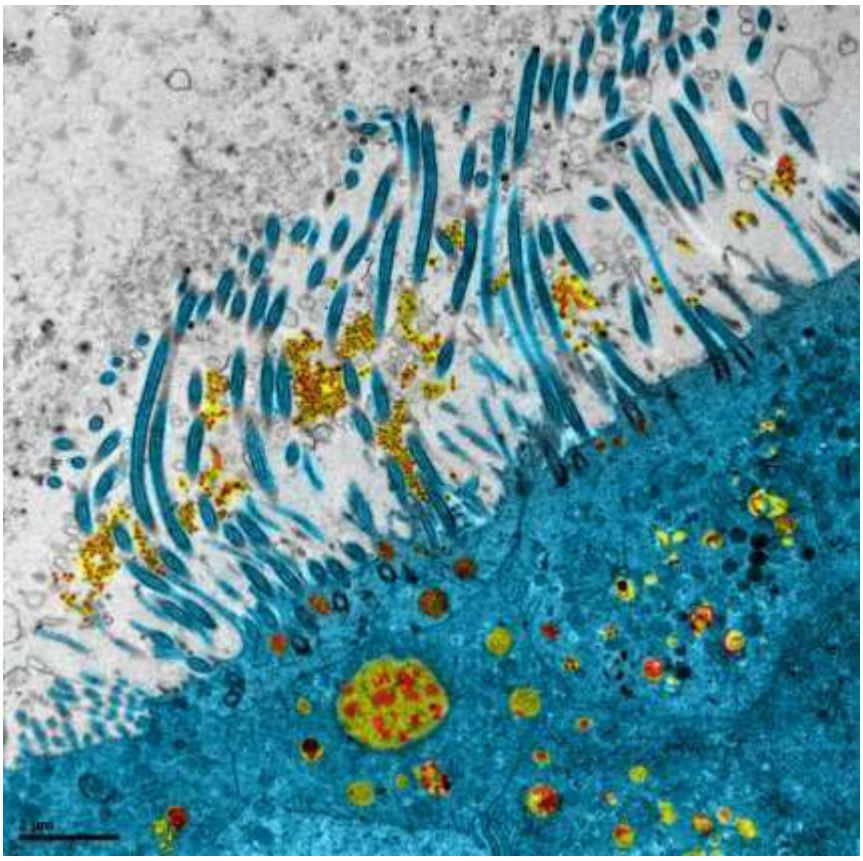
Paris, July 27, 2020

Press information

COVID-19: Together, Remdesivir and Diltiazem Open up New Therapeutic Avenues



SARS-CoV-2 infected human respiratory epithelium. The image shows viral clusters in the cilia of the epithelial cells, numerous highly-characteristic cytoplasmic vesicles containing large electron-dense accumulations of viral material, and numerous viruses being formed. Photo credits: Manuel Rosa-Calatrava, Inserm; Olivier Terrier, CNRS; Andrés Pizzorno, Signia Therapeutics; Elisabeth Errazuriz-Cerda, UCBL1 CIQLE. VirPath (International Research Center for Infectious Diseases U1111 INSERM - JRU 5308 CNRS - ENS Lyon - UCBL1). Colorized by Noa Rosa C.

As the COVID-19 pandemic continues, finding a treatment to effectively combat the disease remains a major research challenge. Researchers from Inserm, CNRS, Université Claude Bernard Lyon 1 and ENS Lyon at the International Research Center for Infectious Diseases have developed a unique strategy for selecting, evaluating and repurposing existing drugs to assess their efficacy against SARS-CoV-2. They have also developed several highly-relevant preclinical models of infection using human respiratory epithelia of nasal and bronchial origin reconstituted *in vitro*. Thanks to their expertise, the researchers show that combining the Ebola treatment remdesivir with the antihypertensive diltiazem could bring significant benefit to COVID-19 patients. Their findings have been published in *Cell Reports Medicine*.

As part of the REACTing program coordinated by Inserm, the VirPath team led by Inserm researcher Manuel Rosa-Calatrava at the International Research Center for Infectious Diseases (Inserm/CNRS/Université Claude Bernard Lyon 1/ENS Lyon) is working on repurposing existing drugs for new therapeutic indications in viral infections.

To test the therapeutic efficacy of these molecules against COVID-19, the team began developing and characterizing experimental models of viral infection in February. This involved the *in vitro* reconstitution – as close as possible to human physiology – of human respiratory epithelia of nasal and bronchial origin. "*We have been using these preclinical infection models, which are highly predictive of* in vivo *infection, for several years,"* clarifies Rosa-Calatrava.

The researchers have also developed protocols for viral-genome and infectious-particle quantification. Their observations and analyses confirm and supplement current knowledge of the mechanisms of SARS-CoV-2 infection and virus-host interactions. "*One particular observation from our models infected with the virus was the induced production of interleukin IL6, which is a marker of the disease's severity,"* says Rosa-Calatrava.

A large number of drug candidates were evaluated using these models, including two molecules of interest: remdesivir and diltiazem, alone and in combination. Remdesivir presents antiviral activity against RNA viruses, including SARS-CoV-2. *In vitro* cell models, animal models, as well as several ongoing clinical trials are showing initial positive results against this virus.

Diltiazem is an antihypertensive used in the treatment of angina pectoris. It has already been characterized and repurposed by VirPath researchers to strongly stimulate the endogenous antiviral innate immune response, particularly against influenza- and respiratory viruses. The human toxicity of these two repurposed molecules has also already been evaluated, significantly reducing the time needed for their clinical development in the new SARS-CoV-2 indication.

The results of this study show a significant reduction in viral load in SARS-CoV-2 infected epithelia when treated with remdesivir. This effect is increased when diltiazem is added in combination. *"By stimulating the innate immune response of the epithelia, diltiazem potentiates the effect of remdesivir and makes it possible to reduce doses. This bearing in mind that remdesivir presents some* in vivo *toxicity in addition to being a very costly drug,"* emphasizes Rosa-Calatrava.

The team is continuing its preclinical tests with this dual therapy in animal models and hopes to launch a clinical trial as early as next winter if the positive results are confirmed.

Sources

Characterization and treatment of SARS-CoV-2 in nasal and bronchial human airway epithelia

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Cell Reports Medicine, Juillet 2020
DOI : https://doi.org/10.1016/j.xcrm.2020.100059

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