**MOUSE GENOME EDITING CORE UNIT**

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Dr María A. Blasco at the CNIO (Telomeres and Telomerase Group, Fundación Humanismo y Ciencia), to characterise these mouse models and their application to study the effect of aging by telomere shortening in COVID19.

**RESEARCH HIGHLIGHTS**

Since the outbreak of the SARS-CoV-2 pandemic in 2020, the Unit has dedicated extra effort to generating and characterising mouse models for COVID disease. For this purpose, and supported by a dedicated grant from the Spanish Institute of Health Carlos III and a SINERGIAS-grant from the Madrid Local Government (CAM), the Unit has created “humanized” mouse models for COVID19 research, in collaboration with the company Gen-H Genetic Engineering, Heidelberg (Germany).

The laboratory mouse is the most widely used animal model in biomedicine, but it is not a permissive species for SARS-CoV-2 infection. Structural differences between the human angiotensin converting enzyme-2 (ACE2) protein, the cellular receptor for SARS-CoV-2, and its murine ortholog are the cause, at least in part, of the different sensitivity to viral infection in humans and mice.

Using the latest gene editing technologies, based on the CRISPR-Cas9 system, we created knockin mice in which the human ACE2 protein is expressed under the transcriptional control of the endogenous mouse Ace2 promoter, interrupting simultaneously the Ace2 coding sequence and resulting in the knockout of the mouse Ace2 gene (FIGURE 1). We generated two knockin mouse models, co-expressing the human ACE2 protein together with a fluorescent reporter or with the human TMPRSS2 serine protease that plays a critical role, together with ACE2, in the virus entry into cells. These humanized mice provide a more physiological platform than the currently available models for studying the long term effects of SARS-CoV-2 infection in the mouse.

We are presently collaborating with Dr Luis Enjuanes (Coronavirus Laboratory) at the National Centre for Biotechnology (CNB-CSIC, Madrid), and with Dr Maria A. Blasco at the CNIO (Telomeres and Telomerase Group, Fundación Humanismo y Ciencia), to characterise these mouse models and their application to study the effect of aging by telomere shortening in COVID19.

**FIGURE 1** Gene editing strategy used to create humanized knockin mouse models to study COVID19. Using CRISPR/Cas9 in embryos, we replaced the mouse Ace2 gene with its human ACE2 ortholog. The human receptor is expressed under the transcriptional control of the mouse Ace2 promoter in the knockin and, simultaneously, the mouse Ace2 gene is knocked out. Created with BioRender.

**PUBLICATIONS**


Cancer encompasses a wide spectrum of extremely complex diseases. Genetic and epigenetic modifications in tumour cells lead to the acquisition of “malignant” phenotypes that enable them to escape normal physiological control. Genome editing and transgenesis technologies are used to accurately reproduce these modifications in the mouse, creating animal models that are crucial to understand and better treat cancer. Tumour cells interact at different levels with other systems in the body such as the immune, cardiovascular or lymphatic systems, which in turn modulate tumour growth, invasion, and expansion. Behavioural factors such as diet also have an impact on cancer development. The study of such complexity demands expansion. Behavioural factors such as diet also have an impact on cancer development.

The Unit has more than 20 years of experience in the design, generation, and validation of genetically modified mouse models using state-of-the-art genome editing techniques. It also maintains a cryoarchive of the hundreds of genetically modified mouse lines created at the CNIO.”