



# SARS-CoV-2 Antiviral Therapy

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**SUMMARY** The development of effective antiviral therapy for COVID-19 is critical for those awaiting vaccination, as well as for those who do not respond robustly to vaccination. This review summarizes 1 year of progress in the race to develop antiviral therapies for COVID-19, including research spanning preclinical and clinical drug development efforts, with an emphasis on antiviral compounds that are in clinical development or that are high priorities for clinical development. The review is divided into sections on compounds that inhibit SARS-CoV-2 enzymes, including its polymerase and proteases; compounds that inhibit virus entry, including monoclonal antibodies; interferons; and repurposed drugs that inhibit host processes required for SARS-CoV-2 replication. The review concludes with a summary of the lessons to be learned from SARS-CoV-2 drug development efforts and the challenges to continued progress.

**KEYWORDS** antiviral therapy, drug repurposing, monoclonal antibody, SARS-CoV-2, nucleoside analogs

## INTRODUCTION

When the COVID-19 pandemic began, the development of effective antiviral treatments appeared promising. Since the 2002-2003 SARS-CoV pandemic and the multiple MERS-CoV outbreaks that began in 2012, many novel and repurposed compounds have been found to possess anticoronavirus activity *in vitro*, and it was expected that one or more effective antiviral treatments would be deployed as a useful stopgap measure pending vaccine development (1–6). One year later, highly effective vaccines have now been introduced and are beginning to slow the spread of SARS-CoV-2. However, despite the emergency use authorization (EUA) by the U.S. Food and

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Drug Administration (FDA) of one nucleoside analog and three monoclonal antibody (MAB) preparations, antiviral therapy has had little impact on COVID-19 clinical outcomes for most patients globally.

The development of effective SARS-CoV-2 antiviral therapy, however, remains critical for those awaiting vaccination, as well as for the estimated millions of immunocompromised persons who are unlikely to respond robustly to vaccination. Moreover, the ongoing emergence and spread of immune-escape variants means that even immunocompetent persons are likely to have higher rates of vaccine failure than what was observed in clinical trials conducted earlier in the pandemic (7–10). Finally, antiviral therapies that target conserved viral proteins are likely to be effective against future pandemic coronaviruses.

Here, we review 1 year of progress in the race to develop antiviral therapies for COVID-19. The review summarizes research spanning preclinical and clinical drug development efforts with an emphasis on antiviral compounds that are in clinical development or that are high priorities for clinical development. The review is divided into four main largely nonoverlapping sections: (i) compounds that inhibit SARS-CoV-2 enzymes, including its polymerase and Main protease (Mpro); (ii) compounds that inhibit virus entry, including MABs; (iii) interferons (IFNs); and (iv) repurposed drugs that inhibit host processes required for SARS-CoV-2 replication.

## POLYMERASE INHIBITORS

RNA-dependent RNA polymerases (RdRps) catalyze phosphodiester bond formation between nucleoside triphosphates in an RNA-templated manner. RdRps are highly conserved in their structural and functional features, even among diverse RNA viruses belonging to different families (11). Nucleoside analog polymerase inhibitors are the most common antiviral compounds comprising a plurality of all licensed antivirals. Because of their broad spectrum of activity, nucleoside analog polymerase inhibitors have been the only successful repurposed directly acting antivirals. For example, tenofovir and lamivudine are among the mainstays of therapy for treating human immunodeficiency virus and hepatitis B infections (12). Most antiviral polymerase inhibitors lack a 3'-hydroxyl group and act as nucleoside analog chain terminators (12). Others contain a 3'-hydroxyl group and yet still result in immediate or delayed chain termination. Finally, some nucleoside analogs are incorporated into viral genomes and inhibit replication by introducing mutations during subsequent rounds of virus replication.

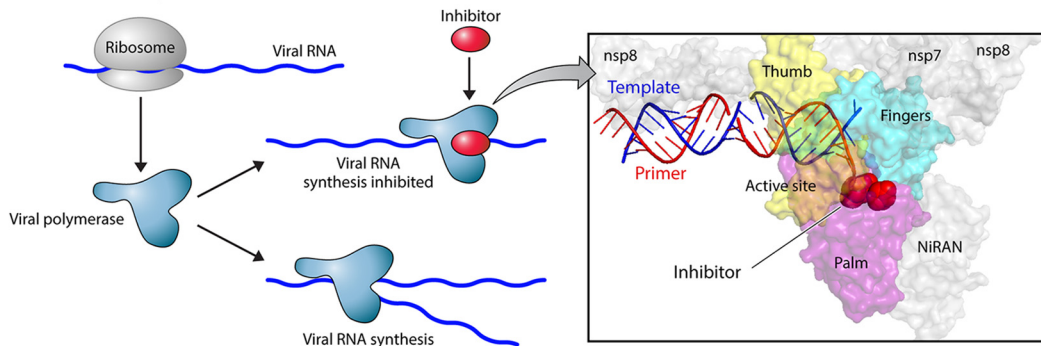
Coronavirus RNA polymerization is more complex than that of other viruses. First, coronaviruses contain a 3'-to-5' exoribonuclease (ExoN; nsp14), which is required for replication fidelity (13). ExoN is responsible for the intrinsic resistance of coronavirus species to ribavirin and several other nucleoside analogs (14, 15). Second, coronavirus genomes are three times larger than most other RNA genomes and thus require increased processivity, which may explain why RdRp (nsp12) requires several accessory proteins, including nsp7 and nsp8. Third, in addition to copying the full virus genome, the coronavirus RdRp transcribes multiple subgenomic mRNAs. Several cryo-electron microscopy (cryo-EM) structures of the nsp12-nsp7-nsp8 replication-transcription complex of SARS-CoV-2 have been published (Fig. 1A) (16–19).

### Remdesivir

Remdesivir (GS-5734, Veklury) is the monophosphate prodrug of the parent 1'-cyano-substituted adenine C-nucleoside analogue GS-441524 (20). The presence of the phosphate group allows for more efficient metabolism of the prodrug to the active nucleoside triphosphate form by bypassing the rate-limiting initial phosphorylation step. Remdesivir contains a 3'-OH group and is therefore a nonobligate chain terminator. It causes delayed chain termination due to a steric clash with S861 after the addition of three trailing nucleosides (Fig. 1B) (21–26). The fact that chain termination does not occur until additional nucleoside triphosphates have been added likely explains how remdesivir eludes the coronavirus exonuclease.

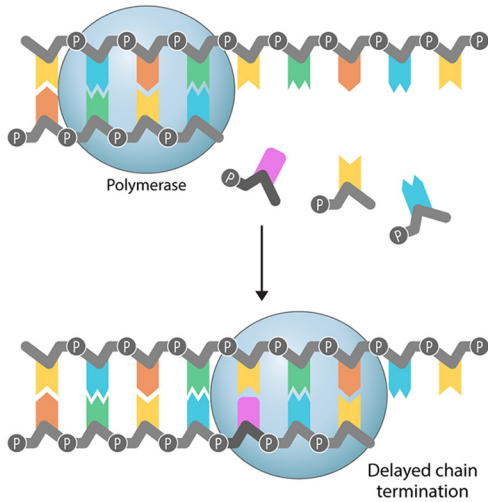
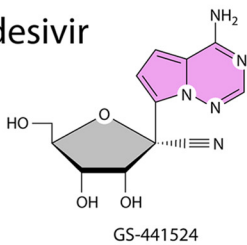
Remdesivir has broad spectrum activity against multiple RNA viruses and inhibits SARS-CoV, MERS-CoV, and SARS-CoV-2 with half-maximal effective concentrations

# A RdRp (polymerase) inhibition



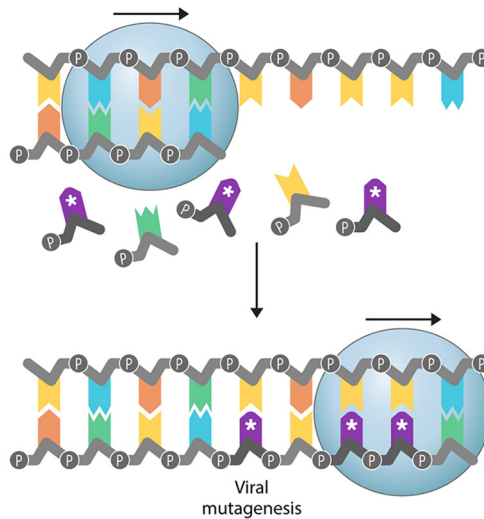
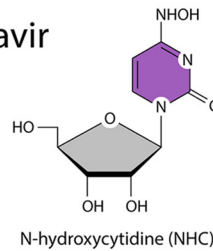
# B

## Remdesivir



# C

## Molnupiravir



**FIG 1** RNA-dependent RNA polymerase (RdRp) inhibition. (A) Coronavirus RdRp enzymes catalyze genome copying and the transcription of multiple subgenomic RNAs. The RdRp-associated replication-transcription complex contains two accessory proteins (nsp7 and nsp8) and an exonuclease (not shown). (B) Remdesivir is a prodrug of GS-441524 which inhibits RdRp by causing delayed chain termination. (C) Molnupiravir is a prodrug of N-hydroxycytidine, which causes lethal viral mutagenesis.

(EC<sub>50</sub>s) generally below 1 μM (27–30). It inhibits coronaviruses in multiple cell types, including primary human airway epithelial cells, and demonstrates a low potential for off-target toxicity in a variety of cellular and biochemical assays (27, 30, 31). Remdesivir reduces lung virus levels and lung damage in mice infected with SARS-CoV and MERS-CoV (27, 32), rhesus macaques infected with MERS-CoV (27, 32), and mice and macaques infected with SARS-CoV-2 (30, 33). Remdesivir resistance in a related coronavirus, murine hepatitis virus, has arisen during prolonged *in vitro* passage experiments due to mutations in the RdRp fingers domain (29). Introducing the homologous substitutions into SARS-CoV (F480L+V557L) resulted in a virus with reduced replication capability and ~6-fold reduced susceptibility to remdesivir (29).

Remdesivir is administered intravenously with a loading dose of 200 mg, followed

by 100 mg daily for 5 to 10 days. After intravenous administration, the achievable maximum remdesivir plasma concentration is predicted to be at least twice as high as most reported  $EC_{50}$ s. Several research groups have argued that remdesivir penetrates poorly into the lungs and that either GS-441524 itself or other GS-441524 prodrugs may be superior to remdesivir (34–38). However, the most detailed pharmacokinetic study has found that at currently approved dosing, remdesivir results in sufficiently high intracellular concentrations of the active triphosphate form GS-443902 in peripheral blood mononuclear cells (39).

As of February 2021, there have been four randomized controlled trials of remdesivir containing a placebo arm (40–43), of which two were blinded (40, 42). The NIH Adaptive Covid-19 Treatment Trial (ACTT-1) randomized 1,063 persons with severe disease to remdesivir for 10 days versus placebo. Persons receiving remdesivir had a median recovery time of 10 days versus 15 days for the placebo group (rate ratio for recovery, 1.29; 95% confidence interval [CI] = 1.12 to 1.49;  $P < 0.001$ ). Kaplan-Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% versus 15.2% at day 29 (hazard ratio [HR] = 0.73; 95% CI = 0.52 to 1.03). A subgroup analysis showed that response to therapy was greater in those not requiring supplemental oxygen or receiving oxygen via nasal cannula than in those requiring high flow oxygen or mechanical ventilation. These results led to an EUA, followed by the eventual approval of remdesivir by the FDA (40, 42).

The open-label WHO Solidarity trial which included 2,750 persons randomized to remdesivir and 4,800 to standard-of-care detected no reduction in mortality, requirement for ventilation, or reduction in hospital stay for those receiving remdesivir (41). It has been proposed that Solidarity trial may not have observed shortened hospital stays with remdesivir because it was an open-label trial that studied patients who received highly heterogeneous routine care and because it required patients receiving remdesivir to remain hospitalized until they completed the full 10-day course of intravenous treatment (44, 45). Another randomized controlled trial compared remdesivir for 10 days versus 5 days versus placebo in persons with moderate disease detected no difference between each of the three arms (43). Remdesivir was not associated with reductions in either upper or lower respiratory tract virus load levels in the one study that examined this outcome (42), possibly because virus levels typically have already begun to decrease by the time patients require hospitalization.

### Molnupiravir

$\beta$ -D- $N^4$ -hydroxycytidine (NHC) is a cytidine analogue that exerts its activity primarily through viral mutagenesis (Fig. 1C). It incorporates into new RNA strands and results in the introduction of many mutations during subsequent rounds of replication (5, 28). Molnupiravir ( $\beta$ -D- $N^4$ -hydroxycytidine-5'-isopropyl ester) is an orally available NHC prodrug that has also been known as MK-4482 and EIDD-2801. The fact that molnupiravir is not a chain terminator may explain the mechanism by which it eludes the proofreading function of coronavirus exonucleases. Biochemical and deep sequencing studies have confirmed that viral mutagenesis is the main mechanism by which molnupiravir inhibits coronaviruses (28, 46, 47). NHC can be metabolized into deoxy-NHC and cause DNA mutations in host cells (48).

Molnupiravir has broad-spectrum antiviral activity against multiple viruses, including SARS-CoV, MERS-CoV, and SARS-CoV-2, with most  $EC_{50}$ s below 1  $\mu$ M (28, 49). It is active in primary human airway epithelial cells, and it reduces virus levels, disease, and lung damage in mouse models of SARS-CoV and MERS-CoV (28, 50) and in hamster (46) and ferret models (51) of SARS-CoV-2. Two first-in-human pharmacokinetic studies have been performed, including a phase 1 dose-ranging study of a 5-day course of oral therapy in healthy adults (52) and phase 1b/2a dose-escalating placebo-controlled trials among adult COVID-19 outpatients within 5 days of symptom onset (53).

A phase II trial examined virological endpoints among persons receiving molnupiravir 200 mg twice daily (BID), 400 mg BID, and 800 mg BID compared to placebo in 176 nonhospitalized COVID-19 patients with fever and/or signs of a respiratory illness (NCT04405570).

Among 74 patients with positive baseline cultures, 6/25 (24%) placebo patients versus 0/49 pooled molnupiravir patients ( $P=0.001$ ) had positive cultures at day 5 (371). Based on this trial, a dose of 800 mg BID was selected for further study. Two large phase II/III trials in hospitalized (NCT04575584) and nonhospitalized (NCT04575597) patients with COVID-19 began in October 2020. The study in hospitalized patients was discontinued for futility after interim data were reviewed by the data safety monitoring board (<https://www.businesswire.com/news/home/20210415005258/en/>). The study in nonhospitalized patients is anticipated to be completed by September/October 2021. Molnupiravir is not being studied in pregnant women or women who might become pregnant because of its mutagenic potential (48, 54).

### Other Nucleoside Analogs

AT-527 is an oral nucleoside analog prodrug of AT-511 that has been previously studied for the treatment of HCV. It inhibits SARS-CoV-2 with an  $EC_{50}$  of  $\sim 0.5 \mu\text{M}$  in human airway epithelial cells (55–57). The mechanism by which it retains activity in the face of coronavirus exonuclease activity has not been described. AT-527 is being evaluated in two phase II placebo-controlled trials of patients with mild-to-moderate disease (NCT04396106 and NCT04709835).

Favipiravir (T-705) is a purine analog prodrug that is ribosylated and phosphorylated intracellularly to form the active metabolite ribofuranosyl-5'-triphosphate (T-705-RTP). It has broad spectrum activity against multiple viral RNA polymerases and appears to act by causing viral mutagenesis (58–61). However, it demonstrates little inhibitory activity *in vitro* against SARS-CoV-2 with  $EC_{50}$ s ranging from 60 to  $>100 \mu\text{M}$  (54, 60, 62–64) consistent with a low rate of favipiravir-RTP incorporation into the RdRp catalytic site (65). It is active in a hamster model but only when used at high doses (66). Several small open-label randomized studies have demonstrated little or no clinical or virological benefit associated with its use (67–70).

The FDA-approved anti-hepatitis C virus (HCV) nucleotide analog sofosbuvir is being studied in several COVID-19 clinical trials. Although it has reported to inhibit SARS-CoV-2 in biochemical studies (71–73), it has little or no inhibitory activity in cell culture (54, 64, 74). One patient-level meta-analysis of three open-label studies totaling 176 patients reported that clinical recovery within 14 days was significantly greater among patients receiving sofosbuvir plus daclastavir (an HCV NS5A inhibitor) than among those receiving standard of care (75). If this preliminary finding is validated, it is possible that the response is due to the fact that daclastavir itself has *in vitro* activity against SARS-CoV-2, although the mechanism for this activity is not known (76).

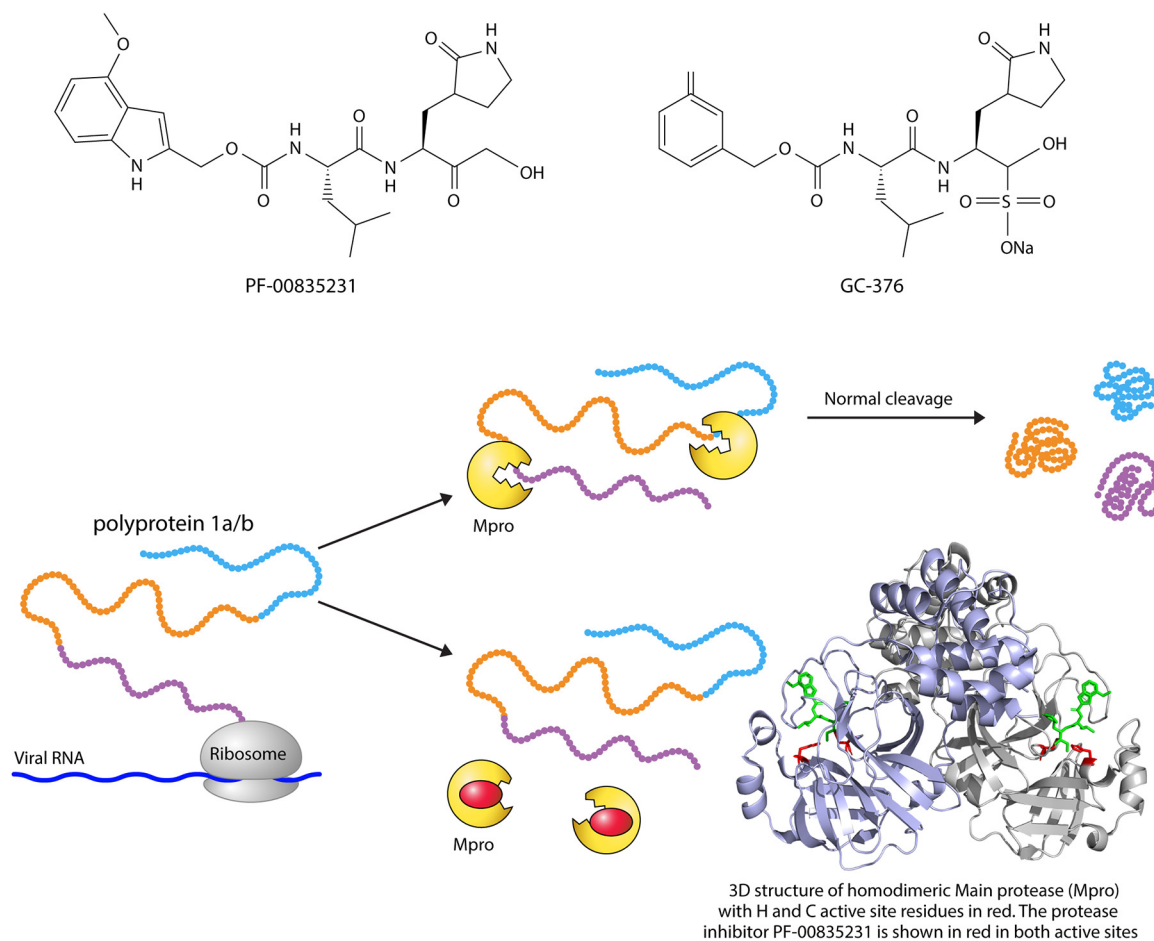
Although ribavirin 5'-monophosphate can be incorporated during RNA synthesis, it is readily excised by the coronavirus exonuclease (15). As a result, ribavirin has little, if any, *in vitro* or *in vivo* activity against coronaviruses, including SARS-CoV, MERS-CoV, and SARS-CoV-2 (54, 77–79).

### PROTEASE INHIBITORS

Coronaviruses contain two protease enzymes: 3 chymotrypsin-like cysteine protease (3CLpro or Mpro; nonstructural protein 5 [nsp5]) and papain-like serine protease (PLpro; nsp3). Mpro cleaves polyprotein 1a/b at 11 sites. It is conserved among several families of RNA viruses, and its cleavage site specificity is similar to the picornavirus family of 3C proteases (80). Mpro contains 306 amino acids and functions as a homodimer. It shares 96% amino acid identity with SARS-CoV Mpro (81). PLpro is part of a 1,922-amino-acid multidomain transmembrane protein. It cleaves polyprotein 1a/b at the nsp1/2, nsp2/3, and nsp3/4 boundaries and several host proteins important for innate immunity such as ubiquitin interferon-stimulated gene product 15 (80).

There are more candidate Mpro inhibitors than PLpro inhibitors because of this enzyme's similarities to proteases of other virus species and because Mpro is smaller, less complicated, and easier to produce in large quantities (80). There have been more than one hundred published Mpro structures, but only a limited number of published PLpro structures (80, 82–84). Although HIV-1 protease inhibitors were used to treat SARS-CoV-2 early in the pandemic, they possess either little or no anticoronavirus

## Protease inhibitor



**FIG 2** The SARS-CoV-2 Main protease (Mpro) enzyme is responsible for cleaving the polyprotein 1a/b at 11 sites. Mpro is a homodimer that is the target of multiple drug development efforts. PF-00835231 and GC-376 are two peptidomimetic SARS-CoV-2 Mpro inhibitors.

activity in biochemical and cell culture studies (62, 63, 85–87), animal models (85, 88), and clinical trials (41, 89, 90).

Drug screens and structure-based designs targeting SARS-CoV-2 Mpro have identified a variety of compounds that inhibit SARS-CoV and SARS-CoV-2 biochemically and in cell culture with 50% inhibitory concentrations ( $IC_{50}$ s) and 50% effective concentrations ( $EC_{50}$ s) ranging from 0.01 to 1  $\mu$ M. These compounds belong to several families of reversible and covalently binding peptidomimetic inhibitors, many of which have been cocrystallized with SARS-CoV-2 Mpro (81, 91–97). These compounds are of interest as chemical scaffolds for potential therapeutic agents; however, some of these compounds may not be sufficiently selective for Mpro, increasing their risk of off-target effects (98, 99). In addition, most current inhibitors bind Mpro covalently, which also increases the risk of off-target effects (80).

PF-00835231 is among the most potent investigational Mpro inhibitors (Fig. 2). It has an  $IC_{50}$  in enzymatic assays of 0.0003  $\mu$ M and an  $EC_{50}$  in cell culture of 0.2  $\mu$ M (96, 100). It has undergone safety studies and pharmacokinetic profiling in rats, dogs, and monkeys (101). PF-07304814 is an intravenously administered phosphate PF-00835231 prodrug that is being studied in a phase I trial of hospitalized patients with mild to moderate COVID-19 disease (NCT04535167). PF-07321332 is an oral prodrug that is being studied in another phase 1 trial (NCT04756531).

Ebselen is an investigational synthetic organoselenium drug with anti-inflammatory

and antioxidant properties that has been studied for the treatment of a variety of illnesses. It was found to inhibit Mpro in a high-throughput drug screen and to have  $IC_{50}$ s in biochemical assays and  $EC_{50}$ s in cell culture assays of about  $1 \mu\text{M}$  (92). It appears to inhibit Mpro allosterically (102) and to also inhibit PLpro (103, 104). It is being studied as an oral drug in two small phase II placebo-controlled trials of patients with mild-to-moderate (NCT04484025) and severe (NCT04483973) COVID-19.

GC376 has been effectively used for treating cats with the rapidly fatal coronavirus disease feline infectious peritonitis (105). It forms covalent bonds with the Mpro active site cysteine and inhibits multiple coronaviruses (106). Its SARS-CoV-2 Mpro  $IC_{50}$  ranges from 0.03 to  $1.5 \mu\text{M}$ , while its cell culture  $EC_{50}$  ranges from 0.2 to  $3.4 \mu\text{M}$  (107–110). GC376 is considered a promising compound for further development (Fig. 2) (111–113).

The approved HCV protease inhibitor boceprevir inhibits Mpro biochemically and in cell culture and is also considered a promising compound for further development (97, 107, 110, 114, 115).

## ENTRY INHIBITORS

The spike glycoprotein is responsible for attachment to host cells and for fusion of viral and cellular membranes. It is a trimer comprising three identical subunits. Each monomer has an exposed S1 attachment domain and a partially hidden S2 fusion domain. The receptor-binding domain (RBD), which is part of S1, alternates between a closed/down position and an open/up position that enables it to bind to the human angiotensin converting enzyme 2 (ACE2) receptor (116, 117). S1 binding occurs on the outer surface of ACE2, whereas angiotensin substrates bind in a deep cleft containing the active site (118–121). RBD-ACE2 binding results in structural changes that lead to S1 dissolution, S2 exposure, and virus-cell fusion (122).

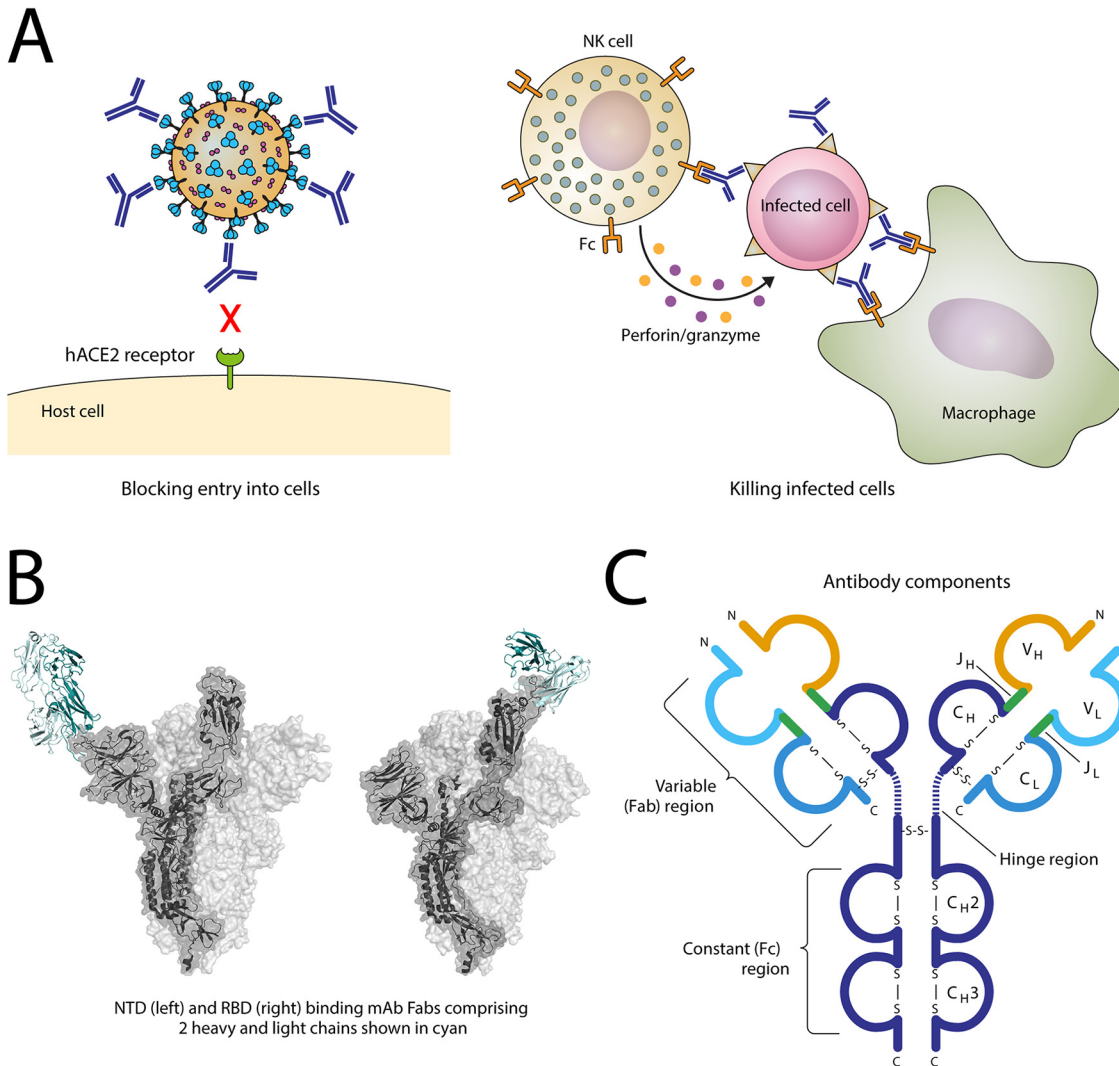
The proteolytic activation of coronavirus spike proteins by host cell proteases is required for the virus spike to transition from receptor attachment to cell fusion. The spike protein has two cleavage sites: one at the S1/S2 boundary and one within S2 referred to as S2'. The sequences of coronavirus spike cleavage sites, the host enzymes required for their cleavage, and the cellular locations where cleavage occurs influence cell tropism and transmissibility (123, 124). For SARS-CoV-2, the S1/S2 cleavage site is a polybasic furin site that is usually posttranslationally cleaved during viral biosynthesis (116, 125–129). Cleavage at the S2' site is carried out by the host protease cathepsin B/L within endosomes and by TMPRSS2 at the plasma membrane (130). Accumulating data suggest that TMPRSS2-mediated S2' cleavage is more important for SARS-CoV-2 cell fusion whereas endosomal cathepsins may have been relatively more important for SARS-CoV (130–134).

S2 contains a fusion peptide and two complementary heptad repeat regions—designated heptad repeat 1 (HR1) and heptad repeat 2 (HR2)—which are alpha helices with repeated patterns of seven amino acids. HR1 and HR2 are complementary allowing them to bind to one other. After RBD-ACE2 binding, the fusion peptide inserts into the host cell membrane. The three HR1 domains then associate with the three HR2 domains to create a six-helix bundle which creates a hairpin that brings the viral and host cell membranes together (123, 135, 136).

## Monoclonal Antibodies

Neutralizing antibodies can block the entry of virus into host cells and recruit host effector pathways to destroy virus-infected cells (Fig. 3). Neutralizing MAbs are effective at preventing or treating multiple viral infections, including those caused by respiratory syncytial virus (137, 138), influenza (139), Ebola virus (140), and MERS-CoV (141). The presence of neutralizing antibodies targeting the SARS-CoV-2 spike RBD correlate with protection in animal models and in previously infected and vaccinated persons, although cellular immune responses and potentially nonneutralizing antibodies are also likely to have contributed to protection in these studies (142–150). Paradoxically, the highest levels of neutralizing antibodies are detected in patients experiencing severe COVID-19 infections (151–154), suggesting that they may play a protective role

# Monoclonal Antibodies (mAbs)



**FIG 3** (A) MAbs function by directly binding to the SARS-CoV-2 spike protein to block binding to the human ACE2 receptor (neutralization) and by recruiting immune effector cells. (B) Most naturally arising SARS-CoV-2 spike antibodies and most MAbs target the receptor binding domain (RBD) while several target the N-terminal domain (NTD). (C) The MAb Fab domains are responsible for antigenic recognition whereas the Fc domains are responsible for immune effector functions. Fc-dependent recruitment of immune effector cells, including Ab-dependent cytotoxicity (ADCC) and Ab-dependent cellular phagocytosis (ADCP) may be particularly important for MAb actions against infected cells. The structures showing the RBD- and NTD-binding MAbs were obtained from entries [7K8T](#) and [7C2L](#), respectively, and rendered using PyMOL.

in patients for whom the initial immunologic response to infection fails to prevent severe disease (155–157). The most common neutralizing antibodies emerging in patients target the S1 RBD (156, 158–161).

Neutralizing MAbs have been isolated most commonly from the memory B cells of persons recovered from SARS-CoV-2, from immunized transgenic mice, and from combinatorial protein display libraries (162). Regardless of their source, antibody-producing cells are screened for their ability to bind either the S trimer or just the RBD. The most potent SARS-CoV-2 MAbs have  $IC_{50}$ s between 1 and 15 ng/ml. Since standard MAbs have a molecular weight of 150 kDa, an  $IC_{50}$  below 150 ng/ml indicates picomolar activity. In addition to preventing viral entry into target cells by directly binding to SARS-CoV-2, MAbs also elicit Fc-effector functions such as antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis (163).

Although no two MAbs share identical epitopes, those binding the RBD are usually classified according to where on the RBD they bind. Two main classes of MAbs bind the ACE2-binding region of the RBD referred to as the receptor-binding motif (RBM), and two classes bind a separate part of the RBD referred to as the RBD core (164–166). The RBD core is more evolutionarily conserved than the ACE2-binding residues in the RBM and MAbs that bind this region can often neutralize SARS-CoV and other SARS-related coronaviruses (167–171). However, non-ACE2-competing MAbs are usually somewhat less inhibitory than those that compete with ACE2 binding. Several laboratories have described potent MAbs that recognize the S1 N-terminal domain rather than the RBD (172, 173). In macaques, hamsters, and various mouse models, the administration of neutralizing MAbs shortly before or after infection with SARS-CoV-2 has consistently resulted in reduced respiratory tract virus levels and signs of illness.

At least seven MAb preparations are in phase III trials. Four of these are MAb combinations: casirivimab plus imdevimab (174–176), bamlanivimab plus etesevimab (177, 178), cilgavimab (COV2-2130) plus tixagevimab (COV2-2196) (179), and BRIL-196 plus BRIL-198. Three are single MAb agents: sotrovimab (VIR-7831) (171), regdanvimab (CT-P59) (180), and TY027. More than 10 additional MAb preparations are in phase I/II trials (181, 182). Four MAb preparations have received FDA EUAs for use in nonhospitalized patients at high-risk of severe COVID-19 illness: bamlanivimab monotherapy, bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab. However, because of an increasing number of reports of SARS-CoV-2 variants that are resistant to bamlanivimab alone, the FDA recently revoked the EUA for bamlanivimab monotherapy.

Ten studies of MAb preparations have been published (149, 183–190, 372) (Table 1). Bamlanivimab plus etesevimab (186), casirivimab plus imdevimab (189), and sotrovimab (190) have been reported to reduce the risk of hospitalization and mortality in nonhospitalized persons with risk factors for severe COVID-19. Bamlanivimab monotherapy (187) and casirivimab plus imdevimab (188) have been reported to reduce the risk of symptomatic and/or overall infection in persons at high risk of infection. Bamlanivimab monotherapy was studied in nursing home residents and staff while casirivimab plus imdevimab was studied in household contacts of infected persons. A study of bamlanivimab monotherapy in hospitalized patients was terminated prematurely as an interim analysis pointed to the unlikelihood of achieving benefit (184). In contrast, one of two studies of casirivimab plus imdevimab in seronegative hospitalized patients (RECOVERY trial) reported a reduction in 28-day mortality compared with patients receiving standard of care (Table 1) (372).

As of June 2021, five SARS-CoV-2 variants have been designated variants of concern (VOCs) by the WHO and/or the U.S. Centers for Disease Control and Prevention (CDC) because they are associated with increased transmissibility, more severe disease, and/or a reduction in antibody neutralization: the U.K. origin B.1.1.7, the South Africa origin B.1.351, the Brazil origin P.1, the India origin B.1.617, and the California origin B.1.427/9 (161). Bamlanivimab plus etesevimab retains activity against the VOC B.1.1.7 but displays an approximately 5- to 10-fold reduced susceptibility against B.1.617 and B.1.427/9 and has little if any residual activity against B.1.351 and P.1 (191–193) (<https://www.fda.gov/media/145802/download>). The combination of casirivimab plus imdevimab appears to retain full susceptibility against each of the VOCs (192, 194) (<https://www.fda.gov/media/145611/download>) likely because casirivimab binds to the RBD receptor binding motif, while imdevimab binds to the more conserved RBD core. Sotrovimab, which binds to the RBD core, also appears to be fully active against B.1.1.7, B.1.351, P.1, and B.1.427/9 (191, 192, 195, 196) (<https://www.fda.gov/media/149534/download>). It has not yet been evaluated against B.1.617. Although sotrovimab appears fully active against all VOCs to which has been tested, its maximal percent inhibition of B.1.1.7 was below 90% in two studies (195, 197).

### Single-Domain Antibodies

Single-domain Abs (sdAbs) are heavy-chain only antibodies that occur naturally in camelids and are increasingly being developed as potential therapeutics (198, 199).

**TABLE 1** MAb findings from published and unpublished clinical trials

Intervention <sup>a</sup>	Trial (reference)	Population	Treatment	Endpoint	Finding
Nonhospitalized patients					
BAM	BLAZE-1, NCT04427501; preplanned interim analysis (183)	n = 452; diagnosis, ≤3 days	0.7 g vs 2.8 g vs 7 g vs placebo	Virological	Mean VL reduction similar for all 3 BAM arms at day 7 (2.9 logs) and day 11 (3.7 logs); at day 3 (0.64 logs) and day 11 (0.53 logs), the 2,800-mg dose had a slightly greater VL reduction compared to placebo.
CAS+IMD	NCT04425629, preplanned interim analysis (149)	n = 275; symptoms, ≤7 days; seropositive (45%), seronegative (41%)	8.0 g vs 2.4 g vs placebo	Hospitalization or ER visit	9/143 (6.3%) of placebo vs 5/309 (1.6%) of pooled MAb recipients were hospitalized or had ER visits
	NCT04425629, final DSMB report (189)	n = 4,057; symptoms, ≤7 days	2.4 g vs 1.2 g vs placebo	Virological	Among seronegative patients, the mean ΔVL from placebo was -0.56 log copies/ml (95% CI = -0.92 to -0.21) for pooled MAb arms. ΔVL was similar for placebo and MAB arms.
BAM + ETE	BLAZE-1, NCT04427501; final analysis of early phase of study (185)	n = 577; diagnosis, ≤3 days	BAM 0.7 g vs BAM 2.8 g vs BAM 7 g vs BAM 2.8 g + ETE 2.8 g vs placebo	Hospitalization or ER visit Hospitalization and mortality	6/182 in the pooled MAB arms vs 6/93 placebo patients (P = NS) 25/2,091 (1.2%) receiving CAS+IMD (pooled) vs 86/2,089 (4.1%) receiving placebo required hospitalization or experienced all-cause mortality (P < 0.001).
	BLAZE-1, NCT04427501; phase 3 part of study (186)	n = 1,035; diagnosis, ≤3 days	BAM 2.8 g + ETE 2.8 g vs placebo	Virological	Compared to placebo, ΔVL at day 11 was 0.1 for 700 mg BAM (P = NS), -0.27 for 2,800 mg (P = NS), 0.31 for 700 mg (P = NS), and -0.57 for BAM+ETE (P = 0.01).
SOT	COMET-ICE, NCT04545060; preplanned interim analysis (190)	n = 583; symptoms, ≤5 days	SOT 0.5 g vs placebo	Hospitalization or ER visit; deaths Hospitalization or death	9/155 (5.8%) of placebo patients vs 6/429 (1.4%) of pooled MAB recipients were hospitalized or required an ER visit. 29% of placebo patients vs 10% of BAM+ETE patients had persistently high VL defined as >5.3 log copies/ml (P < 0.001). 36/517 (7%) of placebo patients vs 11/518 (2%) of BAM + ETE patients were hospitalized or required an ER visit. Ten (2%) placebo patients vs zero (0%) BAM + ETE patients died (P < 0.001). 85% reduction in hospitalization and/or death (P = 0.002; data otherwise not available).

(Continued on next page)

TABLE 1 (Continued)

Intervention <sup>a</sup>	Trial (reference)	Population	Treatment	Endpoint	Finding
Hospitalized patients BAM	ACTIV-3/TICO, NCT04501978 (184); termination for futility	<i>n</i> = 314; symptoms, ≤12 days	7 g vs placebo	Pulmonary status on day 5 <sup>b</sup>	OR of improvement compared to placebo was 0.85 (0.56 to 1.29; <i>P</i> = 0.5)
CAS + IMD	RECOVERY trial (NCT04381936) (372)	Hospitalized SARS-CoV-2-seronegative patients	8.0 g vs standard of care	28-day mortality	396/1,633 (24%) receiving CAS + IMD vs 451/1,520 (30%) receiving standard of care died within 28 days ( <i>P</i> = 0.001)
Prevention studies BAM	BLAZE-2, NCT04497987 (187)	Nursing home residents ( <i>n</i> = 300) and staff ( <i>n</i> = 666)	4.2 g vs placebo	Infection at wk 8	Overall, BAM reduced the incidence of mild or worse COVID-19 from 15.2% to 8.5% ( <i>P</i> < 0.001). The difference was greater among the resident population (22.5% to 8.8%). The risk of any infection by PCR within 4 weeks was 23.3% in the placebo group vs 17.9% in the BAM group ( <i>P</i> = 0.02).
CAS + IMD	NCT04452318 (188)	Household contacts ( <i>n</i> = 1,505)	1.2 g subcutaneous vs placebo	The proportion of participants without evidence of infection who subsequently developed symptomatic infection in the following 28 days	The incidence of symptomatic infection was reduced from 59/752 (7.8%) to 11/753 (1.5%; <i>P</i> < 0.001) with a 92.6% reduction after the first week. Overall infections (including asymptomatic) were reduced by 66.4%.

<sup>a</sup>BAM, bamlanivimab; CAS + IMD, casirivimab plus imdevimab; ETE, etesevimab; SOT, sotrovimab.<sup>b</sup>Seven-category ordinal outcome which correlated significantly with sustained recovery (a time-to-event analysis) through day 90.

They are identified by screening protein display libraries created from the B cells of immunized or nonimmunized camelids as well as from synthetic variable heavy chain libraries (199). sdAbs are easier to manufacture than standard MAbs because they can be expressed in bacterial or yeast cells. They can also often be delivered by inhalation. Although they are generally less potent than complete MAbs, their activity can be increased when engineered in multimeric forms. Many SARS-CoV-2-neutralizing sdAbs have been isolated (200–209), and several have demonstrated efficacy in animal models (208, 210, 211). However, so far none have been evaluated in a clinical trial.

### Convalescent Plasma and Polyclonal Antibody Preparations

There has been one large observational trial and several open label and placebo-controlled trials of convalescent plasma. In the subset of patients in the observational trial that received units with known anti-SARS-CoV-2 antibody levels, mortality was inversely proportional to antibody titer: 115 of 515 patients (22.3%) in the high-titer group, 549 of 2,006 patients (27.4%) in the medium-titer group, and 166 of 561 patients (29.6%) in the low-titer group (212). The benefit of high titer convalescent plasma, however, was observed only among those not receiving mechanical ventilation. Among the placebo-controlled trials, there has generally been no benefit associated with convalescent plasma (213, 214) with the exception of one trial in which high-risk patients older than 75 were treated within 72 h of the onset of COVID-19 symptoms (215). In this trial, the risk of progression to severe disease was reduced in those receiving convalescent plasma: 13 of 80 (16%) versus 25 of 80 (31%), with a relative risk = 0.52 (95% CI = 0.29 to 0.94;  $P = 0.03$ ).

Polyclonal antibody preparations are expected to be less expensive than MAb preparations, although they will have a lower mean binding affinity (216). Several clinical trials are evaluating hyperimmune polyclonal antibody preparations, including IgG fractionated from convalescent patients with high neutralization antibody titers (217) and the more scalable solution of IgG fractionated from immunized animals. The polyclonal antibody preparations from immunized animals include purified equine F(ab)<sub>2</sub> preparations (INM005) (218), swine glyco-humanized IgG (XAV-19) (219), and bovine transchromosomal IgG (SAB-185). Each of these technologies has been shown in phase 1 and 2 human trials to avoid the risk of serum sickness reactions (218–220).

### Fusion Inhibitors

Peptides that mimic SARS-CoV-2 spike HR2 can block virus-cell fusion by preventing the interaction between HR1 and HR2. Several HR2 mimics have been shown to potentially inhibit infection with SARS-CoV, MERS-CoV, and SARS-CoV-2 (135, 221–226). Interest in coronavirus fusion inhibitors is partly motivated by the high degree of conservation among S2 subunits. Although SARS-CoV and SARS-CoV-2 S2 differ in about 10% of their amino acids overall, their HR1 domains differ by only 7%, and their HR2 domains are essentially identical (227).

Prior to the SARS-CoV-2 pandemic, an HR2-mimicking peptide, EK1, was identified as a potential broad-spectrum coronavirus inhibitor because it inhibited both SARS-CoV and MERS-CoV at submicromolar levels and was safe and protective against MERS-CoV when administered intranasally to mice (225). Based on SARS-CoV-2 structural studies, several EK1 amino acid modifications were made and a cholesterol group was added to improve its pharmacokinetic and inhibitory activity (227, 228). This new lipopeptide, named EK1C4, inhibits SARS-CoV-2 fusion about 150 times more potently than EK1, resulting in an EC<sub>50</sub> of 0.04  $\mu$ M.

Several additional highly potent HR2-mimicking SARS-CoV-2 fusion inhibitors have been described, including IPB02 and IPB04 (226), HRC-lipoprotein-SARS-CoV-2 (229), and the dimeric lipoprotein [SARS-HRC-PEG4]-2-*chol* (230). Intranasal administration of [SARS-HRC-PEG4]-2-*chol* to ferrets completely protected them from infection while cohoused with other infected ferrets (230). Despite the potential usefulness of SARS-CoV-2 fusion inhibitors, none have been studied in a clinical trial.

### Soluble ACE2 and Other Molecular Decoys

The ~750-amino-acid soluble recombinant human ACE2 (rhACE2) protects lungs from injury during the acute respiratory distress syndrome (ARDS) (231–234). rhAce2 is safe in human subjects and was being developed as an ARDS treatment prior to the SARS-CoV-2 pandemic (235). It inhibits the binding of SARS-CoV and SARS-CoV-2 to ACE2-expressing cells and also appears to prevent the loss of lung protective effects associated with the internalization of ACE2 following SARS-CoV-2 binding (119, 236). APN1 (Apeiron Biologics) is a clinical-grade soluble rhACE2 preparation that has demonstrated safety in 89 non-SARS-CoV-2 patients and volunteers and is now being evaluated in a 200-person placebo-controlled study of hospitalized SARS-CoV-2 patients (NCT04335136) (234). A press release from Apeiron Biologics announced that preliminary data from this trial showed that persons receiving APN1 experienced reductions in virus load and required mechanical ventilation for fewer days than those receiving placebo (237).

Several research groups have shown that proteins designed to mimic the ACE2 ectodomain are highly potent SARS-CoV-2 inhibitors in cell culture and in pseudovirus entry experiments. Although ACE2 mimics cannot recruit immune cells, they can potentially bind to SARS-CoV-2 as tightly as MAbs and can be easier to manufacture as they do not require expression in mammalian cells. ACE2 mimics have also been fused to Ig Fc domains and to scaffolds to create bivalent or trivalent inhibitors (238–243). CTC-445.2d is a dimeric ACE2 mimic that has been shown to protect SARS-CoV-2-infected hamsters from weight loss and death (244).

An additional strategy to create even smaller ACE2 mimics have involved identifying those ACE2 regions that contribute most strongly to RBD binding (239, 240, 244–246). One of these strategies has involved the use of linked designed ankyrin repeat domains (DARPin) as scaffolds (247, 248). Each domain is about one-tenth of the size of an MAb. The binding portion of each domain is optimized using ribosomal display libraries (247). One trispesific DARPin, ensovibep (MP0420), contains an ACE2 mimicking domain and two additional domains targeting other parts of the spike RBD. It has been shown to potently inhibit SARS-CoV-2 *in vitro* and to reduce weight loss and virus loads in hamsters (248). A phase 1 safety trial of intravenous ensovibep has been completed and a phase 2/3 outpatient trial has begun (NCT04828161).

### Glycosaminoglycan Attachment Inhibitors

Glycosaminoglycans are widely distributed on the surface of mammalian cells and they serve as attachment sites for SARS-CoV-2 and other viruses (249–251). Several compounds that inhibit the interaction between glycosaminoglycans and viruses have antiviral activity, including lactoferrin and the anticoagulants heparin and enoxaparin (250, 252–255). The intranasal administration of heparin has been proposed as a possible way to prevent the spread of SARS-CoV-2 after initial infection without increasing the risk of bleeding (253). Heparin and enoxaparin have also been studied in COVID-19 clinical trials to prevent the thromboembolic complications associated with severe disease.

### INTERFERONS

In response to cellular changes suggestive of a viral infection, interferons (IFNs) induce many genes encoding proteins that inhibit viral replication by slowing cellular metabolism, interfering with the membrane formation required for virus replication, and inducing cytokines that promote adaptive immunity (256). Although there are three IFN families (257), the innate immune sensing of viral nucleic acids leads specifically to the production of type I and type III IFNs (258). Type I IFNs include 13 related IFN- $\alpha$  subtypes, IFN- $\beta$ , and several poorly defined single gene products. Although both type I and type III IFNs activate the same dominant JAK-STAT signaling pathway, their cognate receptor expression differs; receptors for type I IFN have near ubiquitous

expression throughout the mammalian host, whereas type III IFN receptors are largely thought to be confined to tissues of the respiratory and gastrointestinal tracts (259).

The importance of IFNs for combatting SARS-CoV-2 is underscored by the fact that many viruses, particularly coronaviruses, encode multiple proteins that antagonize cellular IFN signaling pathways (6, 260–262). The finding that about 10% of patients with life-threatening COVID-19 have neutralizing type I IFN autoantibodies (263) supports a role for IFNs in protection against SARS-CoV-2. SARS-CoV-2 infection has been associated with a reduced IFN response in some studies (264, 265) and an increased response in other studies (266). IFN- $\alpha$  has also been reported to increase ACE2 expression in upper airway cells (267).

IFN- $\alpha$ , IFN- $\beta$ , and IFN- $\lambda$  each demonstrate inhibitory activity against SARS-CoV-2 at low concentrations of 100 to 1,000 IU/ml in Vero and Calu3 cell lines and in primary human alveolar cells (268–272). IFN- $\alpha$  and IFN- $\beta$  have demonstrated protective effects against SARS-CoV and MERS-CoV in mice (273, 274) and macaques (79, 275, 276), while IFN- $\lambda$  has demonstrated protective effects against SARS-CoV-2 in mice (277). Several studies, however, have reported worse outcomes in mouse models of SARS-CoV and MERS-CoV with delayed administration of type I IFNs (85, 278, 279).

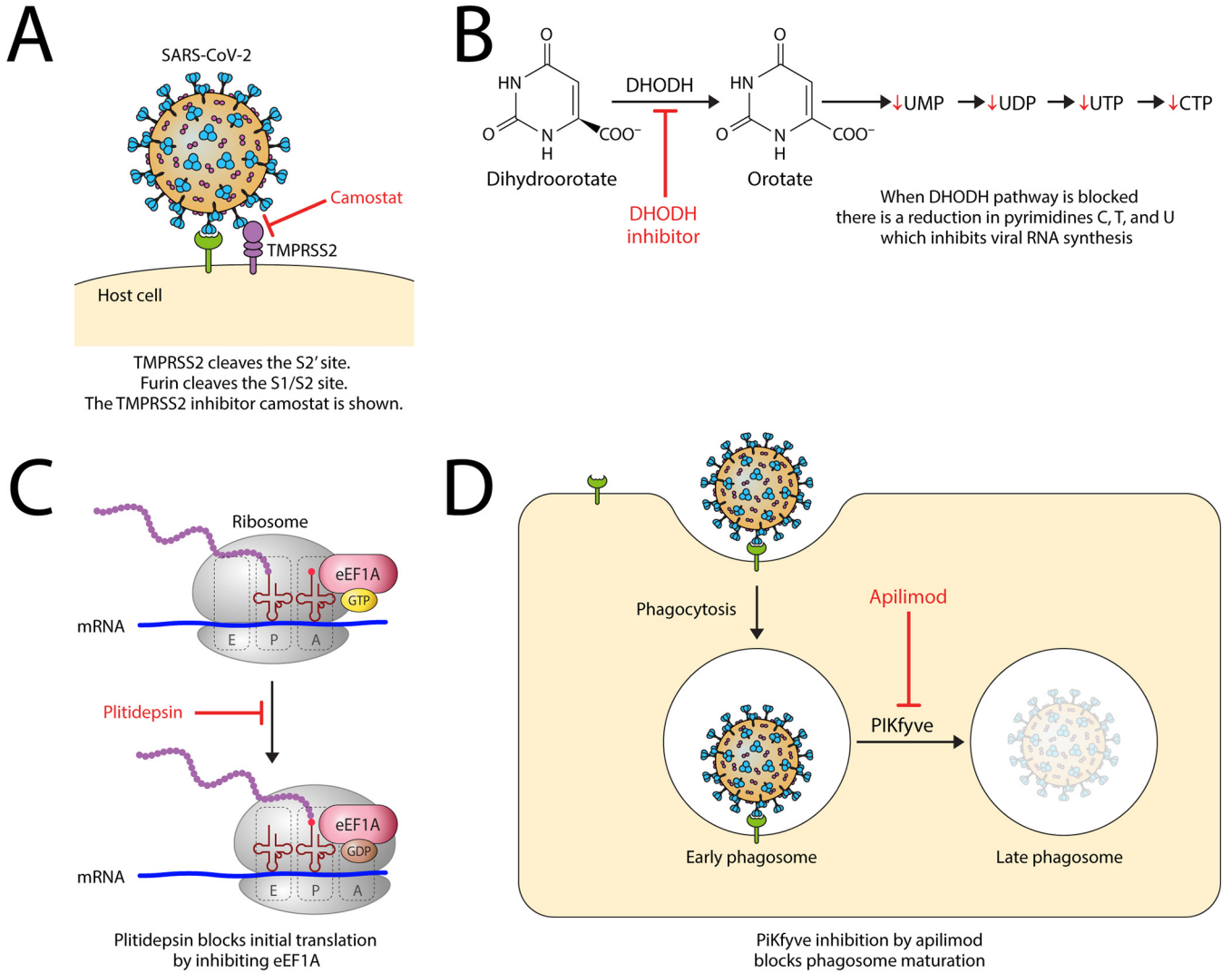
The IFN clinical trials have differed in the formulations studied, route of administration, and design. There has been one phase II randomized placebo-controlled trial of a nebulized IFN- $\beta$  preparation called SNG001 in nonventilated hospitalized patients with COVID-19 receiving supplementary oxygen (280), two phase II randomized placebo-controlled trials of subcutaneous IFN- $\lambda$  in outpatients with mild disease (281, 282), two randomized open-label trials of IFN- $\beta$  (including the SOLIDARITY trial) (41, 283), one open-label trial of IFN- $\alpha$  (284), and one open-label trial of IFN- $\beta$  combined with lopinavir/r and ribavirin (285). The nebulized IFN- $\beta$  preparation SNG001 was found to be associated with an improved outcome, as 6 of 48 patients in the IFN group compared to 11 of 51 patients in the placebo group developed severe disease or died (280). The larger of two phase II IFN- $\lambda$  studies showed no virological benefit in outpatients with mild to moderate SARS-CoV-2 infection (281), whereas the smaller study reported lower virus loads at day 7 among individuals with high baseline viral loads (282). Among the open-label trials, the strongest signal of efficacy was a shorter time to viral clearance and more rapid clinical improvement in patients receiving IFN- $\beta$  combined with lopinavir/r and ribavirin (285).

There is currently one ongoing phase III trial for inhaled SNG001 (NCT04732949), one phase III trial of subcutaneous IFN- $\beta$  given along with remdesivir (ACTT-3, NCT04492475), and one planned study for inhaled Novaféron (IFN- $\alpha$ ) in hospitalized patients with moderate to severe disease (NCT04669015). Subcutaneous IFN- $\lambda$  is being studied in a third phase II trial of outpatients (NCT04344600). The NIH treatment guidelines panel recommends against the use of IFNs for the treatment of severely ill patients with COVID-19 but provide no recommendation for the use of IFNs in earlier disease (<https://www.covid19treatmentguidelines.nih.gov/>).

## HOST-TARGETING COMPOUNDS

Repurposed drugs that have been approved or are being studied for other indications often target host processes required for viral replication. Such host-targeting compounds may be able to inhibit multiple viruses because different viruses often depend on similar host factors and pathways. Although such compounds may have a higher risk of toxicity than those specifically targeting a virus protein, such toxicity may be acceptable for the relatively short time required to treat an acute infection. Many host-targeting compounds that inhibit coronaviruses *in vitro* have been identified. They may act by inhibiting a cellular protein, influencing a signaling pathway, or modifying a cellular organelle (Fig. 4). However, for many inhibitory compounds, the mechanism of action is not known. This section reviews compounds that appear to act primarily by influencing the host rather than the virus and that have favorable safety profiles.

## Drugs targeting host proteins



**FIG 4** Four mechanisms by which repurposed drugs target cellular host pathways. (A) TMPRSS2 inhibitors such as camostat prevent the cleavage at the S2' site thus inhibiting S2-mediated virus-cell fusion. (B) Dihydroorotate inhibitors reduce the high concentrations of pyrimidines required for virus replication. (C) Plitidepsin is an inhibitor of the eukaryotic translation elongation factor eEF1A required to produce the high concentrations of proteins required for virus replication. (D) Apilimod inhibits PIKfyve, an enzyme involved in endosomal trafficking thereby interfering with the early steps of virus replication following the entry of virus into cells.

### Host Protease Inhibitors

The proteolytic activation of coronavirus spike proteins by host cell proteases is required for the virus spike to transition from receptor attachment to cell fusion. These proteases include cell surface proteases such as transmembrane serine protease 2 (TMPRSS2) and other related transmembrane serine proteases, furin, and endosomal cathepsins (123, 135). Accumulating data suggest that furin and TMPRSS2 mediate cleavage at the S1/S2 and S2' sites of SARS-CoV-2, respectively (130, 131). The endosomal cysteine proteases, cathepsins B and L, appear to be less important for SARS-CoV-2 than for SARS-CoV (130–134, 286, 287).

Camostat and nafamostat are serine protease inhibitors used in Japan for the treatment of pancreatitis and disseminated intravascular coagulation. They inhibit TMPRSS2 in biochemical assays and coronaviruses in cell culture (Fig. 4A) (288, 289). In Calu-3 and Caco-2 cells, camostat inhibits SARS-CoV and SARS-CoV-2 with EC<sub>50</sub>s generally below 1 μM, while the EC<sub>50</sub>s for nafamostat are generally ~10-fold lower (130, 287,

290, 291). These compounds, however, are largely inactive in Vero cells because Vero cells do not require TMPRSS2 for virus entry (63, 131, 287). Camostat has protected mice from fatal SARS-CoV infection (292). In animal models and humans, camostat is rapidly converted into the active metabolite 4-(4-guanidinobenzoyloxy) phenylacetic acid (GBPA), which inhibits SARS-CoV-2 entry with nearly the same efficacy as camostat (288, 289).

In a phase 1 study in healthy adults, administration of camostat 600 mg every 6 h in a fasted state or 1 h before meals was associated with a plasma GBPA concentration above  $EC_{50}$  for approximately 12 h (293). In a phase 2 placebo-controlled trial of 205 patients hospitalized for  $\leq 48$  h who were randomized to receive camostat 200 mg orally three times daily or placebo, the median time to a 2-point improvement on a 7-point ordinal scale (the primary endpoint) was 5 days in both arms (294). The proportion of patients dying or requiring mechanical ventilation was 10% in the camostat arm and 18% in the placebo arm (secondary endpoint; odds ratio [OR] = 0.54; 95% CI = 0.25 to 1.18;  $P=0.1$ ). Among those with paired samples, the reduction in virus levels between the camostat and placebo arms were not different. Camostat is currently being studied in the large phase 3 NIH-sponsored adaptive platform treatment trial for outpatients with COVID-19 (Adapt Out COVID) trial (NCT04518410) at a dosage of 200 mg every 6 h for 7 days and in a smaller trial at a dosage of 600 mg every 6 h in patients not receiving oxygen (NCT04657497). Nafamostat, which requires intravenous administration, is associated with higher risk of toxicity compared to camostat. It was associated with hyperkalemia in four consecutive critically ill patients with SARS-CoV-2 (295). Nafamostat is primarily being studied in small open-label trials.

Alpha-1 antitrypsin ( $\alpha 1$ -AT) is an endogenous protease inhibitor used as a treatment for persons with severe  $\alpha 1$ -AT insufficiency. It has been reported to inhibit TMPRSS2 biochemically (296) and to inhibit SARS-CoV-2 *in vitro* in two studies (297, 298) but not in a third study (299).  $\alpha 1$ -AT is being studied in at least three placebo-controlled trials of hospitalized non-ICU patients (NCT04495101, NCT0457140, and NCT04385836) (300). Aprotinin is a 58-amino-acid serine protease inhibitor that inhibits SARS-CoV and SARS-CoV-2 with an  $EC_{50}$  of  $\sim 1 \mu M$  (299). It has been used in Russia intravenously and inhalationally for the treatment of respiratory viral infections. There is one small ongoing open-label trial examining the response to intravenous and inhalational aprotinin (NCT04527133). Bromhexine is an oral mucolytic that has been identified as a TMPRSS2 inhibitor in a high-throughput screen for the treatment of prostate cancer (301). However, it did not inhibit TMPRSS2 in a recent biochemical study (289). Neither bromhexine nor its metabolite ambroxol have been shown to inhibit SARS-CoV-2 *in vitro* (302). However, in a randomized open-label trial of 78 patients, oral administration was reported to significantly reduce ICU admissions, mechanical ventilation, and death (303).

### Nucleotide and Protein Synthesis Inhibitors

Dihydroorotate dehydrogenase (DHODH) is an enzyme in the pyrimidine synthesis pathway. Its inhibition limits the availability of nucleoside triphosphates required for viral replication (Fig. 4B) (304). DHODH inhibitors have also been used to treat autoimmune diseases, organ rejection, and cancer. Leflunomide is a DHODH inhibitor licensed for the treatment of rheumatoid and psoriatic arthritis. Its active metabolite, teriflunomide, has weak *in vitro* SARS-CoV-2-inhibitory activity (305). However, leflunomide did not increase the rate of viral clearance in a randomized open-label trial of 50 patients with prolonged postsymptomatic viral shedding (306). PTC299 is an investigational DHODH inhibitor which has an  $EC_{50}$  in the low nanomolar range and a high selectivity index (307). It is an oral drug that is being developed for oncological indications. A phase 2 placebo-controlled trial of PTC299 in 380 hospitalized patients with COVID-19 began in July (NCT04439071). IMU-838 is another investigational DHODH inhibitor (308) being studied in a phase 2 placebo-controlled trial of 230 patients (NCT04379271).

Plitidepsin is a marine-derived cyclic peptide that inhibits eukaryotic translation elongation factor eEF1A. It has limited clinical approval for the treatment of multiple

myeloma (Fig. 4C). eEF1A has been shown to interact with SARS-CoV-2 nsp9 and plitidepsin has been shown to inhibit SARS-CoV-2 *in vitro* by inhibiting eEF1A. It has an EC<sub>90</sub> of 3 nM in pneumocyte-like cells and a selectivity index of 40 (309). It has activity comparable to remdesivir in a mouse model (309). A phase 1 trial of three different doses of intravenous plitidepsin in 45 hospitalized COVID-19 patients found the drug to be well tolerated, although anaphylaxis occurred in one patient (310). A phase 3 trial in hospitalized patients with moderate disease is planned (NCT04784559).

### Endosomal Trafficking Inhibitors

Apilimod is an investigational compound that has been studied in human clinical trials as an anticancer agent. Apilimod inhibits the intracellular trafficking of several viruses, including SARS-CoV, MERS-CoV, and SARS-CoV-2, during the early stages of virus replication (132, 311). It inhibits a kinase enzyme, phosphatidylinositol-3-phosphate 5-kinase (PIKfyve), involved in endosomal membrane formation (Fig. 4D). Although it does not alter the pH of endosomes or inhibit cathepsin B or L, it blocks entry of multiple viruses in both pseudovirus entry experiments and in cell culture assays (132, 311). In two large-scale screening assays, apilimod was found to have EC<sub>50</sub>s ranging from 10 to 90 nM (312, 313). It has been noted, however, that apilimod may interfere with the cellular immune response to SARS-CoV-2 by interfering with antigen processing in macrophages and T cells (314). Apilimod is being studied in a phase 2 trial for the treatment of mild to moderate COVID-19 (NCT04446377).

Chloroquine analogs are weak bases that, in their nonprotonated form, concentrate within acidic intracellular organelles such as endosomes and interfere with the trafficking of viruses that require a pH-dependent step for entry into the cytoplasm (315, 316). Chloroquine and hydroxychloroquine have modest *in vitro* activity against MERS-CoV (317, 318), SARS-CoV (318–320), and SARS-CoV-2, with most EC<sub>50</sub>s ranging between 1 and 10  $\mu$ M in Vero cells, and higher levels in other cell lines. However, multiple large randomized placebo-controlled (41, 321–323) and open-label (324–326) trials showed no clinical or virological benefit from the use of hydroxychloroquine for COVID-19 treatment. Two additional randomized trials showed that hydroxychloroquine was also ineffective for postexposure prophylaxis (327, 328). Two factors likely explain the lack of clinical efficacy of chloroquine analogs. First, cytoplasmic entry of SARS-CoV-2, particularly in lung cells, depends primarily on the membrane-based enzyme TMPRSS2 rather than on endosomal fusion and acidification making it likely that the weak *in vitro* activity observed in Vero cells was not clinically relevant (132, 329). Second, even at high dosages, chloroquine and hydroxychloroquine may not achieve the drug levels required to inhibit SARS-CoV-2 *in vivo*.

### Inhibitors Acting by Uncertain Mechanisms

Niclosamide is an oral anti-helminthic that exerts its antiparasitic effects by inhibiting oxidative phosphorylation and stimulating mitochondrial ATPase activity (330). In high-throughput drug repurposing screens, niclosamide has been found to have additional biological effects that appear to be associated either with an effect on endosomal acidification, preventing the disruption of autophagy, or inhibiting syncytium formation (331, 332). Niclosamide was also the most active inhibitor of SARS-CoV-2 syncytium formation in a high-throughput screen of 3,000 approved drugs, suppressing the activity of TMEM16/Anoctamin6, a calcium-activated ion channel, and the scramblases responsible for phosphatidylserine cell surface exposure (332). Niclosamide inhibits SARS-CoV, MERS-CoV, and SARS-CoV-2 in cell culture with EC<sub>50</sub>s consistently below 1  $\mu$ M predominantly in Vero cells (333–335). Oral, inhalational, and injectable formulations of niclosamide are being studied in several small phase 1 and 2 trials (336) (NCT04399356, NCT04749173, and NCT04603924). Prophylactic intranasal niclosamide is being studied in one phase 3 trial (NCT04870333).

Clofazimine is an antileprosy drug discovered to have anticoronavirus activity in two high-throughput drug screens (312, 337). It has been shown to reduce lung virus

loads in Syrian hamsters (338). One study suggests that, in a manner similar to niclosamide, it inhibits the calcium channel pathways required for syncytium formation (332).

Nitazoxanide is licensed for the treatment of cryptosporidium infections. It has been reported to inhibit several viruses *in vitro* by interfering with host pathways involved in viral replication, including those involving interferon or mTORC1 (339). Nitazoxanide has also been reported to interfere with SARS-CoV-2-associated syncytium formation (340). The EC<sub>50</sub> for SARS-CoV-2 in Vero cells is reported to be about 1 to 5  $\mu$ M (341, 342). In two randomized placebo-controlled trials of nearly 800 outpatients with mild-to-moderate SARS-CoV-2 infections, nitazoxanide did not influence time to symptom resolution (343, 344), but one trial reported that those receiving nitazoxanide had slightly more rapid virus load reductions (343), and the other reported that those receiving nitazoxanide had a nonstatistically significant reduction in progression to severe disease (344).

Emetine is an FDA-approved drug for treating amebiasis. It has been shown to inhibit multiple coronaviruses *in vitro*, including SARS-CoV, MERS-CoV, and SARS-CoV-2, with EC<sub>50</sub>s below 1.0  $\mu$ M (62, 317, 345, 346). Its mechanism of action is uncertain, although it did inhibit MERS-CoV in an entry inhibitor assay using a pseudotype virus expressing S protein (345). After oral administration, its levels in the lungs are much higher than in the plasma and well above its reported EC<sub>50</sub> levels (347). Emetine is currently not being studied in any SARS-CoV-2 clinical trials.

Ivermectin is an antiparasitic agent that acts by binding to glutamate-gated chloride channels in the membranes of invertebrate nerve and muscle cells. It has been reported to also inhibit human importin alpha/beta-1 nuclear transport proteins, which viruses hijack to enhance infection by suppressing the host antiviral response (348). Ivermectin weakly inhibits SARS-CoV-2 in Vero cells with a reported EC<sub>50</sub> of about 2  $\mu$ M (349). Plasma and lung levels of ivermectin after standard oral dosing have been estimated to be 10- to 100-fold lower than required to inhibit virus infection *in vivo* (350, 351). A retrospective observational study of 173 hospitalized patients found that treatment with ivermectin 200  $\mu$ g/kg was associated with reduced mortality compared to 107 contemporaneous patients not receiving ivermectin, particularly in the subgroup with severe pulmonary disease, which was defined as requiring an FiO<sub>2</sub> of  $\geq$ 50%, high-flow oxygen, or mechanical ventilation (352). However, two randomized placebo-controlled trials of ivermectin—one of 300  $\mu$ g/kg per day for 5 days in 400 patients with symptoms for fewer than 7 days and another of 12 mg per day for 2 days in 112 patients with mild-moderate disease—found no significant virological or clinical improvement associated with the use of ivermectin (353, 354). A meta-analysis that included three additional randomized placebo-controlled trials and five non-placebo-controlled studies also found no clinical benefit associated with ivermectin treatment for COVID-19 (355).

Ciclesonide is an inhaled corticosteroid discovered in a high-throughput drug screen to inhibit coronavirus replication in the low-micromolar range (63, 356, 357). Although its mechanism of action is not known, several SARS-CoV-2 passage experiments resulted in nsp3 and nsp4 mutations that were subsequently shown to reduce ciclesonide susceptibility. The mutated regions of nsp3 and nsp4 are thought to be associated with double membrane formation. There is one ongoing randomized phase 3 placebo-controlled trial of inhaled ciclesonide in patients with mild-to-moderate COVID-19 infection (NCT04377711).

The sigma-1 endoplasmic reticulum receptor (S1R) has been identified as a target for antiviral therapy in two large proteomic studies designed to detect SARS-CoV-2 host dependency factors. However, compounds that influence the activity of this receptor have not been evaluated for their effects on SARS-CoV-2 in cell culture (358, 359). Fluvoxamine, an FDA-approved antidepressant, is an S1R agonist. Although fluvoxamine may inhibit SARS-CoV-2 by interfering with endosomal viral trafficking, most studies suggest that its main benefit is likely to be as an inhibitor of excess cytokine production (360). Indeed, fluvoxamine has also been shown to modulate the response to bacterial

sepsis in a beneficial manner in a mouse model (361). In a double-blind, randomized, placebo-controlled study of 152 outpatients with confirmed SARS-CoV-2 infection, none of 80 patients receiving fluvoxamine compared to 6 of 72 patients receiving placebo experienced clinical deterioration over 15 days ( $P=0.009$ ) (362). A larger study of fluvoxamine in 1,100 patients is currently recruiting participants (NCT04668950).

## CONCLUSIONS

Antiviral development for SARS-CoV-2 has been disappointing. The most notable therapeutic success has been the development of MAbs targeting the SARS-CoV-2 spike protein, which have been shown to prevent infection in persons with high-risk exposures and to prevent hospitalization and mortality in COVID-19 outpatients. Remdesivir, a broad-spectrum nucleoside analog has been found to accelerate clinical improvement in hospitalized COVID-19 patients who do not require high-flow oxygen or mechanical ventilation. Convalescent plasma has been shown to reduce disease severity, but only if it contains high titers of neutralizing antibodies and is administered within the first 3 days of symptom development. A small number of additional drugs are in phase 3 clinical trials while many more are in earlier stages of development.

There are several lessons that can be learned from this disappointing progress. The first lesson is that drugs that are ineffective in preclinical studies and lack a biologically plausible mechanism of action will not be effective in clinical studies. Examples of these drugs included chloroquine analogs, ivermectin, favipiravir, antiretroviral protease inhibitors, and a long tail of other compounds, many of which have not been reviewed here. A second lesson is that uncoordinated, poorly designed, and underpowered clinical trials are wasteful, often produce misleading results, and arguably unethical (363). Many clinical trials of antiviral therapies that were eventually found to be ineffective initially reported positive clinical outcomes, likely indicating researcher or publication bias.

A third lesson is there is currently no model for drug development in the setting of a pandemic. Traditional drug development is an iterative process aimed at maximizing selectivity while improving pharmacokinetic and pharmacodynamic properties (364). However, in the face of a global public health threat, many researchers anticipated that drugs that were already approved or studied in humans for other indications could be repurposed to treat COVID-19, thus bypassing traditional drug discovery approaches. Although high-throughput screens identified several compounds with *in vitro* SARS-CoV-2-inhibitory activity (313, 358, 359, 365–367), the process of creating a clinical trials pathway to investigate existing drugs for new indications has been slow and lacking in transparency. Drug development is expensive and the companies with the financial ability to launch the necessary clinical trials may have lacked economic incentives to foster the development of drugs that were already approved for other indications. Moreover, treatment for acute infectious diseases has not been a priority for the pharmaceutical industry for the past 2 decades (368).

A fourth lesson is that antiviral therapy for COVID-19 must be administered early in the course of infection. This was largely expected based on the finding that virus loads peak early in infection and that severe COVID-19 disease manifestations arise at a time when virus levels have usually begun to decrease. Indeed, neutralizing MAbs, remdesivir, and molnupiravir have been most effective when administered early in the course of infection. Antiviral therapy for influenza is also optimal when administered early; however, the requirement for prompt treatment appears to be stricter for SARS-CoV-2 than for influenza (369, 370). The timely initiation of antiviral therapy for SARS-CoV-2 will require the widespread availability of simple, affordable, and self-administered tests for the early diagnosis of SARS-CoV-2 infection. Moreover, for those persons at highest risk of severe COVID-19 infection, postexposure prophylaxis strategies will need to be considered.

The final lesson is that surrogate markers predictive of clinical endpoints are needed. Without such markers, clinical trials must be large and expensive. Most of the

clinical trials demonstrating the efficacy of MABs and remdesivir required more than 500 patients per arm. With the EUA and likely approval of several neutralizing MAB preparations for SARS-CoV-2-infected persons at high risk of disease progression, it will no longer be unethical to conduct placebo-controlled trials in this population in regions where neutralizing MABs are available. This development will necessitate larger clinical trials enrolling low-risk patients or trials in which new treatments are studied in combination with a neutralizing MAB.

In conclusion, the main therapeutic advance during the pandemic has been the development of highly potent neutralizing MABs for the prevention and treatment of SARS-CoV-2. The administration of remdesivir and possibly the early use of convalescent plasma may have a role in a subset of patients. Several additional treatments that appear promising based on small clinical trials, including molnupiravir, inhaled IFN- $\beta$ , and fluvoxamine. Other treatments have a compelling mechanism of action but are further behind in clinical development, including the oral nucleoside analog AT-527, the oral protease inhibitor PF-07321332, polyclonal antibody preparations, single-domain antibodies, and molecular decoys that bind SARS-CoV-2 spike. Several repurposed drugs that target host processes are also in phase 2 or 3 clinical trials, including camostat, apilimod, the DHODH inhibitor PTC-299, nitazoxanide, and niclosamide. Although these repurposed drugs do not have the same *in vitro* potency as directly acting antivirals, they may prove useful in combination with a directly acting antiviral. Despite the slow start in anti-SARS-CoV-2 drug development and the possible cresting of the pandemic in upper-income countries, continued antiviral drug development remains critical to developing affordable treatments for patients in low- and middle-income countries and for patients at risk of developing COVID-19 despite vaccination. In addition, some of the treatments in clinical development are also likely to be effective against future pandemic viruses.

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