

LY6E is a pan-coronavirus restriction factor in the respiratory tract

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Supplementary Table 1. Scoring for features of acute pneumonia for Fig. 3e.

| Mouse | Relative weight at 3 dpi | Perivascular inflammation (0-3) | Alveolar inflammation (0-3) | Pleural inflammation (0-3) | Hemorrhage (0-3) | Edema (0-3) | Total score (out of 15) |
|------------|--------------------------|---------------------------------|-----------------------------|----------------------------|------------------|-------------|-------------------------|
| Wildtype 1 | 98.2 | 0 | 0 | 0 | 0 | 0 | 0 |
| Wildtype 2 | 100.0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Wildtype 3 | 98.0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Wildtype 4 | 92.3 | 1 | 0 | 0 | 0 | 0 | 1 |
| Wildtype 5 | 100.0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Wildtype 6 | 101.4 | 1 | 0 | 0 | 0 | 0 | 1 |
| Wildtype 7 | 101.4 | 1 | 0 | 0 | 0 | 0 | 1 |
| Wildtype 8 | 103.8 | 1 | 0 | 0 | 0 | 0 | 1 |
| Wildtype 9 | 92.8 | 2 | 1 | 0 | 0 | 0 | 3 |
| Knockout 1 | 92.5 | 2 | 0 | 0 | 0 | 0 | 2 |
| Knockout 2 | 87.6 | 2 | 0 | 0 | 1 | 0 | 3 |
| Knockout 3 | 87.8 | 1 | 0 | 0 | 1 | 0 | 2 |
| Knockout 4 | 92.5 | 0 | 0 | 0 | 0 | 0 | 0 |
| Knockout 5 | 90.1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Knockout 6 | 89.7 | 1 | 0 | 0 | 0 | 0 | 1 |
| Knockout 7 | 86.3 | 2 | 2 | 1 | 1 | 0 | 6 |
| Knockout 8 | 87.8 | 1 | 0 | 1 | 0 | 0 | 2 |
| Knockout 9 | 82.5 | 2 | 1 | 1 | 1 | 1 | 6 |

Supplementary Table 2. Automated quantitation of CD45 and SARS-CoV-2 nucleocapsid immunostaining for Fig. 3g-h, i-j.

| Mouse | Relative weight at 3 dpi | % CD45+ cells | CD45 H-score | % SARS-CoV-2 nucleocapsid+ | SARS-CoV-2 nucleocapsid H-score |
|------------|--------------------------|---------------|--------------|----------------------------|---------------------------------|
| Wildtype 1 | 98.2 | 27.1 | 32.7 | 0.1 | 0.1 |
| Wildtype 2 | 100.0 | 29.9 | 34.9 | 0.4 | 0.5 |
| Wildtype 3 | 98.0 | 28.1 | 33.0 | 0.6 | 0.9 |
| Wildtype 4 | 92.3 | 26.9 | 31.4 | 1.5 | 2.0 |
| Wildtype 5 | 100.0 | 27.2 | 31.6 | 0.5 | 0.6 |
| Wildtype 6 | 101.4 | 29.4 | 33.9 | 0.3 | 0.3 |
| Wildtype 7 | 101.4 | not stained | not stained | not stained | not stained |
| Wildtype 8 | 103.8 | not stained | not stained | not stained | not stained |
| Wildtype 9 | 92.8 | not stained | not stained | not stained | not stained |
| Knockout 1 | 92.5 | 26.0 | 31.3 | 11.7 | 15.6 |
| Knockout 2 | 87.6 | 32.0 | 42.1 | 15.4 | 20.1 |
| Knockout 3 | 87.8 | 27.6 | 34.1 | 7.6 | 10.6 |
| Knockout 4 | 92.5 | 30.2 | 36.9 | 5.4 | 6.6 |
| Knockout 5 | 90.1 | 21.2 | 24.6 | 6.9 | 8.6 |
| Knockout 6 | 89.7 | 26.8 | 31.5 | 8.2 | 10.0 |
| Knockout 7 | 86.3 | not stained | not stained | not stained | not stained |
| Knockout 8 | 87.8 | not stained | not stained | not stained | not stained |
| Knockout 9 | 82.5 | not stained | not stained | not stained | not stained |

Supplementary Table 3. Oligos for targeting human LY6E using lentiCRISPRv2

| | |
|------------------------------|---------------------------|
| Human LY6E sgRNA #4 forward | caccgGCCGACCATCTGCTCCGACC |
| Human LY6E sgRNA #4 reverse | aaacGGTCCGAGCAGATGGTCGGCc |
| Human LY6E sgRNA #12 forward | caccgATTGCTCTTCTGGTTCAAGC |
| Human LY6E sgRNA #12 reverse | aaacGCTTGAACCAGAAGAGCAATc |

Supplementary Table 4. *Mus musculus Scgb1a1* probes.

| | | |
|------|---|--|
| B4P1 | CCTCAACCTACCTCCAACAAGATGTGGGGTGATGTTG TAATGTGT | TAGAGTTGGAGGCTTTGGTGTCTGATTCTCACCATATTCGC TTC |
| B4P2 | CCTCAACCTACCTCCAACAAGATGGACAGCATGACC ACAGTGAT | AGATGTCCGAAGAAGCTGAGCTGCAATTCTCACCATATTCGC TTC |
| B4P3 | CCTCAACCTACCTCCAACAATAACCAGACTCTGATTCC ATGAGGA | GGGTTGAAAGGCTTCAGGGATGCCAATTCTCACCATATTCGC CTTC |
| B4P4 | CCTCAACCTACCTCCAACAATTCAGCTGGGTGCCCGC ATTTTGCA | TCTTGTGGGAGGGTATCCACCAGTCATTCTCACCATATTCGC TTC |
| B4P5 | CCTCAACCTACCTCCAACAATTTTCTCCGTGAGCTTC ATGATGT | TCTTGCTTACACAGAGGACTTGTTAATTCTCACCATATTCGC TTC |
| B4P6 | CCTCAACCTACCTCCAACAATTTAGCAGTAGAATATCT CTGAAAT | CGAGGAGACACAGGGCAGTGACAAGATTCTCACCATATTCGC CTTC |
| B4P7 | CCTCAACCTACCTCCAACAAGAAGGAGGGGTTGGTGT GGGAAGC | GAGATGCTCGCAGTTTATTGCAAAGATTCTCACCATATTCGC TTC |

Supplementary Table 5. *Mus musculus Sftpc* probes.

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|-------|---|--|
| B4P1 | CCTCAACCTACCTCCAACAACCTCTCTCTCTCTCTCTCT CCTCATCT | GCTACTCATGTCCATTTTGTAAAGGTATTCTCACCATATTCGC TTC |
| B4P2 | CCTCAACCTACCTCCAACAACCTGGGACCTGCCGAG TAATCCGGT | GGGACAGCAGGGGATGCGGAACTGGATTCTCACCATATTCGC CTTC |
| B4P3 | CCTCAACCTACCTCCAACAACCACCACCACAACCAC GATGAGAA | GCCCCTACAATCACCACGACAACGAATTC TCACCATATTCGCTTC |
| B4P4 | CCTCAACCTACCTCCAACAATCTCAGTATGTTTTGA CTCATGT | GGTGCTCCGATGCTCATCTCAAGGAATTCTCACCATATTCGC TTC |
| B4P5 | CCTCAACCTACCTCCAACAATGGTGTCTGCTCGCTCA CTCGGGGC | CAGTGGAGCCGATGAAAAGGTAGCATTCTCACCATATTCGC CTTC |
| B4P6 | CCTCAACCTACCTCCAACAACCTGGAGCTGGCTTATAG GCCGTCAG | CCATCTTCATGATGTAGCAGTAGGTATTCTCACCATATTCGC TTC |
| B4P7 | CCTCAACCTACCTCCAACAATAAGCCTCAAGACTAGG GATGCTCT | GCCTGGAAGTCTGGAGTTTTCTAGATTCTCACCATATTCGC TTC |
| B4P8 | CCTCAACCTACCTCCAACAACAGGGTGCTCACAGCA AGGCCTAG | AGATATAGTAGAGTGGTAGCTCTCCATTCTCACCATATTCGC TTC |
| B4P9 | CCTCAACCTACCTCCAACAATTCCTGTCCCCTGCGG TTTCTACC | CTGACAAAAGACCCTTTGCGGAGGGTATTCTCACCATATTCGC TTC |
| B4P10 | CCTCAACCTACCTCCAACAACAGACTTCCACCGGT TCTGGGCA | GGCCCGTAGGAGAGACACCTTTCTATTCTCACCATATTCGC TTC |