Old Drugs for a New Virus: Repurposed Approaches for Combating COVID-19

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ABSTRACT: There is a large global unmet need for effective countermeasures to combat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19). The development of novel antiviral drugs is expensive and too slow to meet the immediate need. The repurposing of drugs that are approved or are under advanced clinical investigation provides a cost- and time-effective therapeutic solution. This review summarizes the major repurposed approaches that have been proposed or are already being studied in clinical trials for COVID-19. Among these approaches are drugs that aim to reduce SARS-CoV-2 replication by targeting either viral enzymatic functions or cellular factors required for the viral life cycle. Drugs that modulate the host immune response to SARS-CoV-2 infection by boosting it to enhance viral clearance or by suppressing it to prevent excessive inflammation and tissue injury represent another category. Lastly, we discuss means to discover repurposed drugs and the ongoing challenges associated with the off-label use of existing drugs in the context of the COVID-19 outbreak.

KEYWORDS: antiviral drugs, repurposing, COVID-19, SARS-CoV-2, small molecule inhibitors, anti-inflammatory drugs, direct acting antivirals, host-targeted approaches

The emergence of the novel, highly pathogenic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has evolved into a global pandemic. While the majority of infected individuals remain asymptomatic or experience a mild to moderate, self-limited illness, a fraction of the patients progresses to develop severe infection that is often complicated by respiratory failure, cardiac complications, and sometimes death. Moreover, it appears that COVID-19 may be causing long-lasting lung and heart injury. As of the 16th of July 2020, more than 13.9 million COVID-19 cases and over 590,000 deaths have been reported worldwide, and the pandemic has taken a huge toll on the health care system and global economy. Measures such as social distancing and home isolation provide a temporary solution to control viral spread; however, in the absence of an effective approved vaccine, the entire world population continues to be at risk for SARS-CoV-2 infection. Hence, there is an urgent need for approaches to treat COVID-19 patients and prevent the short- and long-term complications associated with this disease.

As with other newly emerging viruses that have caused outbreaks within the past two decades, including the coronaviruses implicated in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) as well as the unrelated Ebola (EBOV, filovirus) and Zika (ZIKV, flavivirus) viruses, no approved, clinically effective therapy is available for treating SARS-CoV-2. Since the development of new drugs typically takes 8 to 12 years, this approach cannot...
provide an immediate solution in the context of such outbreaks. In contrast, repurposing already approved or investigational drugs can significantly accelerate the development and deployment of therapies for such emerging viral infections. Repurposing existing drugs that have already been shown to be safe in humans, albeit in a different disease model(s), reduces the clinical risk and facilitates a faster path into the clinic. Moreover, relying on existing human safety, pharmacology, and toxicology data reduces the substantial cost associated with the development of a new drug (over two billion dollars on average).1

Multiple repurposed drugs are currently being studied for COVID-19 in clinical trials, and many more are being investigated in preclinical models. One category of such drugs aims to reduce viral replication and can be classified into direct acting antivirals (DAAs) that target viral enzymes (primarily the viral proteases and polymerase) and host-targeted drugs that inhibit cellular functions required for viral replication. Inhibitors that modulate virus-induced inflammation and tissue injury constitute another category. The major categories of repurposed approaches that are already being studied or have been proposed for COVID-19 treatment with representative examples are discussed below and illustrated in summary tables and figures.

**REPURPOSED APPROACHES THAT PRIMARILY INHIBIT VIRAL REPLICATION**

**Direct Acting Antivirals (DAAs).** SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus whose replication and transcription are catalyzed by an RNA-dependent RNA polymerase (RdRp). The two SARS-CoV-2 proteases, papain like protease (PLpro) and the main protease (Mpro), play a key role in replication and transcription via processing of the viral polyproteins.5 As with other viral infections, due to their known biological functions and active enzymatic sites, the SARS-CoV-2 polymerase and proteases are intuitive therapeutic targets.

**Polymerase Inhibitors.** In the past decade, several chemically distinct nucleoside and nucleotide analogues that inhibit the polymerase of multiple unrelated RNA viruses have been developed. One example is remdesivir, an investigational nucleoside analogue originally developed as a therapy for EBOV disease. Remdesivir gets incorporated into nascent viral RNA chains and results in their premature termination.5 As with other viral infections, due to their known biological functions and active enzymatic sites, the SARS-CoV-2 polymerase and proteases are intuitive therapeutic targets.

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Remdesivir has previously demonstrated in vitro activity against SARS-CoV and MERS-CoV,6 and it reduced disease severity, viral replication, and lung injury in mouse (SARS-CoV) and NHP (MERS-CoV) models.9 Recently, remdesivir was shown to inhibit RNA synthesis by a purified recombinant SARS-CoV-2 RdRp to suppress SAR-CoV-2 infection in both Vero E6 (green monkey kidney) (EC50 = 0.77 μM) and Huh7 (human hepatoma) cells.11 Moreover, remdesivir demonstrated potent inhibition of SARS-CoV-2 replication in human lung cells and primary human airway epithelial cultures (EC50 = 0.01 μM).12 Therapeutic administration of remdesivir in mice infected with SARS-CoV encoding the RdRp of SARS-CoV-2 reduced viral load in the lungs and improved pulmonary function relative to the vehicle.12 In an NHP SARS-CoV-2 infection model that causes lower respiratory tract disease, remdesivir treatment provided protection from respiratory signs and reduced pulmonary infiltrates on radiographs.15 Viral titers in bronchoalveolar lavages, lung viral loads, and lung injury were significantly reduced in remdesivir-treated animals relative to controls.13 A remdesivir compassionate use study in 53 patients hospitalized for severe COVID-19 demonstrated clinical improvement in 68% of the patients; however, no control arm was included in this study. In a double-blind, placebo-controlled, multicenter trial in patients with severe COVID-19, intravenous remdesivir treatment did not improve the time to clinical improvement; however, the study did not reach its target enrollment and was stopped.15 In contrast, preliminary data from the double-blind, randomized, placebo-controlled adaptive COVID-19 treatment trial sponsored by the US National Institute of Health (NIH) (NCT04280705S) involving 1059 hospitalized adult patients (538 assigned to remdesivir and 521, to placebo) with lower respiratory COVID-19 infection showed that a 10-day remdesivir treatment course shortened the median recovery time relative to the placebo from 15 to 11 days (p < 0.001) and reduced the estimates of mortality by 14 days from 11.9% to 7.1% with no increase in serious adverse events.16 Moreover, a randomized, open-label, phase 3 trial involving 397 hospitalized patients with confirmed SARS-CoV-2 infection with oxygen requirements (but not mechanically ventilated) demonstrated comparable efficacy of 5- and 10-day remdesivir treatment courses with clinical improvement of 2 points or more on the ordinal scale detected in 64% and 54% of patients, respectively. Collectively, these findings suggest that remdesivir is moderately effective and is generally safe and led to the recent emergency use approval of this drug for the treatment of COVID-19 by the US Food and Drug Administration (FDA).

The guanine analogue favipiravir, which is approved in Japan for the treatment of influenza A virus infection, is another example for a broad-spectrum polymerase inhibitor.17 Favipiravir moderately inhibits replication of several RNA viruses in vitro,16 albeit with high EC50 values: 61.88 and 67 μM in the case of SARS-CoV-2 and EBOV, respectively.11 High drug concentrations are therefore required to maintain levels above these EC50 values but appear to be effectively achieved and well tolerated. Moreover, by self-inhibiting its metabolism into an inactive oxidative metabolite, favipiravir increases the plasma parent/inactive metabolite ratio, thereby facilitating increased cellular uptake and compensating for the high EC50 values.19 Indeed, favipiravir protected 100% of mice from an EBOV challenge and was shown to prolong survival and reduce viral load in a retrospective EBOV study during the 2014–2015 outbreak.20 In a prospective, randomized, multicenter study (ChiCTR200030254), favipiravir demonstrated no effect in critically ill COVID-19 patients; however, it improved clinical recovery at day 7 in moderate cases relative to Arbidol, a fusion inhibitor also used for influenza treatment (71.4% vs 55.9%, p = 0.019). In a clinical trial involving 80 patients in China (ChiCTR2000029600), the combination of favipiravir with interferon-α reduced SARS-CoV-2 clearance time relative to lopinavir/ritonavir plus interferon-α in the control arm (median of 4 vs 11 days).22 Notably, while the adverse effects attributed to favipiravir treatment were mild and manageable,23 caution is needed due to its teratogenic risk and potential for drug–drug interactions.19 Favipiravir is
Currently being studied in several open label phase 2 clinical trials (NCT04358549, NCT04346628), and it has been recently approved for COVID-19 treatment in China and India.

A third investigational RdRp inhibitor, the adenosine analogue galidesivir, has also shown activity against a wide range of viruses (including coronaviruses) and protected NHP from Marburg virus (filovirus) infection. Galidesivir has recently been shown to tightly bind to SARS-CoV-2 RdRp, and its clinical safety and efficacy are currently being studied in a randomized, double-blind, placebo-controlled clinical COVID-19 trial (NCT03891420).

Viral Protease Inhibitors. Another attractive antiviral target is the viral main protease (Mpro). This chymotrypsin-like cysteine protease proteolytically cleaves protein precursors necessary for viral RNA replication and production of infectious viral particles. Several protease inhibitors have been proposed and/or studied for the treatment of COVID-19. One example is the lopinavir/ritonavir combination, which is approved for the treatment of human immunodeficiency virus (HIV-1) infection. While treatment with these drugs individually has demonstrated moderate anti-SARS-CoV-2 activity in Vero E6 cells (EC\textsubscript{50} = 5.73 μM, lopinavir, and EC\textsubscript{50} = 8.63 μM, ritonavir), their combination showed no benefit beyond supportive care in a randomized, controlled, open-label clinical trial in hospitalized patients with severe COVID-19. The ability of the lopinavir/ritonavir combination to reduce SARS-CoV-2 load in the respiratory tract in patients with mild COVID-19 is currently being studied (NCT0407693). Nelfinavir, another oral protease inhibitor approved for HIV-1 treatment, showed antiviral activity against SARS-CoV\textsuperscript{29} and SARS-CoV-2 (EC\textsubscript{50} = 0.77 μM, CC\textsubscript{50} > 20 μM) in Vero E6 expressing TMPRSS2 cells.\textsuperscript{27}

A potentially more attractive repurposed option that also targets the viral protease is the organoselenium compound, ebselen. Ebselen mimics the action of glutathione peroxidase and thus has anti-inflammatory, antioxidant, and cytoprotective properties. This compound has demonstrated no side effects when tested at high oral doses in humans in several phase 2/3 clinical studies for various indications including hearing loss, diabetes, and stroke. Ebselen emerged as the top hit in a high-throughput activity screening assay of a library of 10,000 approved and investigational drugs, where it demonstrated the strongest inhibition of SARS-CoV-2 Mpro activity (IC\textsubscript{50} = 0.67 μM) and was shown to covalently bind to cysteine 145 within the catalytic dyad of the viral Mpro. Moreover, it showed a moderate anti-SARS-CoV-2 activity in Vero cells, with an EC\textsubscript{50} of 4.67 μM, which could likely be achieved with the previously tested oral dosing. Notably, since it is nonselective, the likelihood of the emergence of viral resistance to ebselen is predicted to be lower than to other protease inhibitors.

Host-Targeted Antiviral Approaches. Viruses replicate within the host cell while relying on cellular machineries for multiple distinct steps in their life cycle. Repurposing inhibitors that target cellular functions required for SARS-CoV-2 infection is thus an attractive approach that may have the added benefit of a higher genetic barrier to the emergence of resistance.\textsuperscript{35}

Inhibitors of Cellular Proteases. Effective SARS-CoV-2 entry requires proteolytic processing for activation of the spike (S) glycoprotein by the cellular endosomal cysteine proteases cathepsin B and L (CatB/L) and the transmembrane serine protease 2 (TMPRSS2). TMPRSS2 is also required for the activation of the S protein of SARS-CoV and MERS-CoV\textsuperscript{37,38} and was shown to be essential for viral spread and pathogenesis in animal models of these infections.\textsuperscript{39} Pharmacological targeting of TMPRSS2 therefore represents an attractive approach to block the entry of coronaviruses.

Camostat mesylate is an oral serine protease inhibitor that has been clinically used in Japan for the treatment of pancreatitis.\textsuperscript{40} Camostat was shown to reduce MERS-CoV, SARS-CoV, and SARS-CoV-2 entry in a lung epithelial cell line (Calu-3) and in primary human lung cells with no apparent cytotoxic effects.\textsuperscript{41} In a mouse model, camostat was effective in protecting mice against death due to a lethal SARS-CoV infection, with a survival rate of ~60% relative to vehicle-treated controls.\textsuperscript{41} Several randomized, placebo-controlled clinical trials to determine the effect of camostat on COVID-19 infection have been initiated (NCT04353284, NCT04321096).

A closely related compound, nafamostat mesylate, is another safe serine protease inhibitor. It is approved in Japan as an anticoagulant and antipancreatitis agent. Nafamostat was previously shown to inhibit the TMPRSS2-dependent entry of MERS-CoV in Calu-3 cells,\textsuperscript{42} and its activity against SARS-CoV-2 entry and overall infection was recently shown to be superior to that of camostat (EC\textsubscript{50} = 5 nM vs 87 nM, respectively).\textsuperscript{43} A randomized, placebo-controlled clinical trial to assess the efficacy of intravenous nafamostat treatment in COVID-19 patients was recently initiated (NCT04352400).

Kinase Inhibitors. Viruses have been shown to hijack a large number of host kinases at distinct stages of their life cycle (reviewed in ref 44). Cellular kinase inhibitors approved as anticancer or anti-inflammatory drugs therefore represent another category of compounds with a great potential to be repurposed into antivirals. Beyond their effect on viral replication, many of these kinase inhibitors have also been shown to reduce inflammation and tissue injury, such as by suppressing the production of cytokines (interleukin 6 (IL-6), tumor necrosis factor α (TNF-α) and transforming growth factor β (TGF-β)) implicated in inflammation and lung fibrosis. These kinase inhibitors may thus potentially achieve a dual role in the treatment of COVID-19 patients.

Members of the Src family of kinases (SFKs) and the Abl family of nonreceptor tyrosine kinases have been implicated in the life cycle of multiple viruses (reviewed in refs 44 and 45). RNAi-mediated depletion of the Src family proteins Lyn and Fyn reduced MERS-CoV infection, suggesting these proteins may be required for coronavirus infection.\textsuperscript{46} The approved anticancer drug dasatinib and the investigational (phase 3) compound saracatinib, with activity against both SFKs and c-Abl (cellular Abelson tyrosine kinase), have been shown to inhibit a broad-spectrum of viruses \textit{in vitro}.\textsuperscript{47,48} Dasatinib was found to inhibit SARS-CoV and MERS-CoV with EC\textsubscript{50} of 2.1 and 5.4 μM in Vero E6 cells.\textsuperscript{49} Saracatinib was shown to inhibit early stages of the MERS-CoV life cycle (EC\textsubscript{50} of 2.9 μM in Huh7 cells) and was synergistic when combined with gemicitabine, which also inhibits MERS-CoV replication.\textsuperscript{46} The inhibition of actin motility was proposed as one mechanism of antiviral action of Src and/or Abl inhibitors in other viral infections;\textsuperscript{50} however, the mechanism of antiviral action and the molecular targets (Abl only or Abl plus Src) that mediate the antiviral action of these drugs in coronavirus infections remain to be uncovered.

Similarly, imatinib and/or nilotinib, approved anticancer c-Abl inhibitors lacking anti-Src family kinase activity, also

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inhibited the replication of coronaviruses and other RNA viruses in cultured cells. Nilotinib and imatinib inhibited SARS-CoV and/or MERS-CoV infections with an EC\textsubscript{50} at a micromolar range (EC\textsubscript{50} ≈ 10–20 \(\mu\)M).\textsuperscript{49} Imatinib was shown to inhibit the fusion of virions at the endosomal membrane by targeting Abl2 kinase,\textsuperscript{52} and it was therefore proposed that it may inhibit the function, localization, or activity of TMPRSS2.\textsuperscript{52} In a murine model of vaccinia virus, imatinib effectively reduced viral load, viral spread, and mortality. In contrast, dasatinib did not protect mice but rather induced immunosuppression, raising a concern about its utility in controlling viral infections in vivo.\textsuperscript{50} The activity of these and other kinase inhibitors against SARS-CoV-2 is currently being studied in preclinical models. Moreover, several studies aimed at testing the safety and efficacy of imatinib in COVID-19 patients are ongoing.

Several kinases in the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway have been shown to be upregulated and essential for the replication of various viruses (reviewed in ref \textsuperscript{44}). Infection with MERS-CoV has been shown to activate this pathway and to be suppressed by two anticancer compounds, trametinib, an FDA-approved MEK1/2 inhibitor, and selumetinib, a recently approved MEK1/ERK1/2 inhibitor.\textsuperscript{53} The anti-SARS-CoV-2 potential of these compounds is currently being studied in preclinical models.

A recent phosphoproteomics analysis revealed changes in the phosphorylation patterns of cellular and viral proteins during SARS-CoV-2 infection.\textsuperscript{64} Among these alterations is the activation of the p38/MAPK signaling pathway, which mediates the response to stress stimuli and was previously shown to be similarly activated in cells infected with SARS-CoV and MERS-CoV.\textsuperscript{53,55} Pharmacological inhibition of this pathway by either gilteritinib, an FDA approved anticancer inhibitor of AXL, or ralimetinib, a p38 inhibitor under phase 2 clinical trials for cancer, demonstrated potent anti-SARS-CoV-2 activity (EC\textsubscript{50} = 0.807 \(\mu\)M and EC\textsubscript{90} = 0.873 \(\mu\)M, respectively).\textsuperscript{54} Prominent activation of PIKfyve (phosphatidylinositol 3-phosphate 5-kinase), a lipid kinase that regulates endosomal trafficking and endosome homeostasis, was also detected.\textsuperscript{54} Apilimod, an investigational oral anti-inflammatory and anticancer (phase 2), safe drug that was developed to inhibit IL-12/23 and later found to target PIKfyve,\textsuperscript{56} was shown to suppress the entry of SARS-CoV-2 pseudovirions and overall replication (EC\textsubscript{50} < 0.08 \(\mu\)M in Vero E6 cells; EC\textsubscript{50} = 0.007 \(\mu\)M in A549 cells expressing ACE2).\textsuperscript{54} The safety and efficacy of apilimod is being studied in a phase 2 randomized, double-blind, placebo-controlled trial in mild COVID-19 patients in an outpatient setting (NCT04446377). Lastly, SARS-CoV-2 infection was shown to promote the shutdown of mitotic kinases, resulting in cell cycle arrest.\textsuperscript{54} Pharmacological inhibition of cyclin-dependent kinases by dinaciclib, an anticancer drug (phase 3), exhibited potent anti-SARS-CoV-2 activity (EC\textsubscript{50} = 0.127 \(\mu\)M in Vero E6 cells; EC\textsubscript{50} = 0.032 \(\mu\)M in A549 cells expressing ACE2).\textsuperscript{54} However, serious hematological toxicities may limit the use of dinaciclib as an anticancer drug.\textsuperscript{54}

**Host-Targeted Drugs with Complexed or Unclear Mechanism of Action (MOA).** Among the approved drugs that exhibit anti-SARS-CoV-2 activity are agents for which the mechanism of antiviral action is complex and unclear. In general, these drugs have multifunctional activities, and their antiviral effect is unlikely to be mediated by the same mechanism that is relevant to the primary indication for which they are approved.

One such example is niclosamide, an FDA-approved drug used to treat tapeworm infection. Niclosamide has previously shown activity against various viruses including MERS-CoV and SARS-CoV with EC\textsubscript{50} values of less than 0.1 \(\mu\)M in Vero cells.\textsuperscript{59–61} It has recently emerged as a potent inhibitor of SARS-CoV-2 infection via high-throughput screening of a drug library (EC\textsubscript{50} = 0.28 \(\mu\)M),\textsuperscript{52} and it is currently being studied in animal models of SARS-CoV-2. While niclosamide exerts its anthelmintic effect by inhibiting oxidative phosphorylation and stimulating adenosine triphosphatase activity in the mitochondria,\textsuperscript{63} it has been shown to regulate multiple signaling pathways and biological processes.\textsuperscript{84} The precise mechanism of antiviral action of this multifunctional drug thus remains unknown. A clinical trial to investigate the efficacy of niclosamide in combination with diltiazem (a calcium channel blocker) for the treatment of mild COVID-19 in patients with comorbidities has been initiated (NCT04372082).

Other antiparasitic drugs demonstrating anti-SARS-CoV-2 activity are chloroquine and its less toxic derivative hydroxychloroquine.\textsuperscript{65} Chloroquine and hydroxychloroquine are approved for the treatment of malaria and inflammatory diseases, such as lupus and rheumatoid arthritis. These drugs have shown activity against multiple viruses in vitro but did not improve virological or clinical outcome in human studies in other viral infections, such as dengue\textsuperscript{66–68} and flu.\textsuperscript{69} They are thought to exert their antiviral effect by preventing endosomal acidification required for virus/cell fusion and by blocking autophagosome–lysosome fusion.\textsuperscript{70} Yet, additional mechanisms, such as interference with the glycosylation of angiotensin-converting enzyme 2 (ACE2), the cellular receptor of coronaviruses, have also been proposed.\textsuperscript{71} Although chloroquine demonstrated in vitro activity against SARS-CoV and MERS-CoV at a concentration that can be achieved in serum by the approved oral dosage,\textsuperscript{65} it did not effectively reduce viral replication in SARS-CoV-infected mice.\textsuperscript{74}

Both drugs were recently shown to moderately inhibit SARS-CoV-2 replication in Vero E6 cells with variable EC\textsubscript{50} values across different studies (0.72–7.36 \(\mu\)M, chloroquine; 4.5–12.96 \(\mu\)M, hydroxychloroquine).\textsuperscript{11,75,76} On the basis of these in vitro data and their anti-inflammatory properties, the utility of hydroxychloroquine and chloroquine for the prevention and treatment of COVID-19 has been assessed in several studies (reviewed in \textsuperscript{77}). The majority of retrospective, observational studies in hospitalized COVID-19 patients have demonstrated no benefit with hydroxychloroquine treatment.\textsuperscript{78}

A reduction in COVID-19 associated mortality was detected in one study in hospitalized patients who received the drug early during their disease course, but only when controlling for COVID-19 risk factors.\textsuperscript{79} Moreover, concerns have been raised about the safety of this approach and, specifically, its association with cardiac toxicity. Indeed, a clinical trial evaluating the safety and efficacy of chloroquine in patients with severe COVID-19 (NCT04323527) was terminated early due to prolongation of the QTc interval leading to increased cardiac toxicity and fatality rates.\textsuperscript{80} As a result, prospective COVID-19 clinical trials with hydroxychloroquine and chloroquine have been terminated, and the emergency use authorization for these drugs has been revoked by the FDA.\textsuperscript{81}

The discussed repurposed approaches that primarily inhibit viral replication are illustrated in Table 1 and Figure 1.
While the immune response induced by SARS-CoV-2 infection is protective, it also plays an important role in disease pathogenesis.82 During the incubation period and early stages of COVID-19, the effective immune response facilitates viral clearance. However, when the response is insufficiently protective, SARS-CoV-2 replicates efficiently in tissues expressing ACE2, such as lungs, heart, and intestines, leading to massive tissue destruction, severe inflammation, vascular hyperpermeability, and ultimately, tissue fibrosis and long-term dysfunction. In the lungs, this excessive inflammatory response leads to acute respiratory distress syndrome (ARDS), which is often fatal,83 or can result in an epidermal growth factor (EGFR)-mediated pulmonary fibrosis, as observed in SARS-CoV infection.84 Strategies that boost the innate immune response during the early stages of viral infection to enhance viral clearance and modulate the excessive inflammatory response to reduce tissue injury during the later stages of infection may both provide benefit. A number of repurposed approaches that aim to achieve these effects are currently being investigated.

Interferons (IFN) are one example. These soluble glycoproteins have strong antiviral, antiproliferative, and immunomodulatory effects. In an ex vivo model of human lung, SARS-CoV-2 largely failed to induce the expression of any IFNs (type I, II, or III),85 indicating that the early innate immune response to this virus is impaired and supporting the use of exogenous IFN to stimulate innate immunity as a candidate therapeutic modality. Type I IFNs (IFN-I, e.g., IFN-α and IFN-β) have been approved for the treatment of chronic hepatitis B and C infections and have previously demonstrated in vitro activity and protection in various animal models of MERS-CoV86 and SARS-CoV.74 In a preliminary, uncontrolled study of patients infected with SARS-CoV, the use of type I IFN plus corticosteroids was associated with a faster resolution of radiographic lung abnormalities and improved oxygen saturation levels than treatment with corticosteroids alone.87 SARS-CoV-2 appears to be more susceptible to IFN-α treatment in vitro than SARS-CoV.88 In a retrospective study of 77 adults with moderate COVID-19, treatment with nebulized IFN-α2b reduced the duration of both detectable virus in the upper respiratory tract and elevated blood levels of inflammatory markers (IL-6 and C-reactive protein).89 Several types and routes of administration of IFN-I are currently being studied in COVID-19 patients.

Perhaps a more attractive candidate approach for COVID-19 treatment is, however, type III IFNs (IFN-λ1−4). Although not approved yet, IFN-λ has been shown to be safe in large phase 1/2/3 trials (involving ∼3000 patients) for the treatment of hepatitis B, C and D infections and have previously demonstrated in vitro activity and protection in various animal models of MERS-CoV86 and SARS-CoV.84 In a preliminary, uncontrolled study of patients infected with SARS-CoV, the use of type I IFN plus corticosteroids was associated with a faster resolution of radiographic lung abnormalities and improved oxygen saturation levels than treatment with corticosteroids alone.87 SARS-CoV-2 appears to be more susceptible to IFN-α treatment in vitro than SARS-CoV.88 In a retrospective study of 77 adults with moderate COVID-19, treatment with nebulized IFN-α2b reduced the duration of both detectable virus in the upper respiratory tract and elevated blood levels of inflammatory markers (IL-6 and C-reactive protein).89 Several types and routes of administration of IFN-1 are currently being studied in COVID-19 patients.

\[\text{Known in vitro data for SARS-CoV-2 and in vivo data for SARS-CoV, MERS-CoV, and SARS-CoV-2 are included. Alternative names for drugs are mentioned. HAE, human airway epithelial cells; Vero, African green monkey kidney epithelial cells; Calu-3, human lung epithelial cells; Huh7, human hepatoma cells; AS-49-ACE2, human lung carcinoma cells expressing ACE2 receptor; RdRp, RNA-dependent RNA polymerase; Mpro, viral main protease; ND, not determined; NI, not initiated.}\]

### MODULATORS OF INFLAMMATION AND TISSUE INJURY

| DAAs | viral polymerase inhibitors | name | type | original indication | cell line | EC50 | mouse model | NHP | target for antiviral activity | COVID-19 stats |
|------|-----------------------------|------|------|---------------------|-----------|------|-------------|-----|-----------------------------|------------------|
|      | remdesivir (GS-5734)        | nucleoside analogue | investigational (Ebola) | Vero E6 | 0.77 μM | SARS-CoV-2/RdRp of SARS-CoV-2 (reduced viral load) | SARS-CoV-2 (reduced viral load and lung injury) | RdRp | emergency use approval by US FDA |
|      | favipiravir (T-705)         | nucleoside analogue | influenza A virus (approval in Japan) | Vero E6 | 0.01 μM | ND | ND | ND | ND | phase 3, approved in China and India |
|      | galidesivir (RBCX430) | nucleoside analogue | investigational | ND | 61.68 μM | ND | ND | ND | RdRp | phase 1 |
|      | lopinavir (LPV)            | protease inhibitor | HIV-1 infection | Vero E6 | 5.73 μM (LPV) | ND | ND | Mpro | phase 2 |
|      | ritonavir (RV)             | protease inhibitor | HIV-1 infection | Vero E6 | 8.63 μM (RV) | ND | ND | Mpro | phase 2 |
|      | nelfinavir (ebov)          | protease inhibitor | organoselenium compound | Vero E6 | 4.67 μM | ND | ND | Mpro | phase 2 |
|      | host-targeted antiviral approaches | oseltamivir mesylate (TOY-305) | neuraminidase inhibitor | Calu-3 | 0.01 μM | SARS-CoV-2 (protection from death) | ND | TMPPS2 | phase 2/3 |
|      | oseltamivir mesylate (TOY-305) | neuraminidase inhibitor | neuraminidase inhibitor | Calu-3 | 0.005 μM | ND | ND | TMPPS2 | phase 2/3 |
|      | darunavir (S175-571)       | anticonvulsant drug | leukemia | Vero E6 | 2.1 μM (SARS-CoV-2) | ND | ND | Srev kinase + Akt kinase | ND |
|      | amprenavir (S175-571)      | anticonvulsant drug | Alzheimer’s disease, cancer | Vero E6 | 9.8 μM (SARS-CoV-2) | ND | ND | Srev kinase + Akt kinase | ND |
|      | atazanavir (Am9107)        | anticonvulsant drug | leukemia | Vero E6 | 17.7 μM (MERS-CoV) | ND | ND | Akt kinase | phase 3 |
|      | abacavir (GS-110212)       | anticonvulsant drug | melanoma | Vero E6 | 0.807 μM | ND | ND | Akt kinase | ND |
|      | remdesivir (GS-5734)       | anticonvulsant drug | neurofibromatosis type | Vero E6 | 0.837 μM | ND | ND | Akt kinase | ND |
|      | ribavirin (1/2T2828)       | anticonvulsant drug | acute myeloid leukemia | Vero E6 | 0.027 μM | ND | ND | Akt kinase | ND |
|      | ritonavir (RV)             | anticonvulsant drug | gribonuria, ovarian cancer | Vero E6 | 0.067 μM | ND | ND | Akt kinase | ND |
|      | abacavir (GS-110212)       | anticonvulsant drug | anti-inflammatory, anti-cancer | Vero E6 | 0.032 μM | ND | ND | Akt kinase | ND |
|      | dolutegravir (S175-571)    | anticonvulsant drug | anti-inflammatory, anti-cancer | Vero E6 | 0.032 μM | ND | ND | Akt kinase | ND |
|      | rilpivirina (SY228280)     | anticonvulsant drug | anti-inflammatory, anti-cancer | Vero E6 | 0.032 μM | ND | ND | Akt kinase | ND |
|      | amsacrine (SY228280)       | anticonvulsant drug | AIDS-related complex (ARC) | Vero E6 | 0.032 μM | ND | ND | Akt kinase | ND |
|      | complexed or nuclear MDA  | anticonvulsant drug | AIDS-related complex (ARC) | Vero E6 | 0.032 μM | ND | ND | Akt kinase | ND |

**Table 1. Repurposed Approaches That Inhibit Viral Replication**

A number of repurposed approaches that aim to achieve these effects are currently being investigated. In an ex vivo model of human lung, SARS-CoV-2 largely failed to induce the expression of any IFNs (type I, II, or III), indicating that the early innate immune response to this virus is impaired and supporting the use of exogenous IFN to stimulate innate immunity as a candidate therapeutic modality. Type I IFNs (IFN-I, e.g., IFN-α and IFN-β) have been approved for the treatment of chronic hepatitis B and C infections and have previously demonstrated in vitro activity and protection in various animal models of MERS-CoV and SARS-CoV.84 In a preliminary, uncontrolled study of patients infected with SARS-CoV, the use of type I IFN plus corticosteroids was associated with a faster resolution of radiographic lung abnormalities and improved oxygen saturation levels than treatment with corticosteroids alone.87 SARS-CoV-2 appears to be more susceptible to IFN-α treatment in vitro than SARS-CoV.88 In a retrospective study of 77 adults with moderate COVID-19, treatment with nebulized IFN-α2b reduced the duration of both detectable virus in the upper respiratory tract and elevated blood levels of inflammatory markers (IL-6 and C-reactive protein).89 Several types and routes of administration of IFN-1 are currently being studied in COVID-19 patients.

Perhaps a more attractive candidate approach for COVID-19 treatment is, however, type III IFNs (IFN-I1−4). Although not approved yet, IFN-λ has been shown to be safe in large phase 1/2/3 trials (involving ∼3000 patients) for the treatment of hepatitis B, C, and D virus infections.85 In
contrast to IFN-α/β that signals through a ubiquitously expressed INF-α/β receptor (IFNAR), IFN-λ signals through the INF-λ receptor (IFNLR), whose expression is restricted to epithelial cells (including lung and gut) and a subset of immune cells (reviewed in ref91). The administration of type III IFN at an early stage of COVID-19 could therefore result in an antiviral response that is localized to epithelial cells, thereby reducing side effects and inflammation associated with the systemic action of type I IFNs.92 In a human airway epithelial cell culture model, IFN-λ3 and IFN-λ4 exhibited antiviral effects against MERS-CoV. 93 IFN-λ restricted SARS-CoV replication in the respiratory and gastrointestinal tracts in knockout mouse strains lacking receptors for type I IFN, type III IFN, or both. 94 Several phase 2 clinical randomized controlled trials to evaluate the safety and efficacy of pegylated INF-λ compared with the placebo in outpatients with uncomplicated COVID-19 (NCT04331899, NCT04344600), hospitalized patients with noncritical illness (NCT04388709), or both ambulatory and hospitalized patients (NCT04354259) are ongoing.

COVID-19 severity was found to positively correlate with the level of proinflammatory cytokines. Increased serum expression levels of IL-2 and IL-6, in particular, appear to predict the severity and prognosis of patients with COVID-19.95 Immunomodulatory agents that directly target these key cytokines may therefore help to reduce the inflammatory responses observed in severe cases.

Various approaches are currently being studied for their potential to reduce inflammation and/or tissue injury in moderate and severe forms of COVID-19. The benefit of using corticosteroids for the treatment of COVID-19 was initially debatable.96,97 A systematic review and meta-analysis of the safety and efficacy of corticosteroids revealed that their use in subjects with SARS-CoV-2, SARS-CoV, and MERS-CoV infections delayed viral clearance and did not convincingly improve survival.98 Nevertheless, the preliminary results of the RECOVERY trial, a large randomized, controlled, open-label trial, have shown a benefit for dexamethasone treatment in severe COVID-19 patients. Specifically, up to a 10-day dexamethasone treatment course in 2104 patients reduced the 28-day mortality by one-third in patients on mechanical ventilation (29% vs 40.7%) and by one-fifth in patients requiring oxygen (21.5% vs 25%) relative to 4321 patients who received the standard of care, yet it had no effect in patients who did not require oxygen.99 Additional phase 3 clinical trials testing various dosing regimens and formulations of corticosteroids in severe COVID-19 patients are currently ongoing.

Another class of anti-inflammatory agents that are being studied clinically are JAK inhibitors. Baricitinib is an oral JAK1/JAK2 inhibitor that has been shown to modulate innate and adaptive immune responses by inhibiting the production of inflammatory cytokines including TNF-α, IL-6, IL-17, and IFN-γ100 and to profoundly reduce inflammation in animal models.101 It is approved in over 65 countries for the treatment of rheumatoid arthritis. A small pilot study in 12 mild to moderate COVID-19 patients in Italy has suggested that baricitinib in combination with lopinavir/ritonavir may be safe for this study population and can improve clinical and laboratory parameters.102 In a noncontrolled, retrospective cohort study of 15 patients with moderate to severe COVID-19, a short course of baricitinib in combination with hydroxychloroquine was tolerated and temporally associated with clinical improvement in 11 of 15 patients and recovery in 12 of 15 patients.103 The safety and efficacy of baricitinib...
Table 2. Repurposed Approaches Aimed at Modulating Inflammatory Responses and Reducing Tissue Injury*  

| Name             | Type               | Status                        | In vitro                                                                 | mouse model                                      | NHP                     | Mechanism of action                                      | COVID-19 status |
|------------------|--------------------|-------------------------------|--------------------------------------------------------------------------|--------------------------------------------------|-------------------------|----------------------------------------------------------|----------------|
| IFN-α/β          | Interferon         | Approved for chronic         | IFN-α/β treatment more susceptible to SARS-CoV-2                         | SARS-CoV-2 (inhibits viral replication)           | MERS-CoV                | Boosts innate immune response                             | Phase 2/3      |
| INF-III (IFN-3)  | Interferon         | Approved for chronic         | INF-3 and INF-3,4 inhibit MERS-CoV                                        | INF-3 and INF-3,4 inhibit MERS-CoV                | ND                      | Boosts innate immune response                             | Phase 2        |
| tocilizumab      | Monoclonal antibody | Approved for inflammatory     | INF-3 and INF-3,4 inhibit MERS-CoV                                        | INF-3 and INF-3,4 inhibit MERS-CoV                | ND                      | Boosts innate immune response                             | Phase 3        |

*Known in vitro and in vivo data for SARS-CoV, MERS-CoV, and SARS-CoV-2 are included. ND, not determined; IFN, interferon; RAS, renin angiotensin system; IL, interleukin.

This urinary serine protease inhibitor has demonstrated significant reduction in the levels of plasma pro-inflammatory cytokines in multiple clinical studies in various inflammatory conditions. 109 Notably, in an animal model of pancreatitis, it was also shown to activate the renin–angiotensin system (RAS) by upregulating the expression of ACE2 as well as the anti-inflammatory factor angiotensin 1−7 (Ang 1−7) and the Mas receptor. 110 This property makes ulinastatin a particularly attractive agent for COVID-19 treatment, since disease severity is thought to be linked in part to an imbalance in the RAS. 111

The cell surface receptor ACE2 converts angiotensin II (Ang II) into Ang 1−7, which then binds to the Mas receptor to counteract the effects of Ang II on vasoconstriction, apoptosis, and inflammation. 112 An unopposed Ang II effect has been previously linked to increased pulmonary vascular permeability in animal models of ARDS. 113 It was previously shown that SARS-CoV infection and the viral spike protein reduce ACE2 expression and that injection of the spike-Fc protein (spike protein fused to the Fc portion of human IgG1) into mice causes acute lung failure, which could be attenuated by blocking the renin–angiotensin pathway. 114,115 By reducing ACE2 expression upon its entry into cells, SARS-CoV-2 may also facilitate such imbalance and enhancement of the Ang II effects, thereby contributing to ARDS and possibly myocarditis. 36,114,115

Ulinastatin may reverse this imbalance and reduce tissue injury by directly upregulating ACE2. Moreover, ulinastatin was shown to protect mice from lipopolysaccharide-induced acute lung injury and improve cardiac function in mice with diabetes by downregulating and reducing cytokine expression. 116,117 Collectively, ulinastatin thus has a potential to reduce inflammation and vasodilatation not only by restoring ACE2 and Ang 1−7 levels but also by reducing the activity of pro-inflammatory cytokines. Ulinastatin has been approved for the treatment of acute pancreatitis and sepsis in Asia 118 and, even more relevant, it was studied for the treatment of ARDS. In a meta-analysis of randomized controlled trials including over 2300 patients with ARDS, ulinastatin treatment reduced mortality and ventilator-associated pneumonia by nearly 50% and also reduced ICU and overall hospital stays. 119 On the basis of these findings and its favorable tolerability in patients, ulinastatin has been individually and/or in combination drug regimens are currently being studied at a larger scale as part of the NIH’s multicenter, adaptive, randomized blinded controlled trial for hospitalized COVID-19 patients (NCT04280705) and other trials (NCT04373044). Similarly, the effect of the early administration of tocilizumab, another oral JAK (JAK1/JAK3) inhibitor approved for various inflammatory diseases, on COVID-19 pneumonia, will also be investigated in a phase 2 study (NCT04332042).

Acalabrutinib is a covalent inhibitor of the Bruton tyrosine kinase (BTK), which mediates inflammation via regulation of macrophage signaling and activation. Acalabrutinib is approved in the United States (US) for the treatment of lymphoid malignancies. 110 Its off-label use for treating 19 patients hospitalized with severe COVID-19 was shown to reduce respiratory distress and levels of the inflammatory markers C-reactive protein and IL-6. 111,112 Additional, phase 2 clinical trials testing the efficacy and safety of acalabrutinib in patients hospitalized with COVID-19 are ongoing in the US (NCT04380688) and Europe (NCT04346199).

Various humanized monoclonal antibodies approved for the treatment of inflammatory diseases or cancer are also being tested for COVID-19 as repurposed candidates. In two retrospective studies, treatment with tocilizumab, an IL-6 receptor (IL-6R) inhibitor approved for rheumatoid arthritis, improved survival of severe COVID-19 patients; however, treatment prolonged their hospital stay and was associated with serious adverse events including transient respiratory worsening and bacterial infections. 106,107 Sarilumab, another IL-6R inhibitor, has recently failed in a US phase 3 trial involving 194 critically ill COVID-19 patients, and the trial has therefore been stopped. 108 The utility of these and other monoclonal antibodies that are currently being studied for COVID-19 treatment, such as bevacizumab that targets vascular endothelial growth factor A (VEGF-A) and nivolumab and camrelizumab that target the programmed cell death protein 1 (PD1), remains uncertain.

Ulinastatin is another anti-inflammatory agent that inhibits IL-6 but may provide additional benefits for severe COVID-19 patients, beyond those provided by IL-6 inhibition, and would likely be safer than the monoclonal antibodies targeting IL-6R.
recommended for the treatment of severe COVID-19 infection in China and a randomized, double-blind, placebo-controlled clinical trial to analyze its safety and efficacy for the treatment of COVID-19 has been initiated (NCT04393311). The utility of an Ang 1–7 peptide,\textsuperscript{120} a different approach designed to reverse the RAS imbalance and reduce tissue injury, is also currently being clinically investigated in COVID-19 patients (NCT04332666).

Lastly, another category of agents being considered for its potential to reduce COVID-19-induced tissue damage are kinase inhibitors that suppress lung fibrosis. Several studies have suggested that the inhibition of epidermal growth factor receptor (EGFR) signaling may prevent the fibrotic response associated with various respiratory infections including SARS-CoV.\textsuperscript{84} Several kinase inhibitors with anti-EGFR activity including gefitinib and erlotinib have been previously shown to inhibit the induction of fibrosis in various mouse models of tissue injury.\textsuperscript{121} Nintedanib, a multikinase inhibitor with activity against fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR), which is approved for idiopathic pulmonary fibrosis, is currently being studied in patients with moderate to severe COVID-19 treatment for its potential effect to prevent pulmonary fibrosis (NCT04338802). The modulators of inflammation and tissue injury mentioned above are illustrated in Table 2 and Figure 2.

**DISCUSSION**

There is an urgent need for countermeasures to combat SARS-CoV-2 infection. It would take many months for a vaccine and much longer for a novel antiviral drug to be developed for effective prevention and treatment of this virus, respectively. Currently, the off-label use of drugs that are approved or are under advanced clinical investigation provides the main solution. Repurposing existing drugs requires significantly less capital and time and diminishes the clinical risks as such drugs have already been rigorously tested (toxicity, pharmacokinetics, pharmacodynamics, dosing, etc.) for their primary indication.

Since the majority of the antiviral drugs approved to date are DAAs that target viral proteins encoded by individual viruses, they typically provide a narrow spectrum of coverage and are therefore unlikely to be attractive candidates for repurposing. One example is provided by the HIV protease inhibitors, lopinavir/ritonavir. In contrast, existing antivirals that have already demonstrated broad-spectrum coverage, such as remdesivir, can facilitate readiness for future outbreaks of emerging pathogens and thus provide an immediate solution.

There are a number of strategies to identify antiviral candidates for repurposing among drugs that have already been approved or studied for other indications. One such approach is high-throughput screening of compound libraries for antiviral activity. Ebelen is one example of a compound that was discovered as having anti-SARS-CoV-2 activity using this approach.\textsuperscript{74} The assembly of libraries that include a larger number of compounds that have already been approved or studied in humans, such as the REFRAME library,\textsuperscript{122} has provided an important resource to support these efforts. Another approach is to identify existing drugs that target cellular factors known to be required for the life cycle of SARS-CoV-2. The discovery of camostat and nafamostat, inhibitors of cellular serine proteases, including TMPRSS2, exemplifies this strategy. Such host-targeted approaches may also have the added benefit of a higher genetic barrier to the emergence of resistance. At a larger scale, genomic and proteomic screens provide unbiased approaches for the discovery of proviral factors including druggable candidates. Mapping the interaction network of the individual SARS-CoV-2 proteins with the human proteome has recently revealed 66 druggable cellular factors that can be targeted by 69 compounds, many of which are either already approved or currently in clinical trials.\textsuperscript{123} Moreover, phosphoproteomics analysis of SARS-CoV-2-infected cells has revealed alterations in various cellular pathways during viral infection and facilitated discovery of small molecule inhibitors of these pathways as repurposing candidates.\textsuperscript{74}

While repurposing of approved drugs as antivirals can offer an immediate solution, it also poses some challenges and raises important concerns. One challenge is that the antiviral effect
observed in vitro often cannot be reproduced in vivo. In the context of COVID-19, this was evident with lopinavir/ritonavir, which inhibited SARS-CoV-2 in cultured cells but did not show a benefit beyond standard care in patients when used by itself.\textsuperscript{28} Furthermore, even a promising effect in animal models cannot guarantee effectiveness in patients, as exemplified by chloroquine for dengue treatment\textsuperscript{66,68} and by remdesivir for EBOV disease treatment.\textsuperscript{6,7}

Pharmacokinetic factors may contribute in part to the observed lack of correlation between preclinical and clinical models. Factors, such as achievable serum and particularly lung levels, have to be carefully evaluated when specific drugs are being considered for repurposing. For example, the pharmacokinetics of chloroquine and hydroxychloroquine, for example, are generally safe when used to treat malaria and inflammatory diseases, yet in the context of SARS-CoV-2 infection, which affects the heart, they increase the risk of cardiac toxicity.\textsuperscript{123} Nevertheless, for some drugs, it may be feasible to find a therapeutic window where the drug level is sufficient to inhibit viral replication with minimal cellular toxicity. Shortening the duration of therapy from months or years required to treat inflammatory diseases or cancer to several days or a few weeks sufficient to treat COVID-19 should further limit toxicity.

The emergence of viral resistance is another potential challenge of any antiviral strategy and particularly DAAs, such as those targeting the SARS-CoV-2 polymerase or protease. Although no phenotypic resistance to the currently used DAAs has been reported to date, there is already genotypic evidence for a high mutation rate in the SARS-CoV-2 RdRp sequence in patients.\textsuperscript{123} While viral resistance can also limit treatment of host-targeted approaches,\textsuperscript{47,126} in general, targeting cellular factors that are not under the genetic control of viruses is more likely to have a higher barrier to resistance than classical DAAs.\textsuperscript{35,127}

Understanding the MOA of repurposed drugs is also often challenging. Cellular proteins function in a complex network of interactions, and their inhibitors are often not selective. The mechanism of antiviral action of host-targeted approaches therefore often remains elusive, and the molecular targets underlying this effect remain unvalidated. For example, erlotinib’s effect on hepatitis C virus infection was first attributed solely to its effect on EGFR, its cancer target, yet it was later demonstrated that the inhibition of GAK, another cellular kinase that is inhibited by erlotinib with a comparable potency to EGFR, also plays a role.\textsuperscript{127,128} For other drugs, such as chloroquine, the MOA is even less clear and appears to be pathogen specific.\textsuperscript{69,129,130}

Access to drugs and cost pose additional challenges to repurposing existing drugs. The demand for specific drugs in the context of an outbreak can far exceed the available stockpiles. Indeed, early on, when used broadly for COVID-19, there was a significant shortage of hydroxychloroquine, which limited its availability for patients with inflammatory diseases who rely on it for their chronic conditions. Similarly, in the face of the upscaled and expedited production, there is an insufficient number of remdesivir doses to meet the global need. The high cost associated with some of the studied repurposed candidates, such as tocilizumab, is another barrier for their wide use in the treatment of COVID-19 patients.

Lastly, there is an urgent need to effectively prioritize among the proposed repurposed approaches and to effectively study them in order to guide clinical practice. The unpredictable nature of outbreaks with respect to size, geographic location, and duration further complicates the design of clinical trials. Consequently, the design of many of the hundreds ongoing clinical trials is somewhat limited, for example, by lacking appropriate controls or by being underpowered to reveal a virological or clinical effect. Moreover, concerns about publication bias are being raised.\textsuperscript{14,131,132} This brings up a global concern that, similarly to the 2014 EBOV disease outbreak in West Africa, many approaches will be studied, yet the cumulative knowledge gained will be somewhat limited. One solution to overcome this challenge is offered by the adaptive platform design; a study design approved by the FDA during the 2014 Ebola outbreak\textsuperscript{132} (NCT02380625) that is currently being implemented in the clinical trial conducted by the US NIH (NCT04280705). Adapted from clinical studies in cancer,\textsuperscript{133} this platform design facilitates the simultaneous investigation of multiple agents individually and in combinations. The interim analysis feature of this platform design enables the entry of new agents as they become available and the removal of failing agents.\textsuperscript{132} The incorporation of response adaptive randomization changes the randomization ratio of assigning treatment regimens to gradually favor the arms that perform better.\textsuperscript{132} The important advantage is that such a study is designed to determine not only whether specific drugs work or not but also, more importantly, which drugs work the best, thereby guiding clinical practice. The integration of the adaptive platform design with a “core protocol” that involves multiple investigative teams and can extend across multiple infectious disease outbreaks may provide an even better solution to address these challenges yet will require tremendous coordination.\textsuperscript{134}

In summary, the discussed examples represent the broad range of repurposed approaches that are already being studied or proposed to combat COVID-19. While a number of these approaches are showing some promise, the clinical utility of the majority of them remains to be determined. Protection against SARS-CoV-2 is more likely to be achieved by a combination of approaches that inhibit viral replication with those that reduce inflammation and tissue injury.

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Notes
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