

a unique series of humanized-ACE2 and Ace2-KO

mouse models available for your COVID-19 research needs

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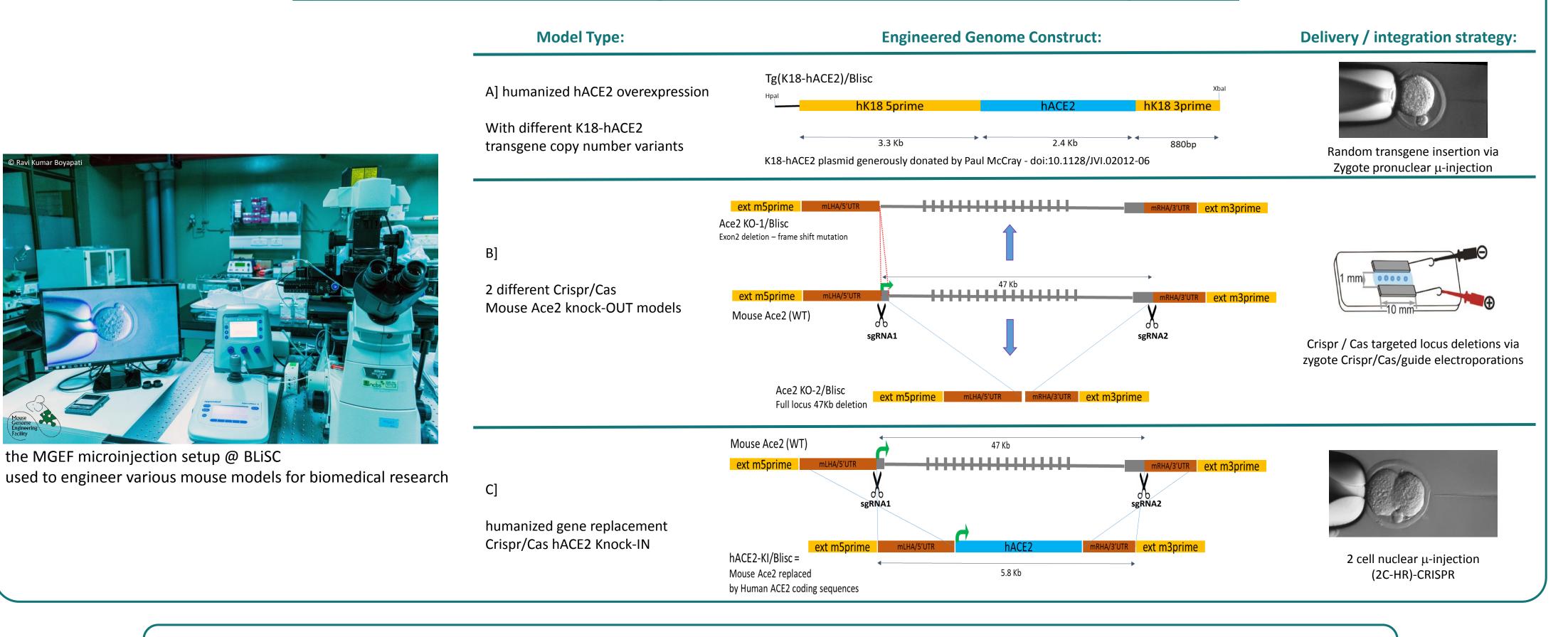


In response to the immediate needs of researchers nationwide, the Mouse Genome Engineering Facility (MGEF) of the Bangalore Life Science Cluster (BLiSC) has leveraged its expertise and infrastructure to address this public health crisis. By August 2020, MGEF designed a series of unique ACE2 mouse models to facilitate SARS-CoV2 /COVID-19 related research and therapeutics projects.

The first set of models are the Transgenic: Tg(K18-hACE2)/Blisc mice. These are humanized models over-expressing the human ACE2 gene under the regulatory sequences of the human keratin 18 (*KRT18*) promoter. 3 different Tg(K18-hACE2)/Blisc founder lines were established and characterized. Each line expressing different levels of the K18-hACE2 transgene leading to different levels of SARS-CoV2 infection responses recapitulating the different severity levels of COVID-19 symptoms.

These Tg(K18-hACE2)/Blisc lines are currently being redistributed across the country for various COVID-19 vaccine and therapeutic assays. Two different mAce2 Knock OUT (KO) mice also have been generated and we have generated constructs to engineer Targeted Knock-IN hACE2-KI/Blisc models in which the mouse Ace2 locus is replaced by the human ACE2 coding sequences. These KI models are being designed in a NSG background and can be customized as unique tools for translational approaches to personalized or population based precision medicine. We will present here our results characterizing the different ACE2 mouse models generated at MGEF/BLiSC and our future plans to enhance vaccine and therapeutic research and screening capacities in India.

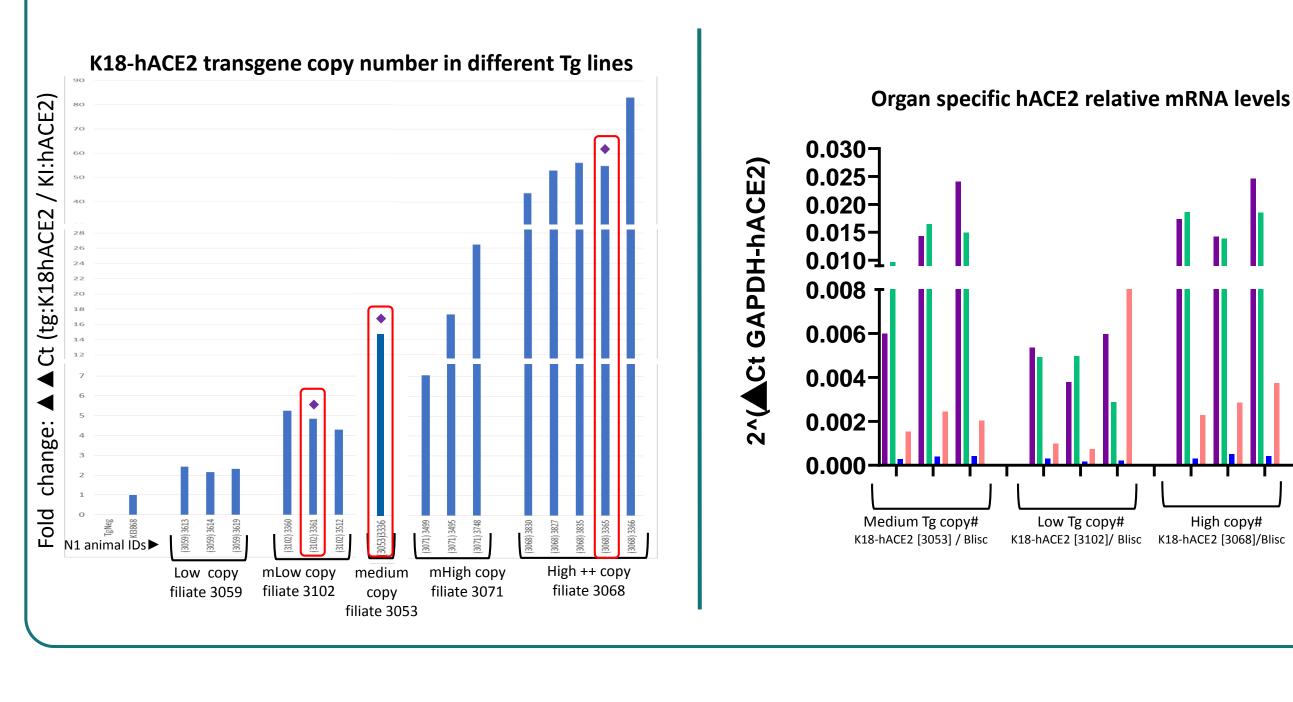
1) Different ACE2 alleles designed to answer different biomedical questions



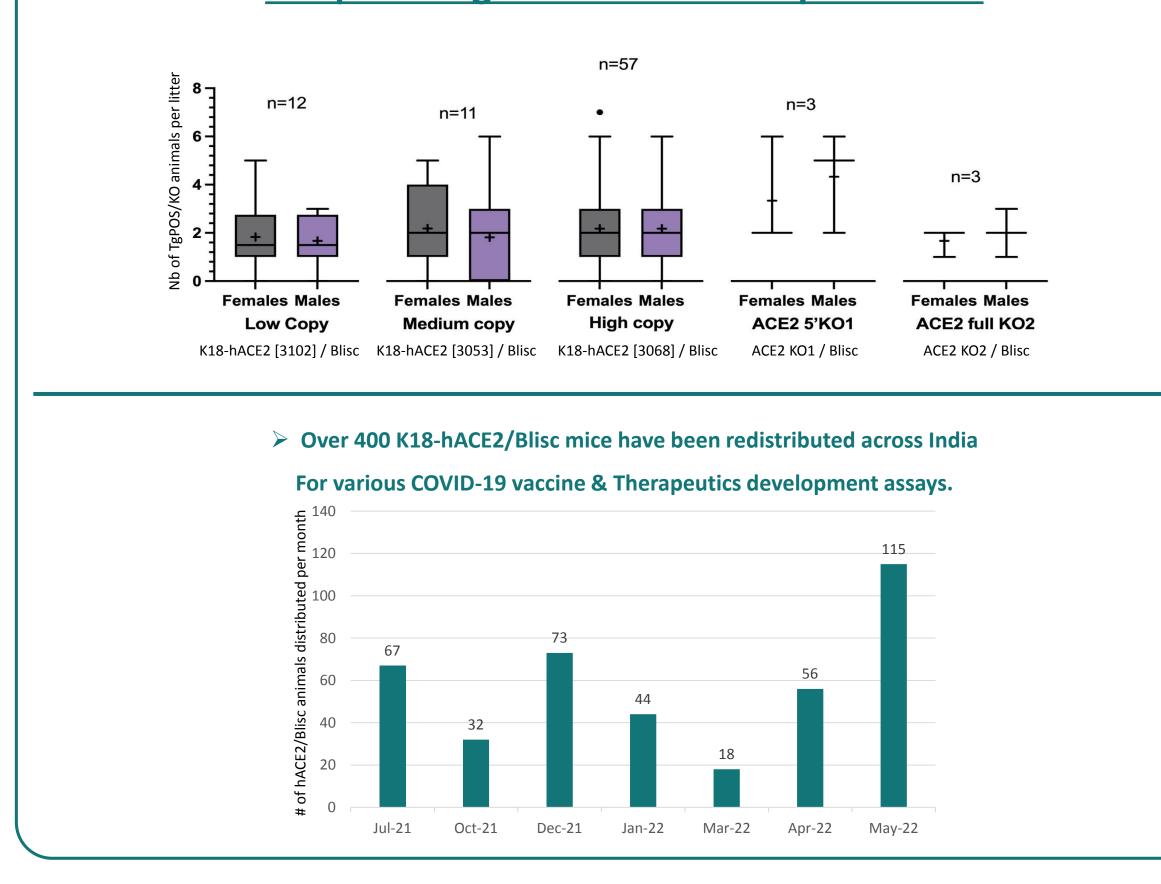
2) hACE2 and mAce2 KO / BLiSC animal colonies maintained in High Barrier SPF facility



3) different K18-hACE2 transgene copy number mouse lines drive different levels of hACE2 expression in different organs



6) MGEF now setup to provide age matched cohorts of up to 50tg Positive animals per cohort

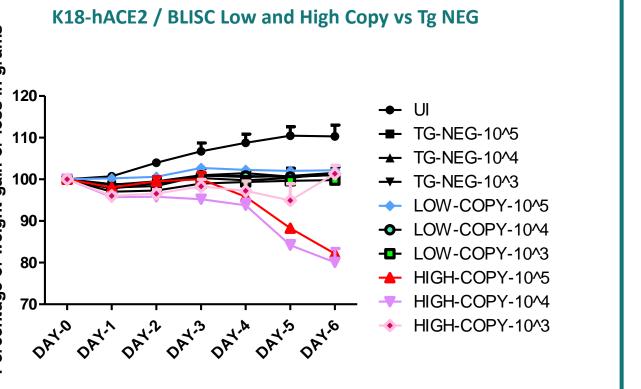


hACE2 / BLISC mice colonies maintained by dedicated staff at ACRC high barrier SPF facility

ACRC high Barrier SPF animal Holding Rooms

4) K18-hACE2/Blisc mice respond to SARS-CoV2 infection

> the different K18-hACE2/Blisc mice were challenged with 1e3-1e6 PFU of SARS-CoV2 [US strain (USA-WA1/2020 obtained from BEI resources)] ▶ K18-hACE2 / BLISC [3068] HIGH copy mice -> very severe lethal phenotype at 5-6 days post infection ▶ K18-hACE2 / BLISC [3053] MEDIUM copy -> longer disease onset response with slow recovery = mimicking Long COVID disease

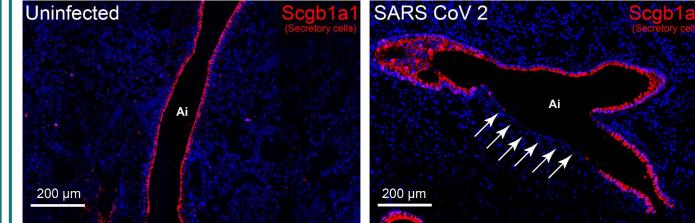


K18-hACE2 / BLISC medium Copy vs Tg NEG - UI-CON - Tg-Neg-10^5 - M-ACE-2/10^5 M-ACE-2/10^3

Different hACE2 mouse models for different purposes: ➤ K18-hACE2 / BLISC [3068] HIGH copy = COVID-19 Vaccine assays K18-hACE2 / BLISC [3053] MEDIUM copy = COVID-19 Therapeutics

7) Protective efficacy of designed vaccine formulations against SARS-CoV2

5) SARS-CoV2 infection induces acute lesions in K18-hACE2/Blisc mouse lungs 200 µm

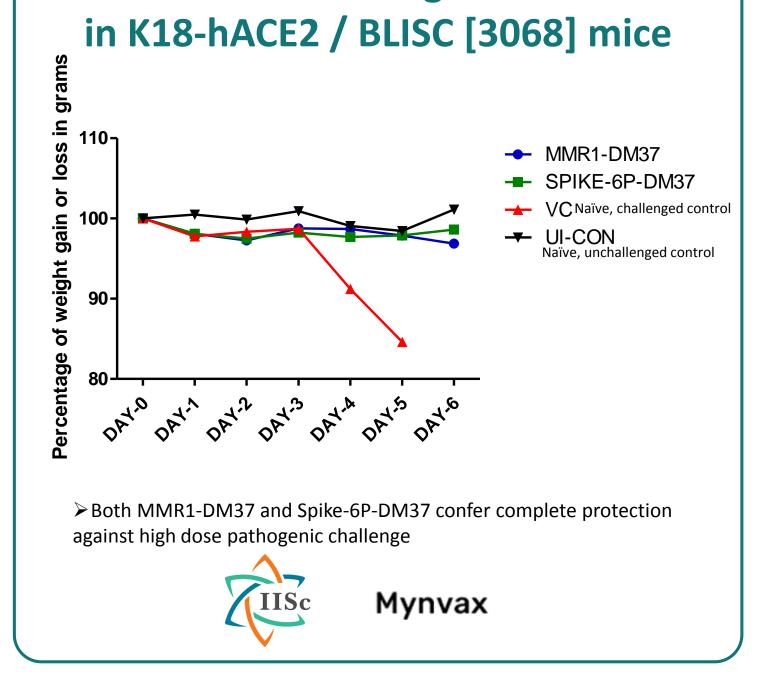


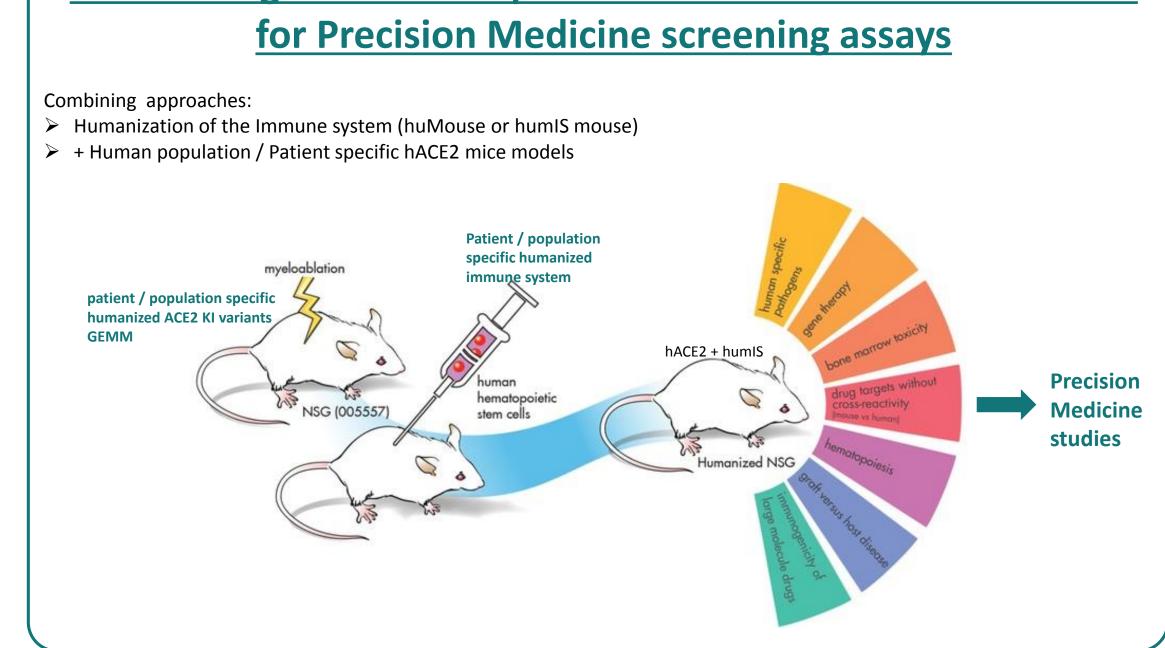
K18-hACE2 / BLISC [3068] HIGH copy animals were infected with hCov19/USA/MD-HP01542/2021 (lineage.1.351) of SARS CoV2 @ 10^5 PFU and sacrificed 4 days post infection. Lungs were harvested, fixed and immuno-stained to assess and visualize the effects of SARS-CoV2 infection compared to non infected littermate controls. Immuno-Staining for SARS-CoV2 Nucleocapsid, Spike1, Spike2 proteins were high in lung secretory cells as well as in alveolar cell subtypes of the infected lungs. K18-hACE2 / BLISC [3068] HIGH copy animals exhibit highly disrupted lung Airways epithelium as well as alveolar cell loss compared to control littermates

8) Future Directions:

Mynvax

Establishing Patient & Population Humanized Mouse models







Contact acrcinfo@ncbs.res.in For K18-hACE2/Blisc animal orders

IISc

Lung

Hear

Live

Brain

TgNEG

High copy#

Low Tg copy#

K18-hACE2 [3102]/ Blisc K18-hACE2 [3068]/Blise

BLiSC Mouse Genome Engineering Facility (MGEF) & Animal Care and Resource Center (ACRC): https://www.ncbs.res.in/research-facilities/acrc

