCATCACCCGGATGTCAAGCTCTTCTGGCTCCTTCTCAG
CCTTGTGCTGTAAGTCTGCTCAGTCCACCATTGAGGAACAGGCCAAGACATTTTGGACAAGTTAAACCACGAAGCCGAAGACC
TGTTCTATCAAAGTTCACCTTGGCTTCTTGGAAATATAACACCAATATTACTGAAGAGAATGTCCAAAACATGAATAATGCTGGGGACA
AATGGTCTGCCTTTTAAAGGAACAGTCCACACTTGCCCAAATGTATCCACTACAAGAAAATTCAGAATCTCACAGTCAAGCTTCAGC
TGCAGGCTCTTCAGCAAAATGGGCTCTCAGTGTCTCAGAAGACAAGAGCAAACCGTTGAACA CAATTCTAATAACAATGAGCACC
ATCTACAGTACTGGAAAAAGTTGTAACCCAGATAATCCACAAGAAATGCTTACTTGAACCAGGTTTGAATGAAATAATGGCAAAAC
AGTTAGACTACAATGAGAGGCTCTGGGCTTGGGAAAGCTGGAGATCTGAGGTCTGAGGTCGGCAAGCAGCTGAGGCCATTTATGAAGT
ATGTGGTCTTGA AAAATGAGATGGCAAAGACAAATCATTATGAGGACTATGGGGATTATTGGAGAGGAGACTATGAAGTAAATGG
GGTAGATGGCTATGACTACAGCCCGCGCCAGTTGATTGAAGATGTGGAACATACCTTTGAAGAGATTAAACCATTATATGAACATC
TTCATGCCTATGTGAGGGCAAAGTTGATGAATGCCTATCCTTCCTATATCAGTCCAATGGATGCCTCCCTGCTCATTGTGCTTGGTG
ATATGTGGGGTAGATTTTGGACAAATCTGTACTCTTGGACAGTTCCCTTTGGACAGAAAACCAACATAGATGTTACTGATGCAATG
GTGGACCAGGCTGGGATGCACAGAGAATATTCAAGGAGGCCGAGAAGTCTTTGTATCTGTTGGTCTTCTAATATGACTCAAGG
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CAGCCACACCTAAGCATTTAAAATCCATTGGTCTTCTGTCAACCCGATTTTCAAGAAGACAATGAAACAGAAAATAAACTTCTGCTCA
AACAAGCACTACGATTGTTGGGACTCTGCCATTTACTTACATGTTAGAGAAGTGGAGGTGGATGGTCTTTAAAGGGGAAAATCCC
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GTGACCCCGCATCTCTGTTCCATGTTTCTAATGATTACTCATTTCATTCGATATTACACAAGGACCCCTTACCAATTCCAGTTTCAAG
AAGCACTTTGTCAAGCAGCTAAACATGAAGGCCCTCTGCACAAATGTGACATCTCAAACCTCTACAGAAGCTGGACAGAAAATGTTT
AATATGCTGAGGCTTGGAAAATCAGAACCCTGGACCCTAGCATTTGGAAAATGTTGTAGGAGCAAAGAACATGAATGTAAGGCCACT
GCTCAACTACTTTGAGCCCTTATTTACCTGGCTGAAAGACCCAGAAACAAGAATTCCTTTTGTGGGATGGAGTACCGACTGGAGTCCAT
ATGCAGACCAAAGCATCAAAGTGAGGATAAGCCATAAATCAGCTCTTGGAGATAAAGCATATGAATGGAACGACAATGAAATGTAC
CTGTTCCGATCATCTGTTGCATATGCTATGAGGCACTTTTTTAAAGTAAAAAATCAGATGATTCTTTTTGGGGAGGAGGATGTG
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GTTGAAAAGGCCATCAGGATGTCCCGGAGCCGATCAATGATGCTTTCGCTGTAATGACAACAGCCTAGAGTTTCTGGGGATACA
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ATTAGCAAAGGAGAAAATAATCCAGGATTCAAAACCTGATGATGTTTTCAGACCTCCTTTTAGCCCCTCCCTCCCTCCCTCCCTAA
CGTACTGGCCGAAGCCGTTGGAATAAGGCCGGTGTGCGTTTGTCTATATGTTATTTCCACCATATTGCCGCTTTTGGCAATGT
GAGGCGCCGGAAAACCTGGCCCTGTCTTCTGACGAGCATCTTACAGGGCTTTCCCTCTCGCCAAAGGAATGCAAGGTCTGTTGA
ATGTCGTGAAGGAAGCAGTCTCTGGAAGCTTCTGGAAGCTTCTGAAGACAACAACAGTCTGTAGCGACCTTTGCAGGCAGCAACCCCA
CCTGGCGACAGGTGCCTCTGCGGCCAAAAGCCACGTGTATAAGATACACCTGCAAAGGCGGCACAACCCAGTGCACGTTGTGA
GTTGGATAGTTGTTGAAAAGAGTCAAATGGCTCTCCTCAAGCTTTTCAACAGGTGTTAAAGGGGCTGAAGGATGCCAGAGGTACCCCATG
ATGGGATCTGATCTGGGGCTCGGTGCACATGCTTTACATGTGTTTGTAGTTCAGGTTAAAAAACGTTCTAGGCCCCCGAACCCG
GGACGTGTTTTCTTTGAAAACACGATGATAAATGGGTTGCTGTTTTCTCCAAAGCCGAGCGAAGGGAGAAGCCGCGCGGAG
AGGCCTGGGAGGCGGCTGTGGCTCGTCCCTTCAAAGCGAACGGACAGGAGAATGGCCACGTGAAGGTAGGATCCGTGAGC
AAGGGCGAG
```


Model #21: Ai63-TIGRE-TRE-hACE2-IRES-tdT

Notes:

- a. The purpose is to create a tetracycline inducible model for hACE2 expression with reporter capability.
- b. The design strategy is to insert an ‘hACE2-IRES’ cassette upstream of the tdT sequence by re-engineering the TIGRE locus described in Daigle, T. L. et al., Cell 174, 465-480.e22 (2018).

The Ai63 mouse contains a TRE promoter followed by Lox-Stop-Lox cassette and tdT. The Lox-Stop-Lox cassette (1190kb region) will be excised using two guide RNAs to insert the hACE2-P2A cassette. The sequence source (for guide search) was from the Addgene plasmid 61576

<https://www.addgene.org/61576/>. The sequences used for guide search are as follows: Same as model #20 except that IRES is used instead of P2A

Sequence near the insertion site (the cleavage location expected for the chosen guide RNA is marked as ‘/’).

ctatt/taaatataacttcgtatagcata::::::::::tatacgaagttatcacgcgt/gtttgggac



Left gRNA Sequence- ATACGAAGTTATATTTAAAT [AGG]

Right gRNA Sequence - ACGAAGTTATCACGCGTGTT [TGG]

Sequence of the Ai63-TIGRE-TRE-hACE2-IRES-tdT ssDNA:

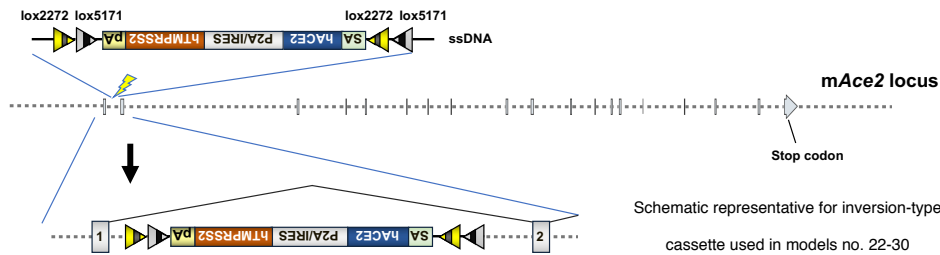
GTTTACTCCCTATCAGTGATAGAGAACGTTATGTCGAGTTTACTCCCTATCAGTGATAGAGAACGTTATGTCGAGTTTACTCCCTATCA
 GTGATAGAGAACGTTATGTCGAGTTTACTCCCTATCAGTGATAGAGAACGTTATGTCGAGTTTACTCCCTATCAGTGATAGAGAACGTTA
 TGTCGAGGTAGGGCGTGTACGGTGGGAGGCCATATAAGCAGAGCTCGTTTGTGAAACCGTCAGATCGCCTATCCACCATGTCAAG
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 TTAACCATTTATGAACATCTTCAACCTATGTGAGGGCAAAGTTGATGAATGCCTATCCCTCCTATACAGTCCAAATGGATGCC
 TCCCTGCTCATTGCTTGGTGATATGTGGGGTAGATTTGGACAAATCTGTACTCTTTGACAGTTCCTTTGGACAGAAACCAAAACA
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 GAAAATCATGTCATTTCTGCAGCCACACCTAAGCATTAAAAATCCATTGGTCTTCTGTCAACCCGATTTTCAAGAAGACAATGAAAC
 AGAAATAAACTCTGCTCAACCAAGCACTCAGATTTGTTGGGACTCTGCACTTACATGTTAGAGAAGTGGAGGTGGATGG
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 AGTACCAGTGGAGTCCATATGCAGACCAAAAGCATCAAAGTGAAGATAAGCCTAAAATCAGCTCTTGGAGATAAAGCATATGAATG
 GAACGACAATGAAATGTACCTGTTCCGATCATCTGTGTCATATGCTATGAGGCACTTTTAAAAAGTAAAAAATCAGATGATTCT
 TTTTGGGGAGGAGGATGTGCGAGTGGCTAATTTGAAACCAAGAATCTCCTTTAATTTCTTTGTCACTGCACCTAAAAATGTGTCTGA
 TATCATTCTAGAACTGAAGTTGAAAAGGCCATCAGGATGTCCCGGAGCCGATCAATGATGCTTTCCGCTGTAATGACAACAGCC
 TAGAGTTTCTGGGGATACAGCCAACACTTGGACCTCCTAACAGCCCTGTTTCCATATGGCTGATTGTTTTTGGAGTTGTGATG
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 TCTCCCTCCCCCCCCCTAAGTACTGGCCGAAGCCGCTTGGAAATAAGGCCGGTGTGCGTGTGCTATATGTTATTTCCACATA
 TTGCCGCTTTTGGCAATGTGAGGGCCGGAAACCTGGCCCTGTCTTTGACGAGCATTCCTAGGGGTTTCCCTCTCGCCAA
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 GCAGGCAGCGGAACCCCTGCGGACAGGTGCCTCTGCGGCCAAAAGCCAGCTGTATAAGATACACCTGCAAAGGGCGGCACA
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 GCCCAGAAGTACCCCATTTGATGGGATCTGATCTGAGGCTCGGTCACATGCTTTTACATGTGTTAGTCGAGGTTAAAAAACC
 TCTAGGCCCCCGAACCCAGGGGACGTGGTTTTCTTTGAAAACACGATGATAAGTTTGGGACGCGTGTAGCGCCACCATGGT
 GAGGACGGCGGAGGAGGTCATCAAAGAGTTCATGCGCTTCAAGGTGCGCATGGAGGGCTCCATGAACGGCCACGAGTTCGAGATC
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 CTCCCGAGGGCTTCAAGTGGGAGCGCGTATGAACTTCGAGGACGGCGTCTGGTGACCGTGACCCAGGACTCCTCCTGCAG
 GACGGC

Models #22, #23 and #24

- 22) *B6.mAce2^{CKO}-hACE2^{CKI}*
- 23) *NSG.mAce2^{CKO}-hACE2^{CKI}*
- 24) *BALB/c.mAce2^{CKO}-hACE2^{CKI}*

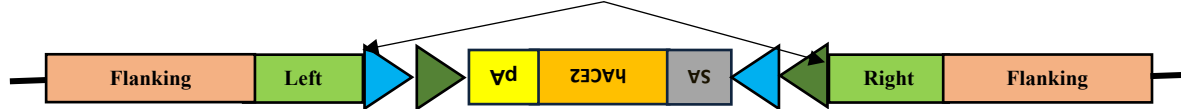
Notes:

- a. The purpose is to create a conditional knock-in (cKI) model for hACE2.
- b. The cKI cassette is a modified version of the XTR strategy described in Camila et al., 2015 (Nat Commun. 5;6:8783.doi: 10.1038/ncomms9783). The source of the XTR cassette was from the Addgene plasmid <https://www.addgene.org/browse/article/16271/>
- c. Exon 1 of *mAce2* is a non-coding exon. The cKI cassette is inserted at 310 bp upstream of the beginning of exon 2 (the first coding exon). The sequence used for gRNA search was from https://uswest.ensembl.org/Mus_musculus/Transcript/Exons?db=core;g=ENSMUSG0000001540;5;r=X:164139332-164188420;t=ENSMUST00000112271.



Sequence near the insertion site (the cleavage location expected for the chosen guide RNA is marked as ‘/’).

aggctataagttccaatatgtgtcccatg/atttctaagtctagccctttctgttatagta



The gRNA sequence (in the intron 1) is GGGCTAGACTTAGAAATCAT [GGG]

Sequence of the *mAce2^{CKO}-hACE2^{CKI}* ssDNA:

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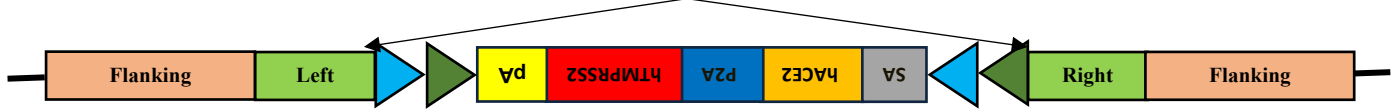
Models #25, #26 and #27

- 25) *B6.mAce2^{CKO}-hACE2-P2A-hTMPRSS2^{CKI}*
- 26) *NSG.mAce2^{CKO}-hACE2-P2A-hTMPRSS2^{CKI}*
- 27) *BALB/c.mAce2^{CKO}-hACE2-P2A-hTMPRSS2^{CKI}*

Notes: These are the same as models #22-#24 except that both hACE2 and hTMPRSS2 will be expressed instead of just hACE2.

Sequence near the insertion site (the cleavage location expected for the chosen guide RNA is marked as ‘/’).

aggctataagttccaatatgtgtcccatg/atttctaagtctagccctttctgttatagta



The gRNA sequence (in the intron 1) is GGGCTAGACTTAGAAATCAT [GGG].

Sequence of the mAce2^{CKO}-hACE2-P2A-hTMPRSS2^{CKI} ssDNA:

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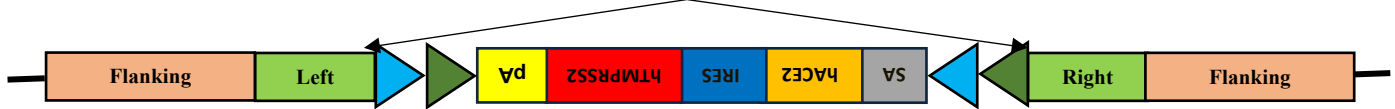
Models #28, #29 and #30

- 28) *B6.mAce2^{CKO}-hACE2-IRES-hTMPRSS2^{CKI}*
- 29) *NSG.mAce2^{CKO}-hACE2-IRES-hTMPRSS2^{CKI}*
- 30) *BALB/c.mAce2^{CKO}-hACE2-IRES-hTMPRSS2^{CKI}*

Notes: These are the same as models #25 to #27 except that IRES is used instead of P2A.

Sequence near the insertion site (the cleavage location expected for the chosen guide RNA is marked as '/').

aggctataagttccaatatgtgtcccatg/atttctaagtctagccctttctgttatagta



The gRNA sequence (in intron 1) is GGGCTAGACTTAGAAATCAT [GGG].
 Sequence of the mAce2^{CKO}-hACE2-IRES-hTMPRSS2^{CKI} ssDNA:

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