

Hydroxychloroquine does not inhibit SARS-CoV-2 infection in preclinical models

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Human organ chips lined with lung cells, originally developed at the Wyss Institute, were one of the complex in vitro models used to demonstrate that the drugs did not have a significant impact on the infection rate of human cells.
Credit: Wyss Institute at Harvard University

An international collaboration of researchers across more than 80

countries has come to the conclusion that chloroquine (CQ) and hydroxchloroquine (HCQ) are unlikely to provide clinical benefit against COVID-19. In a new commentary paper co-authored by Wyss Founding Director Donald Ingber, M.D., Ph.D., a group of scientists describe multiple recent studies in human Organ Chips and other multi-tissue in vitro models, mice, hamsters, and non-human primates, all of which strongly indicate the drugs do not have the efficacy suggested by earlier results obtained from in vitro studies with cultured cell lines. The paper was published today in *Nature Communications*.

"Given the urgency of finding a treatment for COVID-19, repurposing existing drugs is a faster approach than developing completely new drugs from scratch. But, as we've seen, the hype around hydroxychloroquine and chloroquine as potential therapies was based on studies that didn't accurately reflect their effects in humans," said Ingber, who is also the Judah Folkman Professor of Vascular Biology at Harvard Medical School and Boston Children's Hospital, and Professor of Bioengineering at the Harvard John A. Paulson School of Engineering and Applied Sciences (SEAS). "Touting them as 'wonder drugs' before they had undergone thorough, systematic evaluation has been extremely detrimental to the fight against COVID-19, and in this article, authors working in independent labs around the world highlight multiple studies that all suggest the drugs should never have been considered to be effective treatments."

In February 2020 as the COVID-19 outbreak was gaining speed, the World Health Organization (WHO) convened an ad hoc working group of scientists to encourage open data access, help avoid duplication of effort, and reduce the reliance on animal experimentation in the search for treatments for SARS-CoV-2 infection. Preliminary studies conducted using cultured Vero cells, which are derived from kidney cells extracted from an African green monkey, suggested that CQ and HCQ could reduce the likelihood or severity of SARS-CoV-2 infection.

However, it is well known that cells grown in a dish, especially from a non-human species, are a poor proxy for the human body.

Mice are regularly used to test potential drugs, but the animals are naturally resistant to SARS-CoV-2; as a result, either the virus needs to be adapted to be more infectious, or the mice's natural state needs to be changed to allow infection, both of which could compromise the relevance of results obtained from these studies. Nevertheless, work by co-author Matthew Frieman, Ph.D. Associate Professor of Microbiology and Immunology at The University of Maryland School of Medicine demonstrated that when mice were injected with CQ or HCQ, then exposed to a mouse-adapted SARS-CoV strain, [lung inflammation](#) in the treated mice was reduced compared to untreated mice. However, there was no difference in the amount of virus present in their lungs, suggesting that CQ and HCQ did not produce an effective antiviral effect in vivo.

In an effort to provide more accurate data about the drugs' potential activity in humans than could be obtained from in vitro cells or mice, the co-authors of the new paper oversaw research projects in several different countries that evaluated CQ and HCQ's anti-SARS-CoV-2 activity in human Organ Chips and other more complex in vitro human tissue models, as well as hamsters and two species of [non-human primates](#).

Human lung chips developed at the Wyss Institute and commercialized by Emulate, Inc. were used to test CQ's effect on lung cells infected with SARS-CoV-2 pseudoviruses (lentivirus particles engineered to express the SARS-CoV-2 spike protein). CQ did not significantly inhibit the replication of the SARS-CoV-2 Spike pseudotyped viruses in the lung cells, and more recent findings confirmed that HCQ is ineffective as well. Meanwhile, in France, a research team at Inserm developed another complex human in vitro model system called MucilAir, which is derived

from primary nasal or bronchial cells differentiated and cultivated under an air/liquid interface. In alignment with the findings by the Wyss Institute, Inserm concluded that HCQ does not significantly inhibit SARS-CoV-2 infection in their human respiratory tissue model.

Unlike mice, hamsters are naturally susceptible to the SARS-CoV-2 virus, and therefore provide a more accurate rodent model of human infection. Independent groups at Katholieke Universiteit (KU) Leuven, Belgium and Rocky Mountain Laboratories (RML) in Montana, US investigated HCQ's effects in hamsters, either alone or in combination with azithromycin, an antibiotic also purported to treat COVID-19 in humans. In the KU Leuven studies, infected hamsters that were given HCQ alone did not display a significant reduction in detectable viral RNA in their lungs, and hamsters that were given HCQ with azithromycin displayed a 3-fold increase in viral RNA. The RML studies tested HCQ's efficacy as both a prophylactic to prevent SARS-CoV-2 infection and as a treatment post-infection, and revealed no significant difference in infection, disease progression, viral replication, or virus shedding between HCQ-treated and control groups.

Testing drugs in non-human primates is a big step closer to testing them in humans, and two groups evaluated the effect of HCQ on SARS-CoV-2 infection in two different primate species. Researchers at Inserm studied cynomolgus macaques and found no significant anti-viral or clinical benefit of HCQ when given prophylactically or after infection, at several different doses, and with or without azithromycin. The viral loads in the animals' respiratory tract, lesions observed by chest CT scan, and clinical signs were comparable in the treated vs. untreated groups. RML researchers conducted similar studies in rhesus macaques, and found that animals in HCQ-treated and control groups developed similar mild to moderate disease both when HCQ was given prophylactically and after infection, and displayed indistinguishable SARS-CoV-2 replication and shedding in their lower and upper respiratory tracts.

"The fact that all of these studies in different models produced the same results is really convincing evidence that these drugs are very unlikely to be effective in humans, and we should invest our time and energy into exploring other options," said Frieman. The Wyss Institute is also collaborating with Frieman's lab on a DARPA-funded project to identify and test additional drugs that can be repurposed to treat or prevent COVID-19.

More information: S. G. P. Funnell et al. Emerging preclinical evidence does not support broad use of hydroxychloroquine in COVID-19 patients, *Nature Communications* (2020). [DOI: 10.1038/s41467-020-17907-w](https://doi.org/10.1038/s41467-020-17907-w)

Provided by Hansjörg Wyss Institute for Biologically Inspired Engineering

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