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EDITORIAL

The status surrounding chloroquine and other drugs as potential anti-infective agents for COVID-19

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Over the past two decades, we have successfully used old drugs such as the antibiotic and anticancer drug bleomycin to determine how cancer cells confer resistance to this agent. Using state-of-art drug screening approaches, we discovered that there is an uptake transporter called hCT2 (SLC22A16) that resides on the cell surface, which brings bleomycin into the cells [1]. Without the hCT2 transporter, cancer cells become extremely resistant to the cytotoxic and genotoxic effects of bleomycin [1]. Thus, a functional hCT2 is needed before administering the drug [2]. The same drug-screening program led to other findings including the observation that bleomycin has other properties whereby it can damage RNA, and not only DNA. We recently proposed that bleomycin can be repurposed and used as an antiviral agent [2]. Since many viruses such as SARS-CoV2, the cause of the COVID-19 pandemic, contain RNA as the genetic material it seems reasonable that bleomycin can be used to target the viral RNA for destruction. In the first place, our findings also raise a key question how the battery of drugs, including antivirals and antimalarials, that are being tested to potentially manage the treatment of COVID-19 enter the affected cells [3]. The focus of this report is to summarize the current state of the anti-malarial drugs chloroquine and hydroxychloroquine, as well as other agents, as potential treatment regimen for COVID-19. A central dogma on the *in vivo* actions of drug combinations must rely on efficient uptake of the molecules, and recent findings are pointing to the direction of transporters such as SLC6A20 [4]

There are many anti-infective agents that have been used for several specific purposes and are now being tested for roles in antiviral therapy. For example, chloroquine and its derivatives such as hydroxychloroquine have been safely used for over 70 years to treat malaria, as well as other forms of medical conditions such as the autoimmune disorders lupus, and rheumatoid arthritis. These drugs were shown to work by entering cells and concentrating on one of the cellular organelles called lysosome. Both forms of chloroquine can decrease the acidity of the lysosome thereby impairing its function. The normal functioning lysosome is required to promote virus attachment to the cell. It is believed that blocking the lysosomal function will reduce the viral activities. So far there are no approved drugs for preventing COVID-19, although there are mixed views that chloroquine and its derivatives might be effective. At least four independent studies have tested whether chloroquine and hydroxychloroquine can be used to control COVID-19. In these four separate trials (randomized and non-randomized) performed in the United States, China, Brazil, and France, all reported no benefits but even more complications, including the risk of increased death [5–8]. In the case of the Brazilian trial that examined the safety and efficacy of high doses of these anti-malarial drugs, this had to be prematurely terminated as the drugs led to more toxicity, death and increase in arrhythmias in patients suffering with a severe form of COVID-19 [5,9]. In fact, these drugs when used at unacceptable doses can cause several additional side effects one of which is irreversible damage to the visual field. However, for the Brazilian trials the patients were also receiving azithromycin and/or oseltamivir, which controls heart conditions, making it difficult to clearly assess the effects of chloroquine or hydroxychlorqiune alone in this trial [5]. While advocates of chloroquine and hydroxychloroquine claimed the trials were blemished as the drug(s) was given late in the disease stage, it was noted that further controlled trials would be needed to ascertain the usefulness of both drugs. Following these observations, the U.S. Food and Drug Administration immediately highlighted the risk of using these agents outside of controlled settings such as hospitals or clinical trials [6].

Because of the paucity of evidence on the safety and efficacy of the anti-malarial drugs, both the Infectious Diseases Society of America and the National Institutes of Health could not recommend any specific treatments for patients with COVID-19. Nonetheless, various national task-forces have put together recommendations to carefully retest the anti-malarial drugs to address the knowledge gap. So far, there are two trials – known as ORCHID and RECOVERY – that have started with the intent of systematically evaluating both the safety and efficacy of these anti-malarial drugs in the treatment of COVID-19 patients. It is noteworthy that very recently, there have been growing concerns regarding the validity of the data on hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19.

esides anti-malarial drugs, several other treatments are being evaluated in order to make recommendations for

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COVID-19 patients. These include using combinations of HIV antivirals such as lopinavir and ritonavir, or other antivirals such as remdesivir, together with interferon [3,10]. Other single or combination drugs proposed to be tested include ribavirin, oseltamivir as well as inhibitors to block the angiotensin receptor to prevent docking of the SARS-CoV-2 S-protein [3]. With the vast array of clinical trials, over 450 being conducted globally, there will be promising drug combinations and gene therapy that will prevent SARS-CoV-2 infection if not spare the life of the affected patients. It is noteworthy that gene therapy takes advantage of using the adeno-associated virus for rapid and targeted delivery of specific antibody against SARS-CoV-2 in the upper airways, whereby the antibody could mount a response within a week and the protection can last for nearly a year. Of particular note, passive immunization with convalescent blood plasma from COVID-19 patients who recovered and harbor a spectrum of polyclonal and monoclonal antibodies against the virus can provide short-term immunity [3].

While the body's natural defense is strong enough to defend against COVID-19 – and may explain why many individuals are asymptomatic – vaccination against SARS-CoV-2 will provide a stronger response as well as life-long protection. While the news circulating the BCG vaccine for tuberculosis may provide immunity against many viruses, it remains uncertain if it would also target the SARS-CoV-2 virus causing COVID-19. The current threat posed by SARS-CoV-2 to human health and the global economy implies that we must be prepared to take immediate actions against viruses that are capable of human emergence in the future.

To our knowledge and expertise, an important consideration when using any of the abovementioned drugs is to determine whether they can be transported into the affected cells. The nucleoside analogs, such as Remdesivir and β-D-N4-hydroxycytidine, which mimic the bases in the RNA genome of the virus, are misincorporated into the nascent RNA chains to interrupt the division of the viral genome [11]. These nucleoside analogs must be actively transported into the cells by nucleoside transporters in order to be effective. Therefore, the efficacy of these antivirals would depend on whether the COVID-19 patients maintain active transport mechanism(s) to take up the drugs, otherwise these therapeutic agents will confer no benefits and may even lead to severe side effects. As such, the most effective therapy would rely on several factors that include high-affinity drug transport mechanism and a combination of anti-infective agents that would block several steps of the SARS-CoV-2 virus physiological pathway.

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•• **These publications provide significant update on the latest development on COVID-19 therapies**

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