Anti-inflammatory drug protects against lethal inflammation from COVID-19 in animal models

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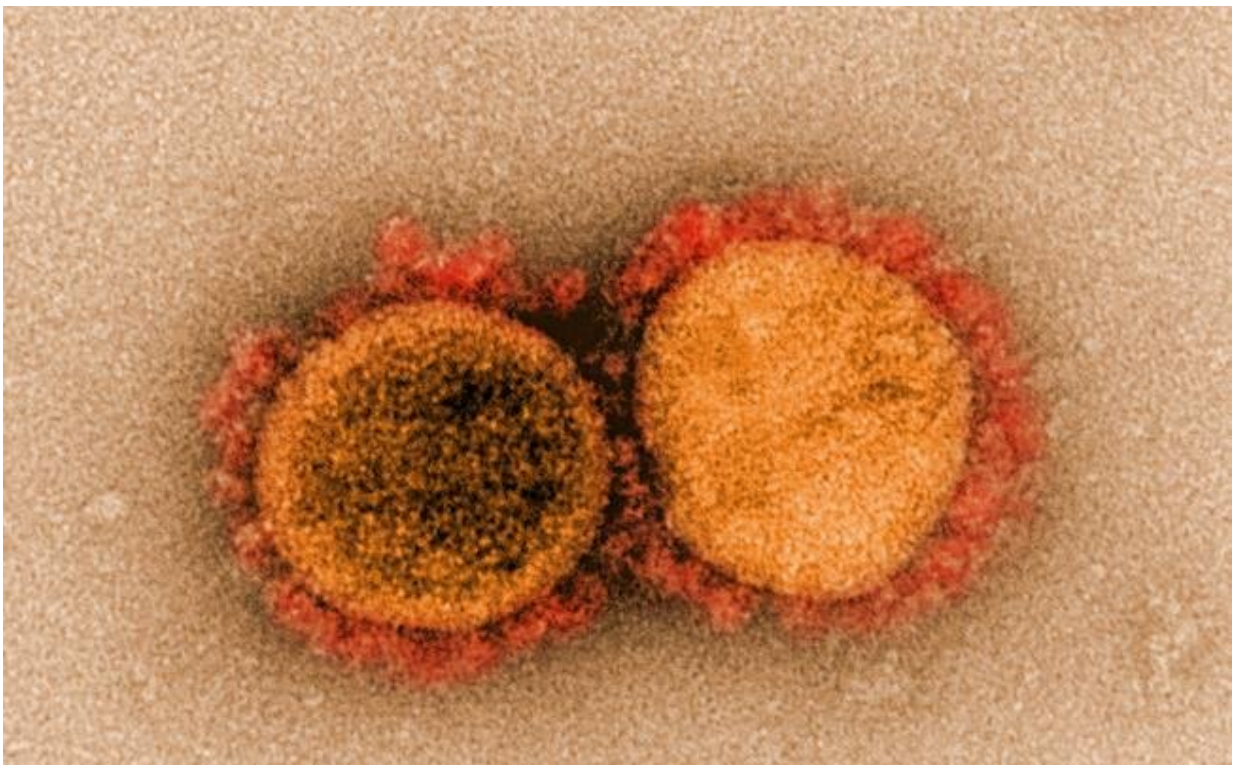

Transmission electron micrograph of SARS-CoV-2 virus particles, isolated from a patient. Image captured and color-enhanced at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIAID

Mount Sinai researchers have found that a widely available and

inexpensive drug targeting inflammatory genes has reduced morbidity and mortality in mice infected with SARS-CoV-2, the virus that causes COVID-19. In a study published today in the journal *Cell*, the team reported that the drug, Topotecan (TPT), inhibited the expression of inflammatory genes in the lungs of mice as late as four days after infection, a finding with potential implications for treatment of humans.

"So far, in pre-clinical models of SARS-CoV-2, there are no therapies—either antiviral, antibody, or plasma—shown to reduce the SARS-CoV-2 disease burden when administered after more than one day post-infection" says senior author Ivan Marazzi, Ph.D., Associate Professor of Microbiology at the Icahn School of Medicine at Mount Sinai. "This is a huge problem because people who have severe COVID19 and get hospitalized, often do not present symptoms until many days after infection. We took a different approach, and sought to find a potential therapy that can be used during later stages of the disease. We found that the TOP1 inhibitors given days after the infection can still limit the expression of hyper-inflammatory genes in the lungs of infected animals and improve infection outcomes." Moreover, says Dr. Marazzi, topotecan (TPT), an FDA-approved Topoisomerase I (TOP1) inhibitor, as well as its derivatives, are inexpensive clinical-grade inhibitors available in most countries around the world for use as antibiotic and anti-cancer agents.

Although the pathophysiology of SARS-CoV-2 is not yet fully understood, scientists have observed that the virus triggers excess production of cytokines and chemokines—chemicals which are secreted by cells of the immune system to help fight infection. An exaggerated immune system response, which characteristically occurs in the lungs of COVID-19 patients, can flood the infected area with white blood cells, resulting in inflammation, possible tissue damage, organ failure, and death. Reduction of the inflammatory state in such patients could therefore improve their clinical outcomes.

In a previous study published in Science in 2016, the same group at Mount Sinai found that inhibiting the activation of inflammatory genes could help prevent animal deaths from viral and bacterial infections and suggested this could be a potent strategy against future pandemics. The current study, led by Mount Sinai along with partners from Singapore, Hong Kong, the United Kingdom, the United States, and other global sites, expands on that earlier work to show how epigenetic therapy (which addresses the chemical modifications that influence gene expression) could be harnessed against severe cases of COVID-19.

The team's research suggests that many other anti-inflammatory agents are less effective against COVID-19 because they target only a single inflammatory mediators, such as IL6 or IL1, or a specific gene expression program. "The fact is, a multitude of inflammatory genes and signaling pathways are dysregulated during a SARS-CoV-2 infection," explained lead author Jessica Sook Yuin Ho, Ph.D., a postdoctoral researcher at Icahn Mount Sinai. "We demonstrated that TOP1 inhibitors were able to broadly or systemically dampen inflammatory gene expression in animal models, regardless of the gene or activation pathway."

Co-author Mikhail Spivakov, Ph.D., head of the Functional Gene Control group at the MRC London Institute of Medical Sciences added, "We found that infection prompts extensive changes in the 3D connections between inflammatory genes and the 'molecular switch' regions that control their expression. This may partially explain why inhibiting topoisomerase, a protein that helps reshape DNA, helps dampen the cells' hyper-inflammatory response."

The safety and efficacy of this treatment strategy in humans will soon be evaluated at clinical sites around the world, including India, where a trial recently began and Singapore, where the National Medical Research Council of Singapore has also funded a phase 1 clinical trial of

topoisomerase 1 inhibition in COVID-19. The World Health Organization (WHO) is also expected to play an important role in subsequent studies.

"Findings from our work suggest that repurposing the TOP1 inhibitor could be a valuable global strategy for treating severe cases of COVID-19," emphasizes Dr. Marazzi. "Particularly attractive is the fact that TPT is already FDA-approved and that its derivatives are inexpensive, with generic formulations existing throughout the world. This makes these drugs readily accessible and available for immediate use in both developing and developed countries across the world."

More information: Jessica Sook Yuin Ho et al, TOP1 inhibition therapy protects against SARS-CoV-2-induced lethal inflammation., *Cell* (2021). DOI: 10.1016/j.cell.2021.03.051

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