Research identifies potential antiviral compound for COVID-19, flu, other viral infection

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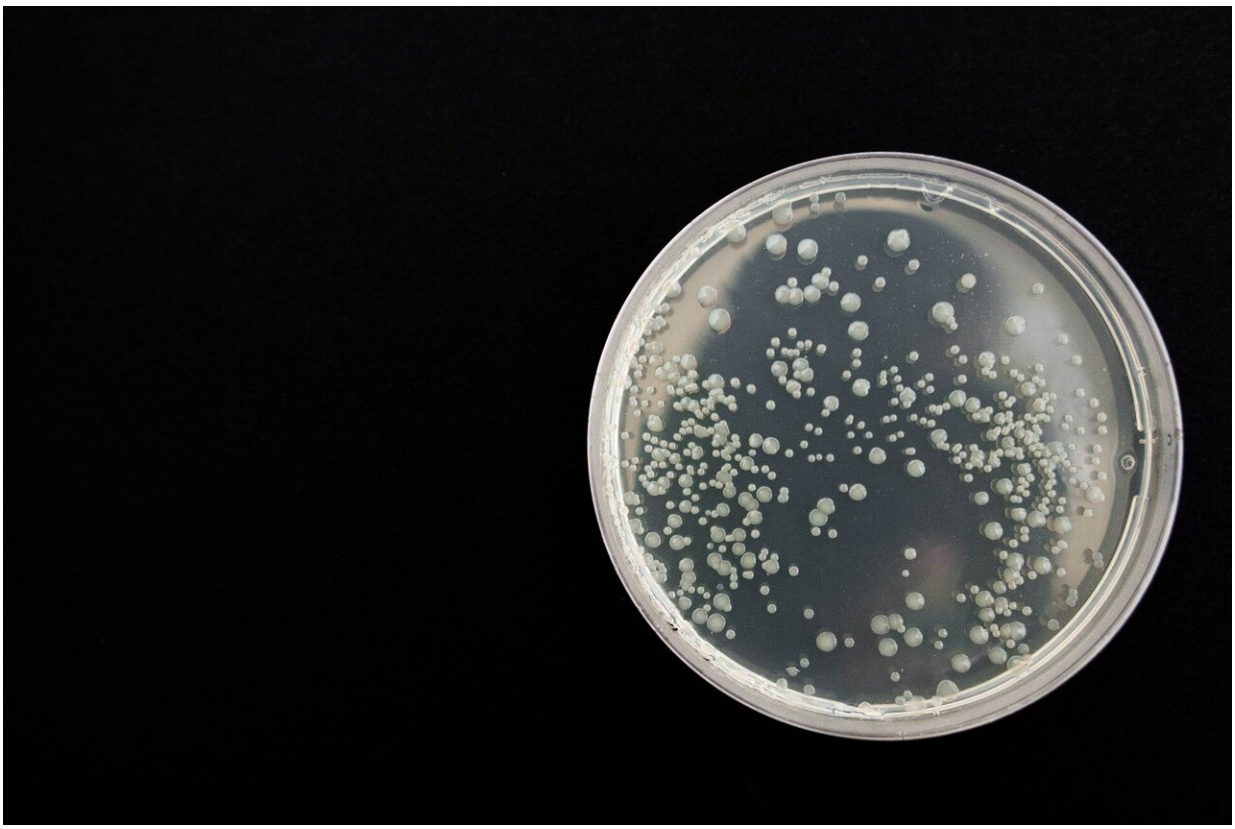

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UMass Medical School scientists Katherine A. Fitzgerald, Ph.D.; Fiachra Humphries, Ph.D.; and Liraz Galia, Ph.D., working with the British-

based pharmaceutical company GlaxoSmithKline, have identified a novel molecule capable of stimulating the innate immune system against SARS-CoV-2 virus. A trigger for the STING (stimulator of interferon genes) pathway, the compound, diamidobenzimidazole (diABZI-4), protected animal models and human cells in the lab from SARS-CoV-2 infection. Published in *Science Immunology*, these results show that diABZI-4 has the potential to be an effective antiviral prophylaxis against COVID-19.

"Identifying antiviral therapies for SARS-CoV-2 is still desperately needed while vaccines continue to rollout worldwide," said Dr. Fitzgerald, the Worcester Foundation for Biomedical Research Chair, professor of medicine, vice chair of research in the Department of Medicine and director of the Program in Innate Immunity. "An approach like this, using a STING agonist, could be deployed to protect those at highest risk in this pandemic but also in future pandemics before we have drugs that target the virus itself." Fitzgerald and Dr. Galia, a postdoctoral associate in the Fitzgerald lab, are authors on the paper.

Dr. Humphries, instructor in medicine and first author of the study, added, "Not everybody can receive a vaccine. For those who are immuno-compromised or have allergies, this treatment, which could be delivered through an inhaler, can be a viable alternative for boosting the immune response."

Vaccines work by stimulating the adaptive immune system, which creates antibodies against diseases and viruses. By taking a small piece of a virus that doesn't cause infection, in the case of SARS-CoV-2 a part of the spike protein that latches onto and infects epithelial cells, scientists can teach the adaptive immune system to recognize specific viral invaders. Once the adaptive immune system has been trained, it can more quickly respond to subsequent encounters by producing the antibodies that fight off the virus. This prevents serious illness, such as

COVID-19, and in some cases entirely blocks infection.

The innate immune system, however, is more of a generalist, explained Humphries. The innate immune system identifies any pathogen that it may encounter—whether it be bacterial, viral or fungal. One of its chief functions is to produce cytokines that serve as a first line of defense, antiviral responder. It also alerts the immune system to the presence of the invader and triggers the adaptive immune system to wake up.

The intracellular protein STING is like an early alarm system for the immune system. Once it has been activated, it triggers production of the cytokine interferon. This activity stimulates the adaptive immune system to fight off the infection. A STING agonist, such as diABZI-4, could potentially serve a wake-up call to the immune system, giving it a boost to fight off pathogens before they get established.

Humphries and colleagues believed that the immune stimulating properties of diABZI-4 could also serve as an antiviral drug. It is already being tested as an immunotherapy for cancer.

By administering diABZI-4 intranasally, directly to the site of infection in mice, Humphries showed that it could activate the immune system and eliminate viral infection, such as SARS-CoV-2.

"It was kind of amazing," said Humphries. "A single dose was able to protect 100 percent of the mice from severe disease. After taking diABZI-4, the mice were completely protected from infection."

Subsequent cell studies showed that diABZI-4 was able to stimulate the innate immune response by activating the STING pathway that produces interferon I.

In part, what makes SARS-CoV-2 so effective is its ability to circumvent

the antiviral response of the innate immune system, said Fitzgerald. "But what we show is we can use a STING agonist to illicit antiviral immunity and be effective."

Use of diABZI-4, which is stable at room temperature and can be produced relatively easily, may be an important adjuvant for current vaccine treatments for COVID-19. "You could see this being important for breakthrough infections and emerging variants," said Humphries. "You could potentially take this through an inhaler shortly after a potential exposure or even prophylactically before entering a high-risk environment such as an airplane and you'd have a short-lived antiviral boost to your immune system that would clear any virus before infection is established."

Fitzgerald and Humphries also showed that this antiviral response extended beyond SARS-CoV-2. It protected against influenza and herpes simplex virus as well. "Ultimately, this could have very broad antiviral applications," said Humphries.

More information: Fiachra Humphries et al, A diamidobenzimidazole STING agonist protects against SARS-CoV-2 infection, *Science Immunology* (2021). DOI: 10.1126/sciimmunol.abi9002

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