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Why do we lack a specific magic anti-COVID-19 drug? Analyses and solutions

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The Coronavirus 2019 (COVID-19) pandemic represents the greatest worldwide public health crisis of recent times. The lack of proven effective therapies means that COVID-19 rages relatively unchecked. Current anti-COVID-19 pharmacotherapies are drugs originally designed for other diseases, and administered orally or intravascularly. Thus, they can have various adverse effects. A specific anti-Coronavirus drug should not only target the virus per se, but also treat the related respiratory and cardiovascular symptoms. Here, we examine the advantages and disadvantages of current anti-COVID-19 pharmacotherapies, and analyze the reasons why in the era of big data we have not yet established specific coronavirus therapies and related technical bottlenecks. Finally, we present our design of a novel nebulized S-nitrosocaptopril that is under development for targeting both coronaviruses and their related symptoms.

Introduction

As of December 30, 2020, COVID-19 had spread to more than 222 countries and regions with more than 82.1 million confirmed cases, and more than 1.79 million confirmed deaths worldwide. Billions of lives have been affected as a result of mandatory isolations and quarantines. It is the first time ever in modern history that such a virus has resulted in a global economy crisis, and paralyzed our normal lives. This pandemic is testing the strength of global healthcare systems as well as the political governance of each country. Patients with COVID-19 primarily died of severe pneumonias and acute respiratory distress syndrome (ARDS). Why do we still lack a specific anti-COVID-19 drug to combat coronaviruses?

Since the 2003 outbreak of severe acute respiratory syndrome (SARS) caused by the coronavirus SARS-CoV, no specific anti-coronavirus drug has been developed as a magic bullet [1–3], although human coronaviruses were isolated from patient samples and their molecular structures analyzed early on during outbreak [4]. Some might assume that the benefit of any unproven drug as the 'last resort' will likely outweigh any adverse effects, but this might not be the case. Historically, many candidate drugs shown in preclinical settings to be effective eventually failed in clinical trials.

Coronaviruses and major pharmacotherapeutics

Coronaviruses are classified as alpha, beta, gamma, or delta viruses. They infect both humans and animals. Beta coronaviruses are pathogenic for humans and have a single-strand (ss)RNA genome, encapsulated by a membrane envelope. The coronavirus crown-like morphology is created by transmembrane spike glycoproteins (S proteins), which form homotrimers protruding from the viral surface. The S proteins of SARS-CoV and SARS-CoV-2 display structural homology and conserved ectodomains [5]. Many strategies have focused on preventing binding of SARS-CoV to its host cell

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receptor angiotensin-converting enzyme 2 (ACE2). ACE2 is an exopeptidase expressed on epithelial cells of the respiratory tract. It constitutes a pharmacological target to limit the cellular entry of SARS-CoV-2 [6].

Many treatments used for COVID-19 are drugs originally designed for other diseases [7]. For example, remdesivir (GS-5734; CAS number: 1809249–37-3) is an adenine analog approved as an HIV reverse transcriptase inhibitor, which is now in COVID-19 trials. Remdesivir displays antiviral activity against other ssRNA viruses, including filoviruses, pneumoviruses, paramyxoviruses, and the coronaviruses Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV. Remdesivir is a prodrug that is metabolized into its active form, GS-441524, an adenine nucleotide analog that interferes with the activity of viral RNA-dependent RNA polymerase (RdRp) and that promotes evasion of proofreading by viral exoribonuclease, leading to inhibition of viral RNA synthesis. Remdesivir acts early in infection, and decreases viral RNA levels in a dose-dependent manner that parallels impairment of viral load *in vitro*.

A recent study demonstrated in cell culture experiments with simian Vero E6 cells infected with SARS-CoV-2 that remdesivir is inhibitive against SARS-CoV-2 infection at EC90 of 1.76 μM, a concentration achieved *in vivo* in nonhuman primate models. It was further shown that remdesivir efficiently inhibited SARS-CoV-2 infection of human liver cancer Huh-7 cells, which are sensitive to SARS-CoV-2 infection. Prophylactic treatment of rhesus monkeys with remdesivir initiated 24 h before inoculation of MERS-CoV completely prevented virus-induced disease, inhibited virus replication in respiratory tissues, and prevented the occurrence of lung lesions. Remdesivir treatment of rhesus monkeys 12 h after inoculation with MERS-CoV also provided a significant clinical benefit, with reduction in clinical signs, reduced virus replication in respiratory tissues, and decreased occurrence and severity of lung lesions. Human safety data of remdesivir can be obtained from a randomized controlled trial of Ebola virus therapeutics that was conducted in response to the Ebola virus outbreak in the Democratic Republic of Congo in August 2018. In a subgroup of 175 patients treated with remdesivir (loading dose of 200 mg on day 1, followed by a maintenance dose of 100 mg for 9–13 days), only nine patients experienced serious adverse events, indicating that remdesivir is a relatively safe drug. A recent clinical trial with remdesivir for compassionate use in 53 patients with COVID-19 receiving oxygen support or mechanical ventilation because of an oxygen saturation of 94% or less demonstrated that intravenous treatment with 200 mg remdesivir at day 1, followed by 100 mg daily for 9 days, resulted in clinical improvement in 36 of the 53 patients (68%). However, the mortality rate was 18% among patients receiving invasive ventilation and 5% among patients not receiving invasive ventilation, suggesting that remdesivir constitutes a therapeutic option for patients with COVID-19 not receiving invasive ventilation. Based on these experimental and clinical results, clinical trials with remdesivir in patients with COVID-19 have been initiated in China, USA, Republic of Korea, Singapore, Hong Kong, Taiwan, and France.

Lopinavir/Ritonavir combination (Kaletra™) was initially used for HIV treatment. Lopinavir (ABT-378) is a potent *in vitro* inhibitor of the HIV protease and was developed in 1998 to circumvent HIV resistance towards the protease inhibitor ritonavir (ABT-538). Ritonavir inhibits metabolism of lopinavir, maintaining effective blood levels of the latter. Therefore, concomitant oral administration of lopinavir and ritonavir is often clinically recommended. Co-administration of 400 mg lopinavir with 50 mg ritonavir to healthy human volunteers enhanced the area under the concentration curve of lopinavir in plasma by 77-fold over that observed after dosing with lopinavir alone, and the mean concentrations of blood lopinavir exceeded its *in vitro* EC50 for >24 h.

Lopinavir/ritonavir clinical trials in patients with COVID-19 have been conducted in Europe (DisCoVeRy Trial), Republic of Korea, China, and Hong Kong to investigate the effects of remdesivir, lopinavir/ritonavir, and lopinavir/ritonavir plus interferon (IFN)-β-1a [8]. IFNs (α, β, and γ) are used against an array of viruses [9]. Lopinavir and ritonavir have been tested in at least two randomized trials in China. In a randomized, controlled open-label trial of 199 patients with COVID-19, no significant benefit was observed with lopinavir/ritonavir combination beyond standard care [10]. In another three-arm randomized study of 44 patients, lopinavir/ritonavir treatment was found to have little benefit for improving clinical symptoms of mild to moderate COVID-19 [11].

Chloroquine (C18H26ClN3; MW319.872) was originally approved for malaria and is now used as a broad-spectrum antiviral agent based its inhibition of endosomal acidification, which is required for virus–host cell fusion. Chloroquine has been used for decades in patients with malaria and some autoimmune diseases. The modified version, hydroxychloroquine, is less toxic. Indirect evidence supporting the use of chloroquine for COVID-19 came from studies of the original SARS-CoV. Chloroquine suppressed SARS-CoV replication in an *in vitro* primate cell study, and the replication of SARS-CoV-2 in an *in vitro* study of Vero E6 cells. By contrast, chloroquine failed to prevent influenza infection in a clinical trial and increased viral load in an HIV trial. None of the 23 ongoing trials with chloroquine in China had reported any results at the time of writing.

A French observational study enrolled 36 of 42 eligible patients with COVID-19. Twenty-six of the 36 patients were treated with hydroxychloroquine [12]. Another ten from the same hospital plus another six patients from another hospital were used as the 'control' group. The hydroxychloroquine-treated patients were much older than the controls (51.2 versus 37.3 years). Six patients were 'lost' in the follow-up study because of early cessation of hydroxychloroquine. Based on the reported patient choice and accidents during the trial, it is difficult to believe the study conclusion that 'hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin' [12].

By contrast, a French cohort study of 11 patients from the University of Paris with almost identical treatment regimens did not find any apparent benefit for early virus clearance [13]. Of the 11 patients treated with a hydroxychloroquine and azithromycin combination, one died, two were transferred to the intensive care unit (ICU), and another discontinued treatment because of significant prolongation of the QT interval. In contrast to the earlier French report [12], the virus clearance on day 5–6 was only 20%.

Hydroxychloroquine has significant toxicities, particularly in the heart, where it can prolong the QT interval, particularly when combined with azithromycin. It can also cause an irreversible retinopathy in rare cases. Chloroquine and hydroxychloroquine have high affinity with melanin. They are easily deposited in melanin-rich tissues, such as retina and iris ciliary body. Such ocular toxicity manifests as corneal deposition, dysregulation of ocular reflex, and retinopathy. The biological half-life of chloroquine and hydroxychloroquine is typically long, ranging from 30 to 60 days [14]. The volume of distribution of chloroquine is high (~800 l/kg) and its clearance is 1 l/h/kg. The whole-blood concentrations of chloroquine are eight to ten times higher than in plasma, indicating that chloroquine and hydroxychloroquine are highly concentrated in red blood cells [14,15].

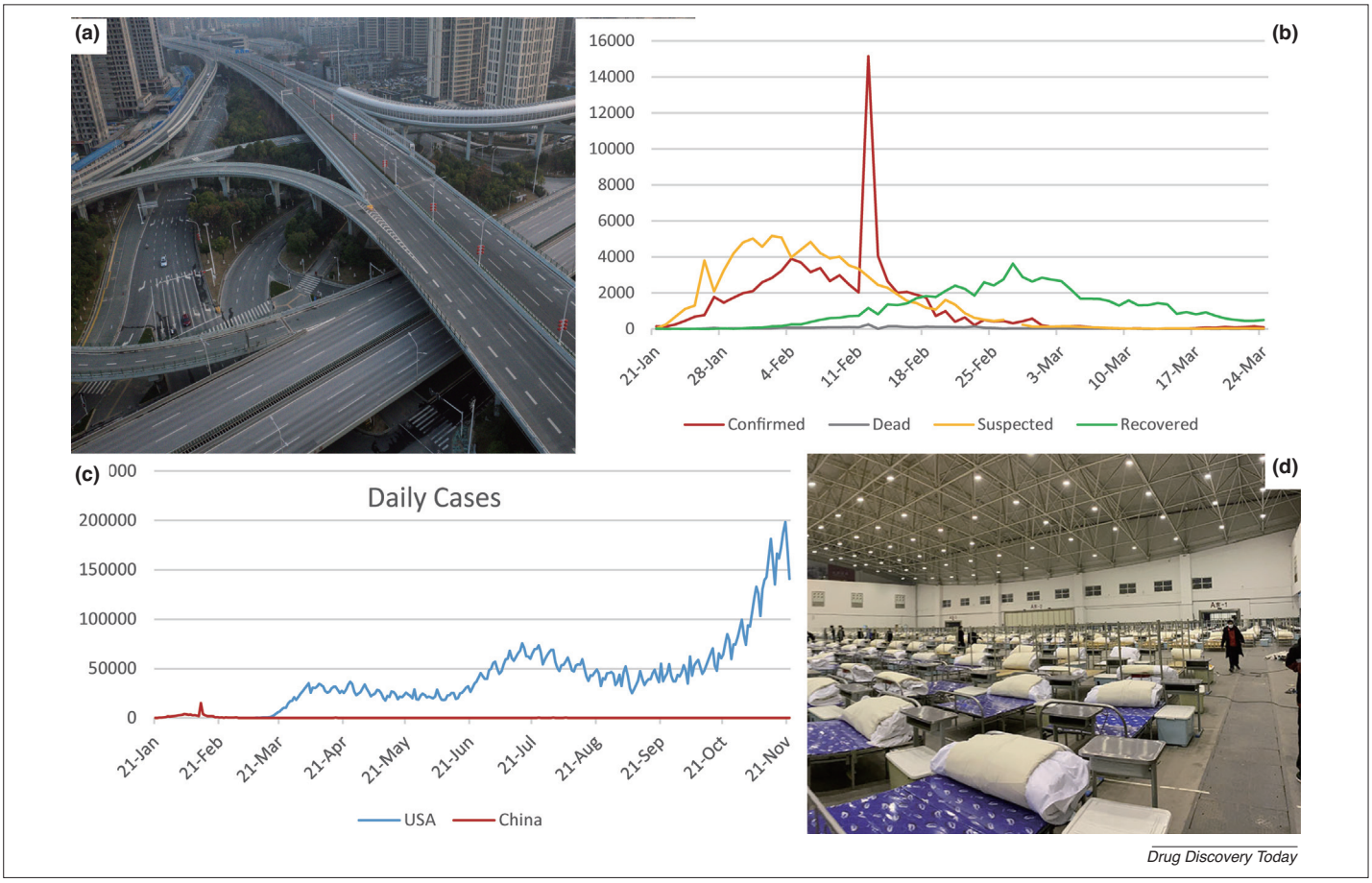

FIG. 1

Chinese political governance contained the spread of Coronavirus 2019 (COVID-19) within ~1 month after the virus was initially identified. **(a)** A typical morning in Wuhan after its lockdown during early February 2020. **(b)** The peak of the COVID-19 outbreak in China quickly decreased 1 month after locking down and sealing Wuhan off from all outside contact to stop the spread of the virus. The red curve represents the number of confirmed COVID-19; green indicates recovered; and yellow indicates suspected COVID-19 cases. **(c)** Comparison of the daily confirmed COVID-19 cases in China (red line) versus the USA. **(d)** A typical mobile cabin hospital that was remodeled from a Wuhan university gymnasium in early February 2020 and was prepared for closure in early March, 2020. Photos from Xinhua Agency.

According to online reports, hydroxychloroquine is being widely used to treat patients with COVID-19 off label. However, on July 4, 2020, the WHO discontinued hydroxychloroquine and lopinavir/ritonavir trials for COVID-19 because 'these interim trial results show that hydroxychloroquine and lopinavir/ritonavir produce little or no reduction in the mortality of hospitalized COVID-19 patients when compared to standard of care' [16].

Supportive traditional Chinese medicines, such as ShuFengJieDu and LianHuaQingWen capsules, are not specific anti-COVID-19 drugs but have been used during the COVID-19 outbreak [17]. At the time of writing there were still no approved vaccines for COVID-19, however, since then, vaccines produced by Sinovac (Inactivated virus), Sinopharm (Inactivated virus), AstraZeneca (Viral vector), Moderna (RNA based) and Pfizer (RNA based) have been approved for emergency use and are now being administered.

Pharmaceutical difficulties and profit uncertainty for anticoronavirus drug development

Why is the pace of anticoronavirus drug development and marketing so slow and disappointing? What are the bottlenecks in anticoronavirus drug development? Are governmental drug regulations on anticoronavirus unhelpful, and if so, what could we do to revise these policies?

Before the global COVID-19 pandemic, no pharmaceutical company and/or venture capital appeared to have a focus on developing anticoronavirus drugs, for the following main reasons: (i) the market size appeared too small to result in a profit for a company to survive and grow compared with the market for other kinds of drug, such as cancer drugs; (ii) the coronavirus pandemic could be contained quickly, becoming a transient disease if strict quarantine is implemented by governments (Fig. 1); (iii) new genetic variants of coronaviruses can quickly develop. The replication mutation rate of viruses is high, and drug-resistant strains can quickly result. The gene and enzyme targets of COVID-19 might disappear during the next pandemic and, hence, anti-COVID-19 drugs developed might soon be useless during the next pandemic; (iv) patients who have survived could develop immunity to the coronavirus after infection and might no longer require anticoronavirus drugs for future infections. During the pandemic period in Wuhan, doctors isolated COVID-19-specific antibodies from the plasma of patients who had recovered from pneumonia for use in clinical trials; (v) significant differences between coronavirus-induced diseases and

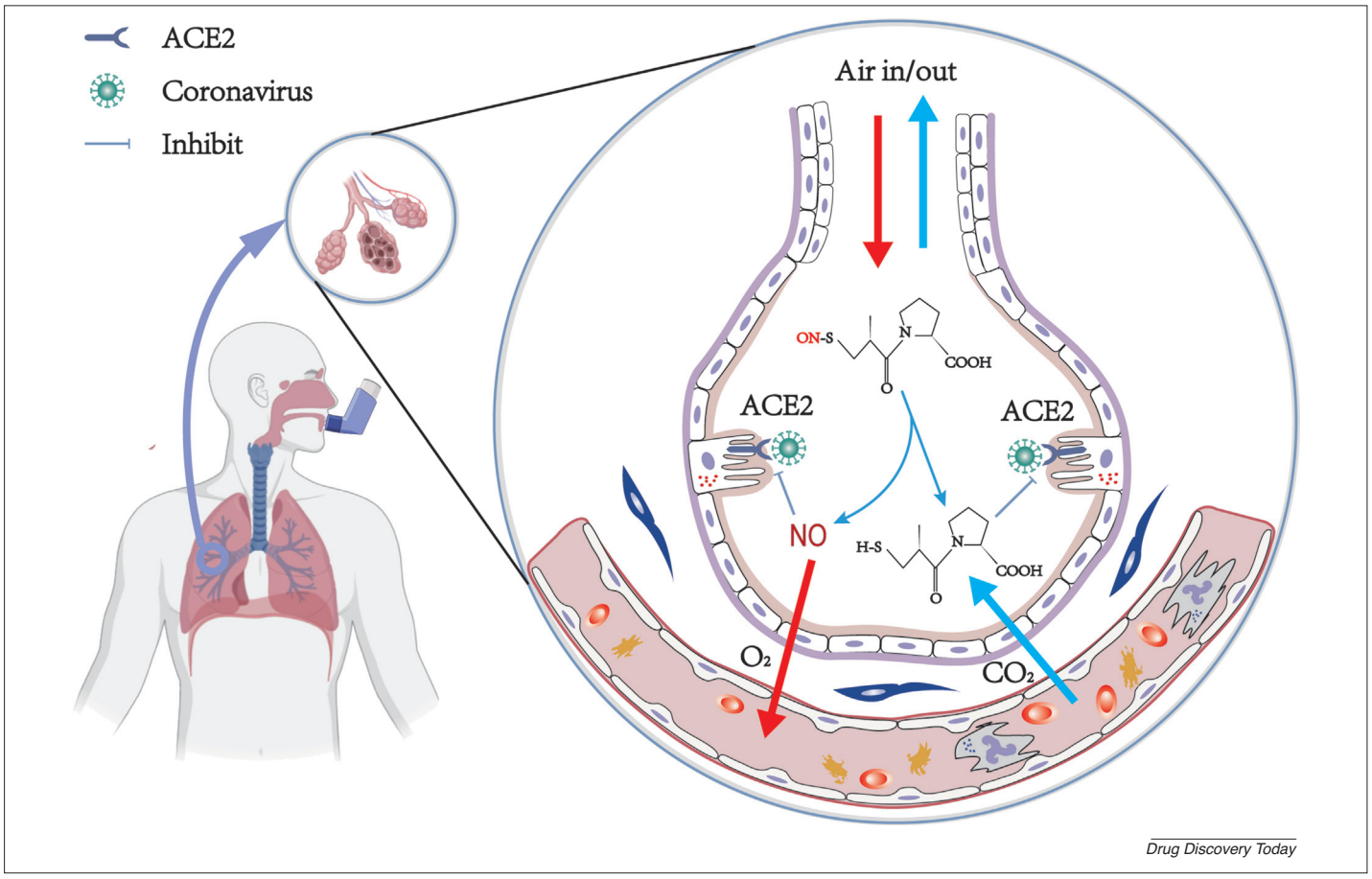

FIG. 2

Proposed action of nebulized *S*-nitrosocaptopril (CapNO) as an anticoronavirus drug. CapNO is a combination of nitric oxide (NO) and the angiotensin-converting enzyme inhibitor (ACEi) captopril. It shows potential as a specific anticoronavirus drug that both acts against COVID-19 and treats the resulting symptoms by competing with the virus for the ACE2 receptor for entry/fusion into the host cells, improving pulmonary gas/blood exchange, and reducing respiratory resistance in lungs, and the viscosity and elasticity of sputum. Inhaled NO (iNO) has been used for acute respiratory distress syndrome (ARDS) supportive treatment for >20 years to improve ARDS symptoms and pulmonary gas/blood exchange [22].

other intensively studied diseases (e.g., cardiovascular diseases and tumors) are that the former are transmitted from human to human or from animal to human, whereas the latter are non-infectious; in addition, the former have a transient peak period of infection, which can be controlled by strict quarantine measures during outbreaks (Fig. 1) and can infect all age groups, with varying degrees of severity; (vi) there are technical challenges to the development of anticoronavirus drugs that must not only inhibit the viruses, but also treat the infection-related ARDS. Many proposed anticoronavirus drugs do not have effects against ARDS and the related cardiovascular events, such as vascular endothelial lesions and blood coagulation; (vii) proposed anticoronavirus drugs are often given orally or intravenously, rather than by respiratory aerosol or nebulization, which can deliver drugs directly to pulmonary alveoli to target viruses and their infected tissues to maximize their antiviral effects; and (viii) screening of anticoronavirus drugs requires biosafe P3 laboratories with strict regulations. The establishment of such laboratories takes a significant amount of time and resources and, therefore, few P3 laboratories have been established for anti-virus drug research and development.

Pharmaceutical and regulatory solutions for the fast development of anticoronavirus drugs

Given our earlier discussion of the reasons for the apparent lack of investment by pharmaceutical companies in the development of anticoronavirus drugs, here we propose solutions to expedite pharmaceutical development and marketing of anti-coronavirus drugs.

Repurposing existing drugs and combining them to achieve a synergistic effect that not only targets different key points of coronavirus binding/entry, transcription/replication, assembly and release/exocytosis, but also alleviates ARDS. The combination design should be based on interdisciplinary understanding of the virology, respiratory theranostics and pharmacology. Drug repurposing is the process of finding new uses for exiting drugs outside the scope of their original medical indications. It involves mechanistic creativity to find new indications, and improved versions of existing drugs in addition to combining therapeutic drugs into one therapeutic. Given that the combination drugs are selected from existing drugs, the adverse effects and pharmacology of the drugs are well known and can be summarized for investigational new drug (IND) applications.

Therefore, for IND applications, we urge pharmaceutical regulatory authorities to approve potential anticoronavirus drugs for clinical trials as quickly as possible. Current policy regards an old drug for a new indication as a new drug and, therefore, it can take a long time to reach both IND and new drug applications (NDA) for anticoronavirus candidate drugs. Such regulations and guidance should be revised to

meet the current urgent need for specific anticoronavirus drugs. For example, the Chinese National Medical Products Administration (NMPA) does not require new good laboratory practice (GLP) studies of an IND for a repurposed drug.

Before the COVID-19 outbreak, we had been developing a new molecule, *S*-nitrosocaptopril, which is a *S*-nitrosylated captopril (Fig. 2) originally developed >20 years ago [18–20], although the technical bottleneck of its large-scale synthesis was only overcome recently [21]. *S*-nitrosocaptopril is metabolized to captopril (an angiotensin-converting enzyme inhibitor; ACEi), disulfide captopril, nitric oxide (NO), and NO2. Inhaled NO (iNO) has been used as supportive treatment for more than 20 years to improve ARDS symptoms and pulmonary gas/blood exchange [22]. During the COVID-19 outbreak, the Health Products and Food Branch (HPFB) of Health Canada quickly approved iNO for COVID-19 treatment [23]. High-dose iNO clinical trials (160 ppm for 6 h, daily, for 2 days) for patients with COVID-19 in ICU are currently underway [24]. On March 20, 2020, the US Food and Drug Administration (FDA) granted emergency expanded access to an iNO delivery system (INOpulse®) for immediate use as a COVID-19 treatment. Kuba *et al.* [25] demonstrated that, *in vivo*, SARS-CoV downregulates ACE2 via spike protein binding, leading to severe lung injury. Thus, the ACEi captopril might competitively bind to SARS-CoV-2 to neutralize the virus and regulate cellular ACE2 activity to protect the lungs from injury [26]. Currently, captopril is under clinical evaluation for its therapeutic potential against COVID-19 [23]. We originally developed novel and stable *S*-nitrosocaptopril monohydrate crystals for treating pulmonary arterial hypertension, and these might now be of use against COVID-19, preventing virus entry/fusion into the host cells via the ACE2 receptor, improving pulmonary gas/blood exchange, and reducing respiratory resistance, viscosity, and sputum elasticity. Thus, clinical trials involving *S*-nitrosocaptopril against COVID-19 are urgently required.

The FDA has taken actions in response to COVID-19 both in the USA and abroad [27]. Sponsors wishing to develop therapeutics for COVID-19 are encouraged to submit information and questions via the FDA's Pre-IND Consultation Program. The WHO published regulatory issues in microbicide development in 2009 [28]. In addition, Alan stated that 'an existing chemical entity designated by regulators as generally regarded as safe may not need to undergo some of the preclinical studies required for a new chemical entity. Such exceptions should be discussed with regulators on a case-by-case basis' [28]. This emergency-use IND status would be vital to facilitate anticoronavirus drug development and marketing. The NMPA has already utilized the emergency-use IND status to approve three drugs (favipiravir, chloroquine phosphate, and remdesivir) for clinical trials to address the COVID-19 crisis [29]. A drug repurposed for anticoronavirus indication should be allowed to enter clinical trials if its *in vitro* data are sufficient enough to show the selectivity index of the drug, which is a ratio of the concentration at which the candidate drug inhibits a 50% growth of human lung epithelial cells versus the concentration at which the candidate drug produces a 50% reduction in virus replication in the presence of the human lung epithelial cells [30].

Concluding remarks

COVID-19 continues to cause a severe global pandemic and social-economic crisis. To quickly control this infection, mandatory isolation and quarantine are an effective approach for preventing COVID-19 transmission, as demonstrated in China (Fig. 1). Drug reproposing is a faster way of discovering old drugs for use against COVID-19. However, a specific anticoronavirus drug should not only target the virus per se, but also treat the related respiratory and cardiovascular symptoms. Current COVID-19 drugs in clinical trials do not meet these dual requirements. Our preclinical studies demonstrated the potential of nebulized *S*-nitrosocaptopril as a good anticoronavirus candidate that meets these dual requirements. Nevertheless, the current crisis forces pharmaceutical regulation reform to expedite anticoronavirus drug development and to prepare for future pandemics.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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