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Genetically engineered models **(GEMS)**

Humanized ACE2 (hACE2) Knockin Mouse

MODEL	Humanized ACE2 Knockin Mouse
STRAIN	C57BL/6Hsd-*ACE*$^{em1(ACE2)Env}$
LOCATION	U.S., U.K.
AVAILABILITY	Live colony

CHARACTERISTICS/HUSBANDRY

- Background strain: C57BL/6

ZYGOSITY GENOTYPE

- Homozygous and Hemizygous (X-linked)

RESEARCH USE

- Infectious disease
- COVID-19
- SARS

ORIGIN

The humanized ACE2 (hACE2) knockin (KI) mouse model was created at the Inotiv St. Louis, MO, model creation facility in 2020 and is maintained and distributed by Inotiv.

DESCRIPTION

Mouse angiotensin-converting enzyme 2 (ACE2) is a 49kb X-linked gene harboring 19 exons. ACE2 is a key enzyme in the renin-angiotensin system (RAS). RAS regulates blood volume and arterial tone, as such, it is a common target for the treatment of hypertension. ACE2 is highly expressed in several human tissues including the gastrointestinal tract, liver, gallbladder, kidney, urinary bladder, testes, placenta and fallopian tube, with lower expression levels in the lungs and pancreas. It also serves as the primary receptor for cell entry for the SARS-CoV and SARS-CoV-2 viruses. Binding of the coronavirus spike (S) protein to ACE2 initiates fusion of the cell and viral membranes for cell entry. ACE2-S protein binding is the critical initial step for coronavirus infection and is being investigated as a potential coronavirus drug target.

This hACE2 KI mouse model was generated by integrating a codon optimized human ACE2 cDNA expression cassette into the mouse *Ace2* gene through CRISPR-based technology. As a result, the mouse *Ace2* gene promoter and other regulatory elements drive expression of the human ACE2 protein while terminating mouse *Ace2* gene expression.

Figure 1. Relative human ACE2 expression in hACE2 KI mouse model (Founder 37). *The expression of human ACE2 mRNA was measured in a heterozygous (Het) female (n=1), homozygous (Homo) female (n=1), hemizygous (Hemi) males (n=2) and a C57BL/6 wild type (WT) animal (n=1). $2^{-\Delta\Delta CT}$ was used to calculate relative expression, and then the data was normalized to the group with highest expression. Error bars were calculated using STDEV/SQRT (numbers of sample).*

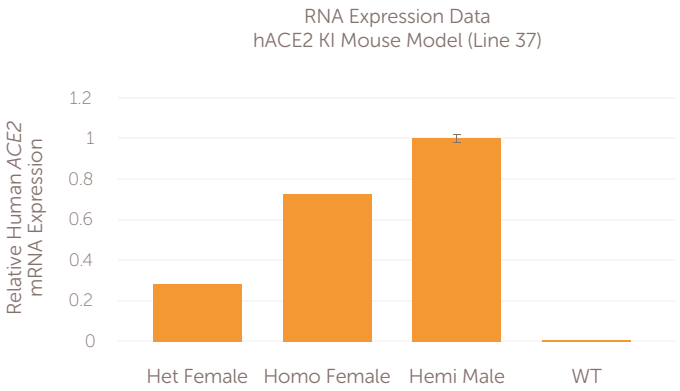

Figure 2. Weight loss in hACE2 KI mice infected with SARS-CoV-2. *Homozygous (Homo) females (n=3), hemizygous (Hemi) males (n=4), and control hACE2 transgenic animals (TG; n=8) were intranasally infected with 1 x 10^5 PFU virus per mouse. Mouse body weights were monitored daily for 14 days. Each dot represents the average daily weight for each group. Error bars were calculated using STEDEV/SQRT (numbers of sample). Data from Dr. M. Kumar at Georgia State University.*

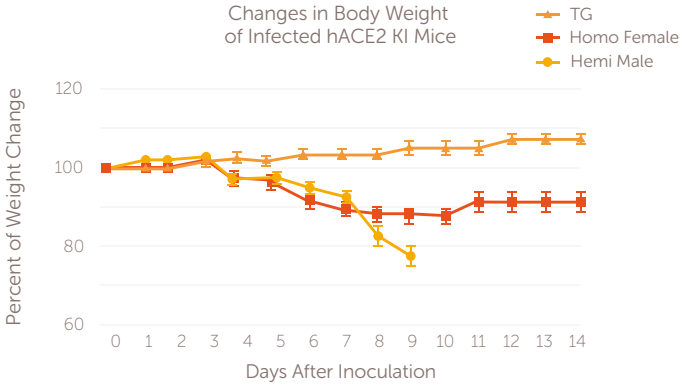

Figure 3. SARS-CoV-2 neutralizing antibodies in infected hACE2 KI mice. *Sera from SARS-CoV-2 infected homozygous (Homo) females (n=3) and control hACE2 transgenic mice (TG; n=8), or PBS as a control, were assayed for SARS-CoV-2 neutralizing antibodies using a plaque reduction neutralization (PRNT) assay. Bars represent average antibody titer that was able to induce 50% reduction of SARS-CoV-2 plaques. Error bars were calculated using STEDEV/SQRT (numbers of sample). Data from Dr. M. Kumar at Georgia State University.*