MOUSE GENOME EDITING CORE UNIT

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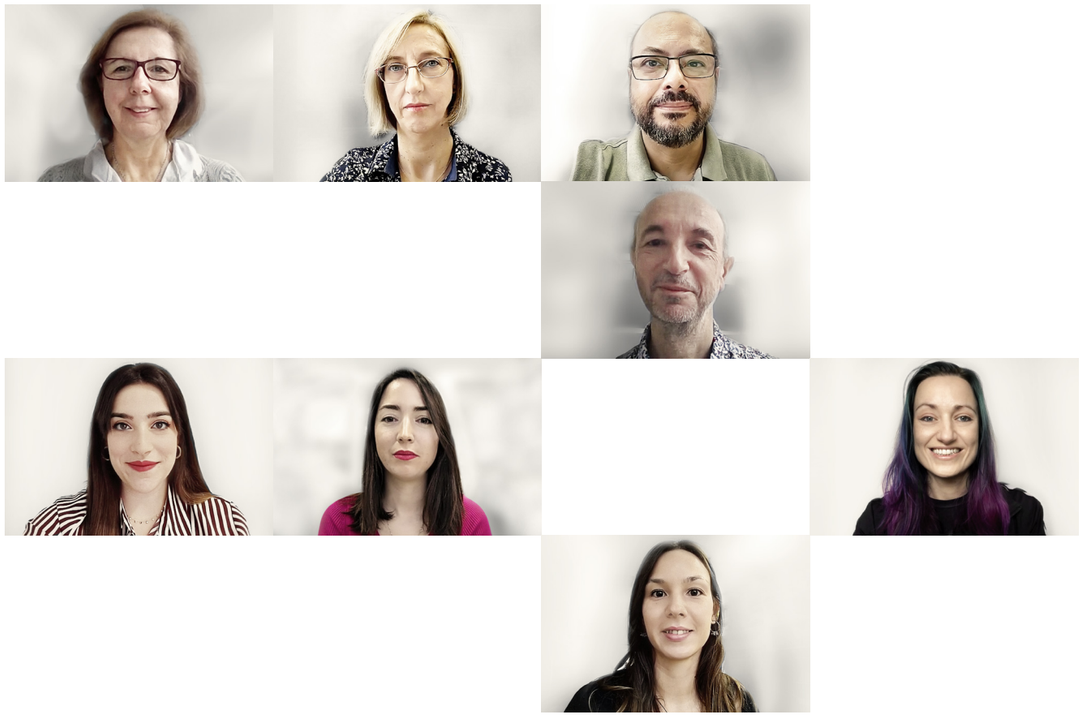

OVERVIEW

Genetically modified mouse models are an essential part of any discipline of biomedical research, including cancer. Our Unit has created about 500 mouse models to support cancer research, using state-of-the-art mouse genetics and gene editing technologies.

The term "cancer" encompasses a whole spectrum of extremely complex diseases in which tumour cells interact, at different levels, with various physiological components, such as the immune system, blood vessels or stromal tissue, which in turn modulate tumour growth, invasion, and expansion. The study of such complexity requires *in vivo* models that reproduce all the features of cancer in a "whole body" context, including the specific genetic alterations that lead to tumour development in each particular tumour type. The precise, targeted, and controlled modification of the mouse genome, using the most advanced genome editing tools, sustains the generation of genetic mouse models of cancer that are crucial for understanding the molecular basis of tumour development and the preclinical validation of new and more efficient cancer therapies.

The Mouse Genome Editing Unit has more than 20 years of experience in the design, generation, and validation of genetically modified mouse models. In addition, it has created a collection of currently over 1,000 cryopreserved mouse strains from which the entire scientific community may benefit in many different research disciplines.

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**Plan de Empleo Joven-Licenciado* (Youth Employment Plan-Graduate)
***Titulado Superior* (Advanced Degree)

RESEARCH HIGHLIGHTS

COVID19 preclinical mouse models

The emergence in 2019 of the new coronavirus strain SARSCoV2/SARS-2 and the expansion of the pandemic called COVID-19, prompted the global scientific community to dedicate an unprecedented effort to developing strategies aimed at halting SARS-2 spread and protecting against COVID disease. However, one of the main limitations in COVID research is the lack of adequate models to study SARSCoV2 infection, especially animal models, where the complex interactions established between the virus and its host are reproduced in a physiological context.

The laboratory mouse is the most widely used animal model in biomedicine, but it is not a permissive species for SARSCoV2 infection. Structural differences between the human Angiotensin Converting Enzyme-2 (ACE2) protein, the virus cellular receptor, and its murine orthologous are the cause of the different response in human and mouse. Supported by a dedicated grant from the Spanish Institute of Health *Carlos III*, and with the collaboration of Gen-H Genetic Engineering, Heidelberg, during 2020, the Unit created "humanised" mouse models optimised for the study of COVID-19 that, once characterised, will be available for the scientific community. These models were created using the latest gene editing technologies, and present unique advantages over the models available so far for COVID-19.

We created 2 different types of mouse models. In the first one, using a knockin approach, the human ACE2 protein is expressed under the transcriptional control of the endogenous mouse *Ace2* promoter, interrupting simultaneously the *Ace2* coding sequence resulting in the knockout of the mouse *Ace2* gene. As an alternative, we used a BAC transgene approach to drive expression of human ACE2 under the control of the *Ace2* promoter. In both cases, the expression of human ACE2 recapitulates the pattern and regulation of endogenous Ace2 expression. Both models are currently being characterised for SARS-CoV2 infection response. ■

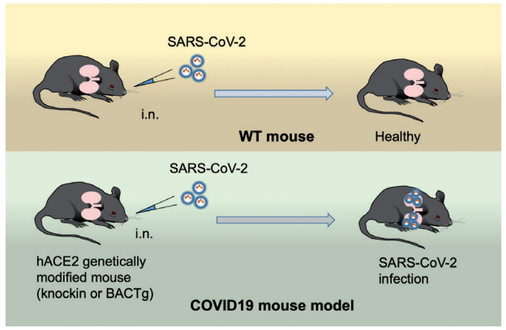

FIGURE Humanised mice as animal models of COVID-19. Expression of the human form of the ACE2 protein in mice makes them susceptible to SARS-CoV2 infection by intranasal (i.n.) inoculation of the virus. We have used two different strategies to express human ACE2 with the same transcriptional control of the endogenous *Ace2* gene, knockin and BAC-transgenesis.

PUBLICATIONS

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