CRISPR technology demonstrates success in preventing and treating COVID

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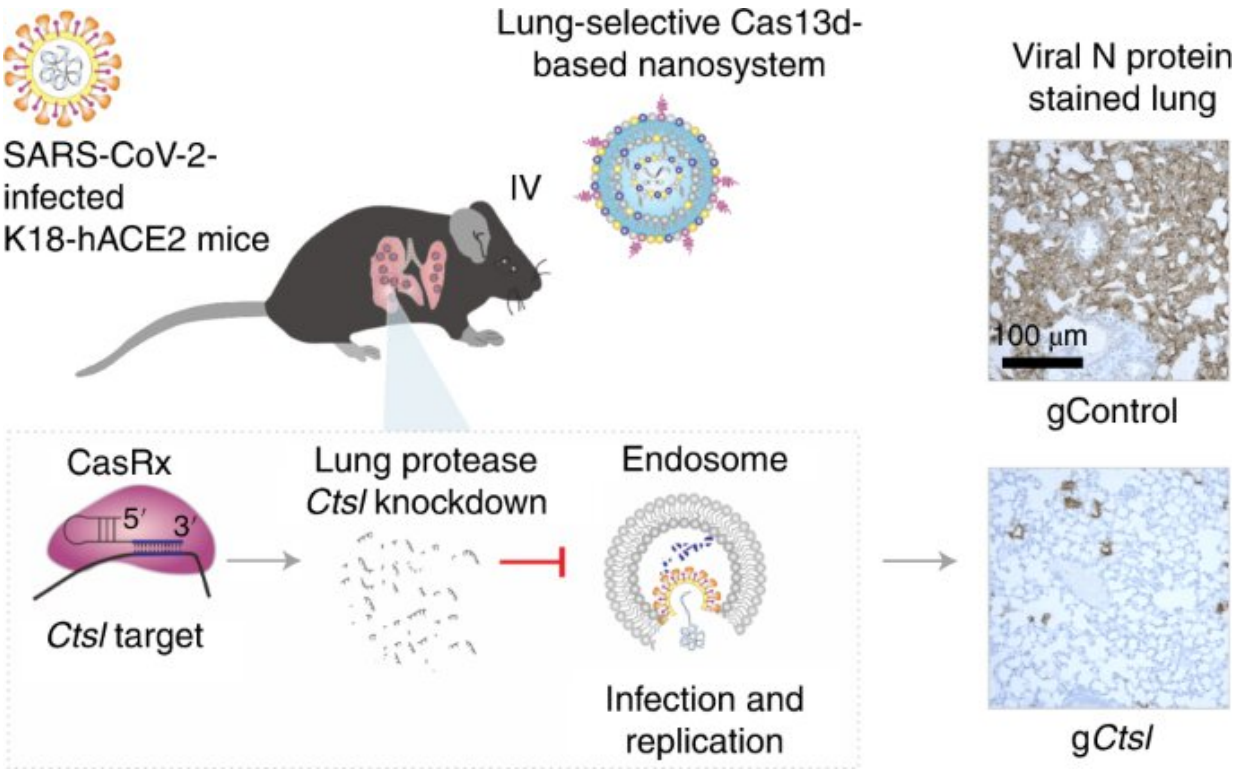

Graphical abstract. Credit: *Nature Chemical Biology* (2022). DOI: 10.1038/s41589-022-01094-4

In what is believed to be a first, a research team led by Duke Health has demonstrated a way to use CRISPR technology to successfully prevent and treat COVID infections.

The proof-of-concept experiments, conducted in mice, modified a currently available lipid nanoparticle to deliver a specific CRISPR/Cas13 mRNA that generates an inhospitable environment in the lungs for SARS-CoV-2 infection.

If further research in humans validates the approach, it could lead to a prevention strategy that is not dependent on the ability of antibodies to recognize specific viral structures, so it would be effective regardless of how the virus mutates. The approach also has a treatment benefit, lowering the virus burden and forestalling an immune overreaction that can become deadly during infections.

The research appears online July 25 in the journal *Nature Chemical Biology*.

"Our results suggest that CRISPR technology represents a unique strategy for controlling SARS-CoV-2 infection and should be pursued as a potential approach for treating COVID," said senior author Qianben Wang, Ph.D., professor in the Department of Pathology at Duke University School of Medicine.

Wang and colleagues focused on a protease—an enzyme that breaks down protein—called cathepsin L, or CTSL. This protease is abundant in the lungs and has long been identified as playing a key role in SARS-CoV-2 and many other coronavirus infections, enabling the virus to enter host cells and proliferate.

Teams of other researchers have attempted to use CTSL inhibitors to thwart coronavirus infections for many years. Lab experiments were promising, but tests in animals showed disappointing results.

Applying CRISPR technology—basically turning down genes to knock out certain misfunctions or, in this case, the function of CTSL—Wang's

team created a way to safely initiate CTSL inhibition.

The CRISPR/Cas13, delivered intravenously through a lipid nanoparticle, diminished CTSL in the animals' lungs, which effectively and safely blocked the SARS-CoV-2 virus from entering cells and infecting the host.

The benefits of the approach as a COVID prevention were time-limited, lasting several days rather than the months or years that vaccines offer. But if the delivery system can be developed as an inhalant instead of an IV, the drug could be self-administered as a preventive measure prior to or shortly after an airline trip or a large gathering.

Not only did the approach prevent infection, it also showed potential as a treatment. Further experiments in COVID-infected animals showed that the CRISPR-loaded nanoparticle decreased the viral load in the lungs of animals with COVID infections and inhibited the immune storm that triggers lethal cases. Treated animals had higher survival rates.

Wang said there are challenges ahead, notably developing a way to deliver the therapy as an inhalant, similar to how asthma therapies are taken.

"To the best of our knowledge, this is the first study demonstrating that CRISPR/Cas13can be used as a treatment for SARS-CoV-2 infection," Wang said. "This nanosystem can be easily adapted in the future to target infection by other DNA viruses such as hepatitis B."

More information: Zhifen Cui et al, Cas13d knockdown of lung protease Ctsl prevents and treats SARS-CoV-2 infection, *Nature Chemical Biology* (2022). DOI: 10.1038/s41589-022-01094-4

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