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REVIEW

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

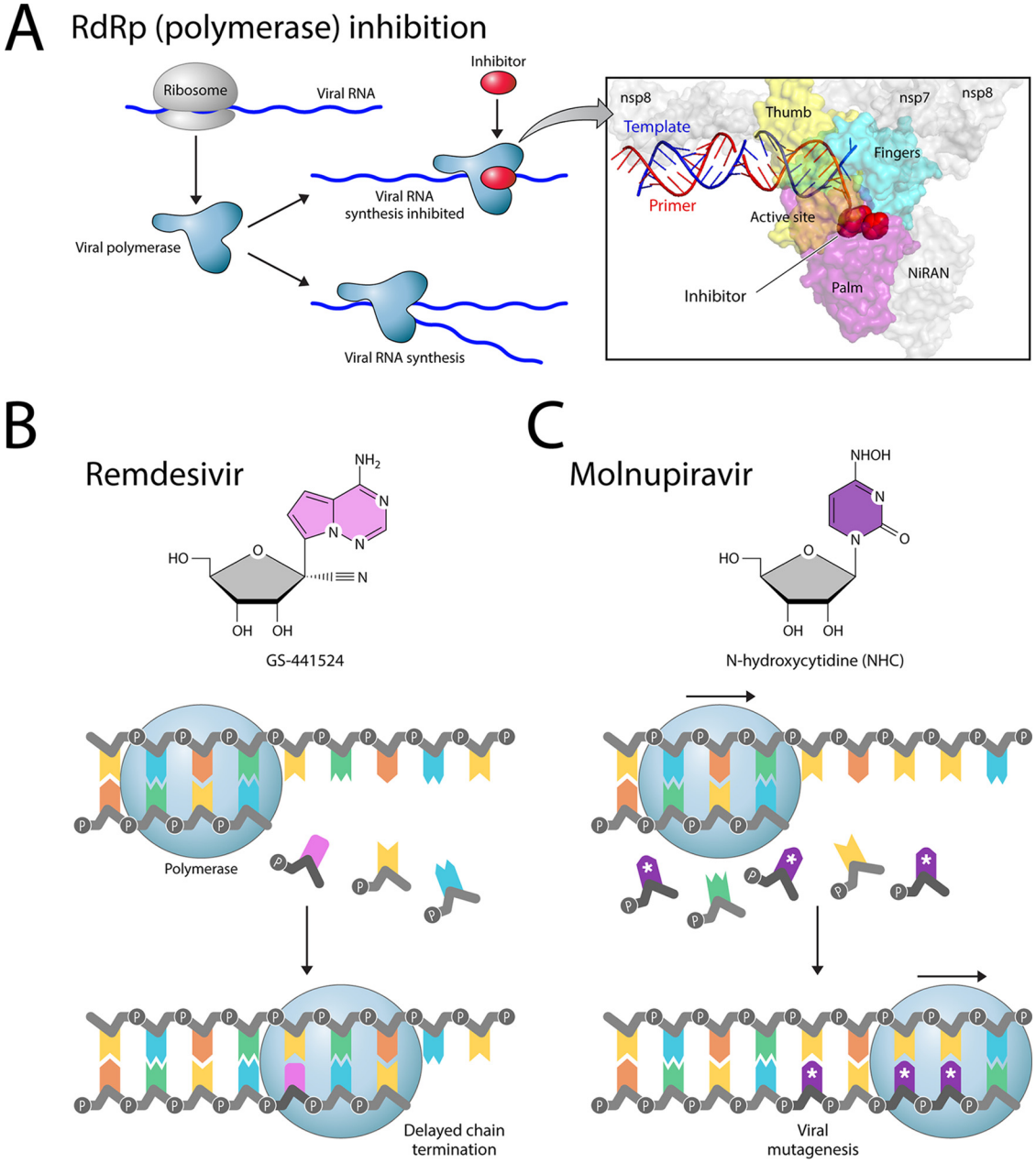

FIG 1 RNA-dependent RNA polymerase (RdRp) inhibition. (A) Coronavirus RdRp enzymes catalyze genome copying and the transcription of multiple subgenomic RNAs. The RdRp-associated replication-transcription complex contains two accessory proteins (nsp7 and nsp8) and an exonuclease (not shown). (B) Remdesivir 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_{50}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 heterogenous 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

β-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 (β-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 μM (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_{90} of $\sim 0.5\,\mu M$ 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 $>100\,\mu M$ (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

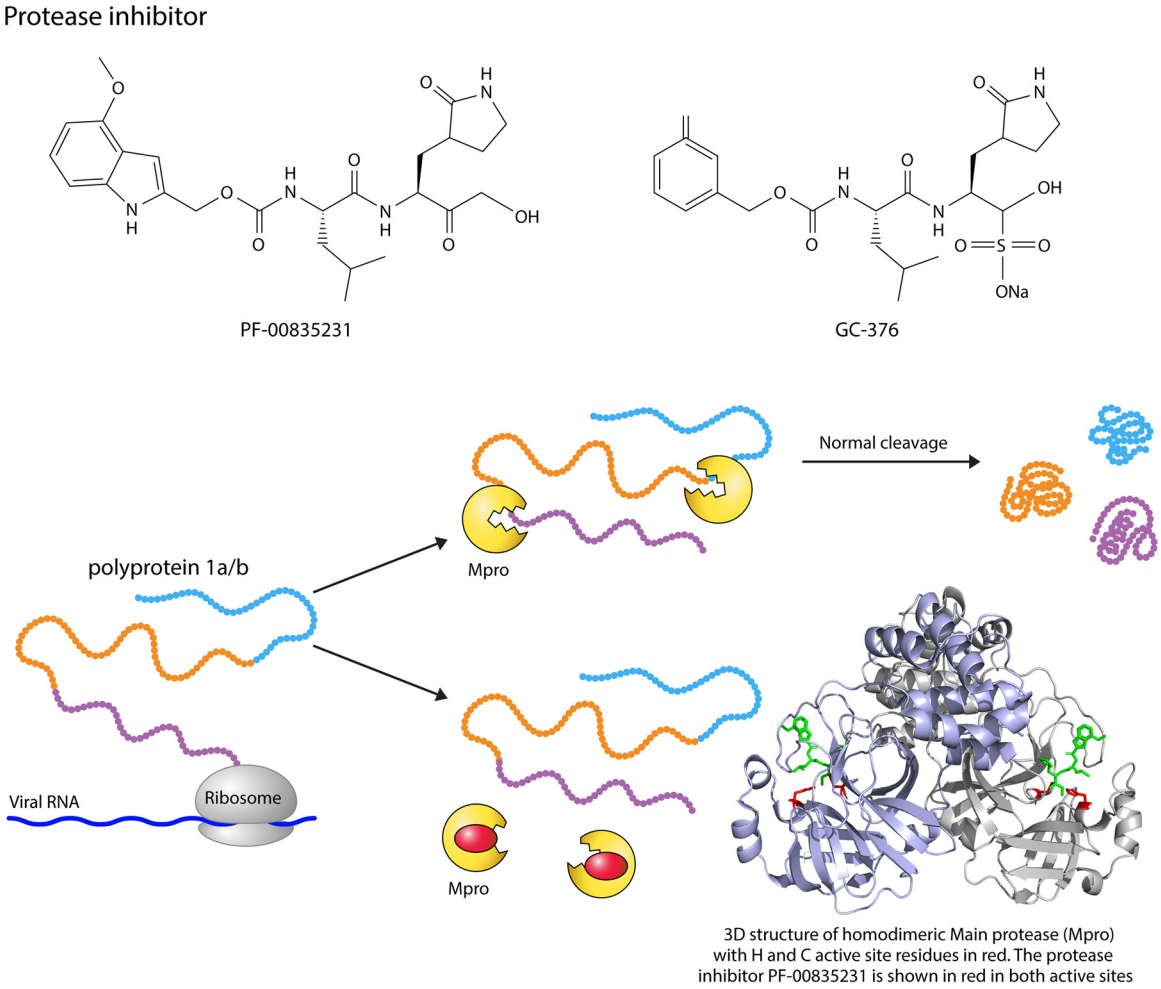

FIG 2 The SARS-CoV-2 Main protease (Mpro) enzyme is responsible for cleaving the polyprotein 1a/b at 11 sites. Mpro is a homodimer that is the target of multiple drug development efforts. PF-00835231 and GC-376 are two peptidomimetic SARS-CoV-2 Mpro inhibitors.

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 μM. 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 μM and an EC_{50} in cell culture of 0.2 μM (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 μM (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 μM, while its cell culture EC_{50} ranges from 0.2 to 3.4 μM (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

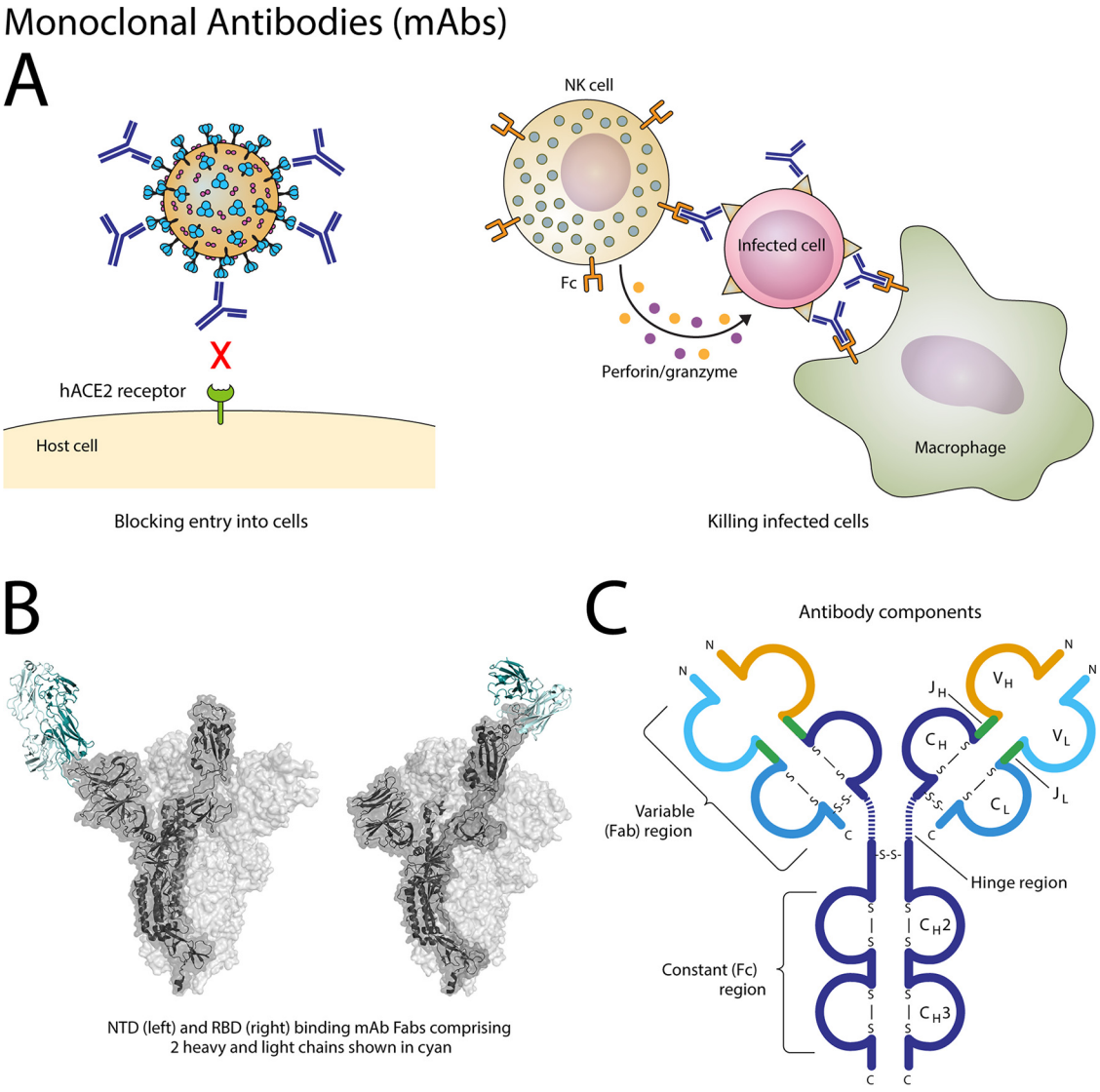

FIG 3 (A) MAbs function by directly binding to the SARS-CoV-2 spike protein to block binding to the human ACE2 receptor (neutralization) and by recruiting immune effector cells. (B) Most naturally arising SARS-CoV-2 spike antibodies and most MAbs target the receptor binding domain (RBD) while several 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 BRII-196 plus BRII-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 sotrovirmab. 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 sotrovirmab (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[a]	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.
				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
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	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. Among seropositive patients, the mean ΔVL was similar for placebo and MAb arms.
				Hospitalization or ER visit	6/182 in the pooled MAb arms vs 6/93 placebo patients (P = NS)
	NCT04425629, final DSMB report (189)	$n = 4,057$; symptoms, ≤7 days	2.4 g vs 1.2 g vs placebo	Hospitalization and mortality	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).
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 vs BAM 7 g vs 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).
				Hospitalization or ER visit	9/155 (5.8%) of placebo patients vs 6/429 (1.4%) of pooled MAb recipients were hospitalized or required an ER visit.
	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	29% of placebo patients vs 10% of BAM+ETE patients had persistently high VL defined as >5.3 log copies/ml ($P <$ 0.001).
				Hospitalization or ER visit; deaths	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).
SOT	COMET-ICE, NCT04545060; preplanned interim analysis (190)	$n = 583$; symptoms, ≤5 days	SOT 0.5 g vs placebo	Hospitalization or death	85% reduction in hospitalization and/or death (P = 0.002; data otherwise not available).

(Continued on next page)

TABLE 1 (Continued)

Intervention[a]	Trial (reference)	Population	Treatment	Endpoint	Finding
Hospitalized patients					
BAM	ACTIV-3/TICO, NCT04501978 (184); termination for futility	$n = 314$; symptoms, ≤12 days	7 g vs placebo	Pulmonary status on day 5[b]	OR of improvement compared to placebo was 0.85 (0.56 to 1.29; $P = 0.5$)
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 ($P = 0.001$)
Prevention studies					
BAM	BLAZE-2, NCT04497987 (187)	Nursing home residents ($n = 300$) and staff ($n = 666$)	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% ($P < 0.001$). 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 ($P = 0.02$).
CAS+IMD	NCT04452318 (188)	Household contacts ($n = 1,505$)	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%; $P < 0.001$) with a 92.6% reduction after the first week. Overall infections (including asymptomatic) were reduced by 66.4%.

[a]BAM, bamlanivimab; CAS+IMD, casirivimab plus imdevimab; ETE, etesevimab; SOT, sotrovimab.
[b]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 then 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 $F(ab)_2$ preparations (INM005) (218), swine glyco-humanized IgG (XAV-19) (219), and bovine transchromosomic 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 potently 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_{50} of 0.04 μM.

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 trispecific 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 gylcosaminoglycans 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-α subtypes, IFN-β, 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-α has also been reported to increase ACE2 expression in upper airway cells (267).

IFN-α, IFN-β, and IFN-λ 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-α and IFN-β have demonstrated protective effects against SARS-CoV and MERS-CoV in mice (273, 274) and macaques (79, 275, 276), while IFN-λ 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-β preparation called SNG001 in nonventilated hospitalized patients with COVID-19 receiving supplementary oxygen (280), two phase II randomized placebo-controlled trials of subcutaneous IFN-λ in outpatients with mild disease (281, 282), two randomized open-label trials of IFN-β (including the SOLIDARITY trial) (41, 283), one open-label trial of IFN-α (284), and one open-label trial of IFN-β combined with lopinavir/r and ribavirin (285). The nebulized IFN-β 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-λ 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-β 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-β given along with remdesivir (ACTT-3, NCT04492475), and one planned study for inhaled Novaferon (IFN-α) in hospitalized patients with moderate to severe disease (NCT04669015). Subcutaneous IFN-λ 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.

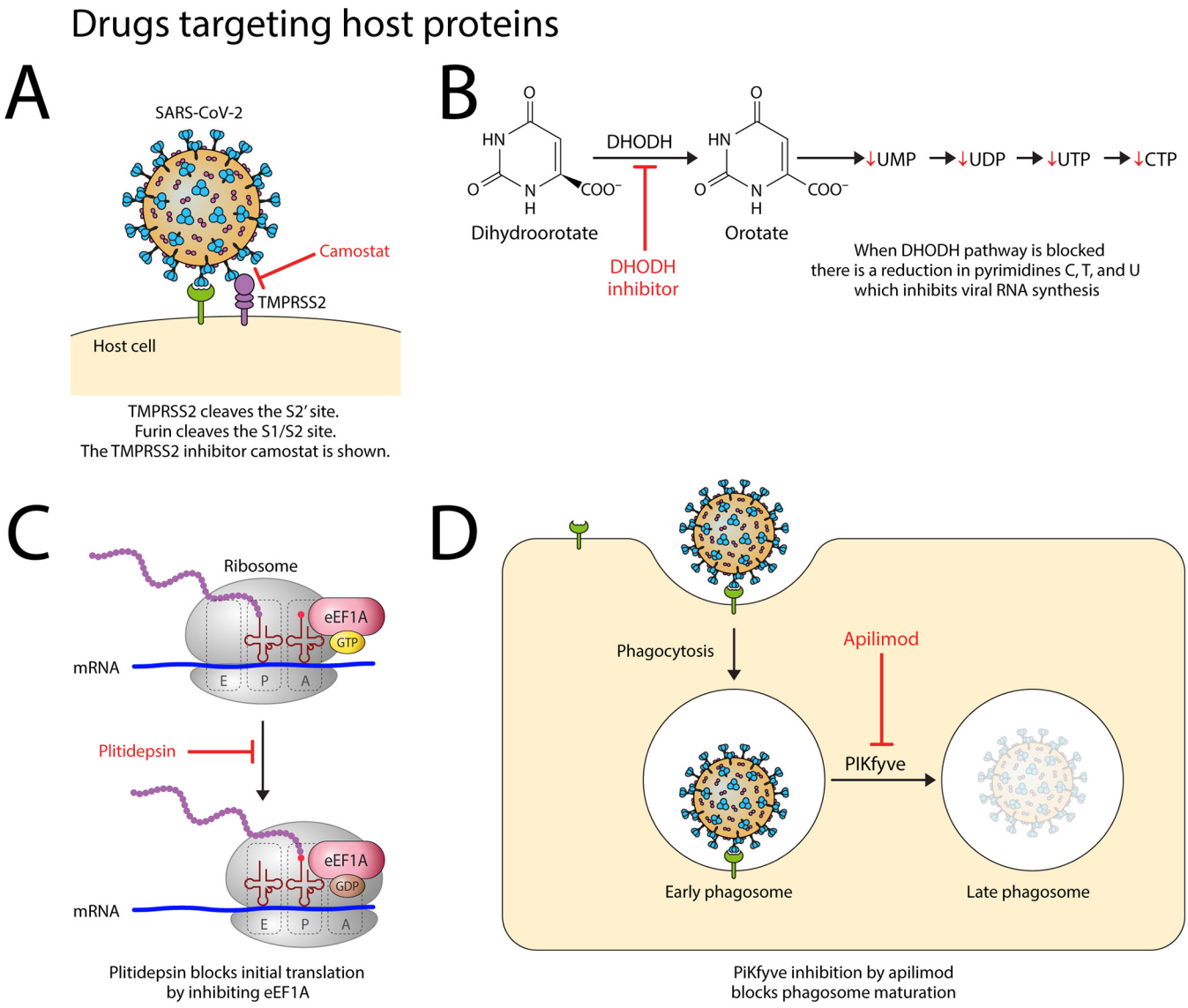

FIG 4 Four mechanisms by which repurposed drugs target cellular host pathways. (A) TMPRSS2 inhibitors such as camostat prevent the cleavage at the S2′ site thus inhibiting S2-mediated virus-cell fusion. (B) Dihydroorotate inhibitors reduce the high concentrations of pyrimidines required for virus replication. (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_{50}s generally below 1 μM, while the EC_{50}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 (α1-AT) is an endogenous protease inhibitor used as a treatment for persons with severe α1-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). α1-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). Bromehexine 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 bromehexine 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_{90} 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_{50}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_{50}s ranging between 1 and 10 μM 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_{50}s consistently below 1 μM 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_{50} for SARS-CoV-2 in Vero cells is reported to be about 1 to 5 μM (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_{50}s below 1.0 μM (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_{50} 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_{50} of about 2 μM (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 μg/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_2 of $\geq$50%, high-flow oxygen, or mechanical ventilation (352). However, two randomized placebo-controlled trials of ivermectin—one of 300 μg/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 suggests 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-β, 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.

REFERENCES

1. Zumla A, Chan JFW, Azhar EI, Hui DSC, Yuen K-Y. 2016. Coronaviruses: drug discovery and therapeutic options. Nat Rev Drug Discov 15:327–347. https://doi.org/10.1038/nrd.2015.37.
2. Li G, De Clercq E. 2020. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov 19:149–150. https://doi.org/10.1038/d41573-020-00016-0.
3. Adedeji AO, Sarafianos SG. 2014. Antiviral drugs specific for coronaviruses in preclinical development. Curr Opin Virol 8:45–53. https://doi.org/10.1016/j.coviro.2014.06.002.
4. Jin Y, Lei C, Hu D, Dimitrov DS, Ying T. 2017. Human monoclonal antibodies as candidate therapeutics against emerging viruses. Front Med 11:462–470. https://doi.org/10.1007/s11684-017-0596-6.
5. Pruijssers AJ, Denison MR. 2019. Nucleoside analogues for the treatment of coronavirus infections. Curr Opin Virol 35:57–62. https://doi.org/10.1016/j.coviro.2019.04.002.
6. Wang BX, Fish EN. 2019. Global virus outbreaks: interferons as 1st responders. Semin Immunol 43:101300. https://doi.org/10.1016/j.smim.2019.101300.
7. Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S, Blane B, Bonsall D, Cicconi P, Charlton S, Clutterbuck EA, Collins AM, Cox T, Darton TC, Dold C, Douglas AD, Duncan CJA, Ewer KJ, Flaxman AL, Faust SN, Ferreira DM, Feng S, Finn A, Folegatti PM, Fuskova M, Galiza E, Goodman AL, Green CM, Green CA, Greenland M, Hallis B, Heath PT, Hay J, Hill HC, Jenkin D, Kerridge S, Lazarus R, Libri V, Lillie PJ, Ludden C, Marchevsky NG, Minassian AM, McGregor AC, Mujadidi YF, Phillips DJ, Plested E, Pollock KM, Robinson H, Smith A, Song R, Snape MD, Sutherland RK, et al. 2021. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. Lancet 397:1351–1362. https://doi.org/10.1016/S0140-6736(21)00628-0.
8. Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L, Lalloo U, Masilela MSL, Moodley D, Hanley S, Fouche L, Louw C, Tameris M, Singh N, Goga A, Dheda K, Grobbelaar C, Kruger G, Carrim-Ganey N, Baillie V, de Oliveira T, Lombard Koen A, Lombaard JJ, Mngqibisa R, Bhorat AE, Benadé G, Lalloo N, Pitsi A, Vollgraaff P-L, Luabeya A, Esmail A, Petrick FG, Oommen-Jose A, Foulkes S, Ahmed K, Thombrayil A, Fries L, Cloney-Clark S, Zhu M, Bennett C, Albert G, Faust E, Plested JS, Robertson A, Neal S, Cho I, Glenn GM, Dubovsky F, Madhi SA, 2019nCoV-501 Study Group. 2021. Efficacy of NVX-CoV2373 Covid-19 vaccine against the B.1.351 variant. N Engl J Med 384:1899–1909. https://doi.org/10.1056/NEJMoa2103055.
9. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, Padayachee SD, Dheda K, Barnabas SL, Bhorat QE, Briner C, Kwatra G, Ahmed K, Aley P, Bhikha S, Bhiman JN, Bhorat AE, Plessis J, Du Esmail A, Groenewald M, Horne E, Hwa S-H, Jose A, Lambe T, Laubscher M, Malahleha M, Masenya M, Masilela M, McKenzie S, Molapo K, Moultrie A, Oelofse S, Patel F, Pillay S, Rhead S, Rodel H, Rossouw L, Taoushanis C, Tegally H, Thombrayil A, van Eck S, Wibmer CK, Durham NM, Kelly EJ, Villafana TL, Gilbert S, Pollard AJ, Oliveira T, de Moore PL, Sigal A, et al. Wits-VIDA COVID Group. 2021. Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B.1.351 variant. N Engl J Med 384:1885–1898. https://doi.org/10.1056/NEJMoa2102214.
10. Abu-Raddad LJ, Chemaitelly H, Butt AA. 2021. Effectiveness of the BNT162b2 COVID-19 vaccine against the B.1.1.7 and B.1.351 variants. N Engl J Med https://doi.org/10.1056/NEJMc2104974.
11. Peersen OB. 2019. A comprehensive superposition of viral polymerase structures. Viruses 11:745. https://doi.org/10.3390/v11080745.
12. De Clercq E, Li G. 2016. Approved antiviral drugs over the past 50 years. Clin Microbiol Rev 29:695–747. https://doi.org/10.1128/CMR.00102-15.
13. Minskaia E, Hertzig T, Gorbalenya AE, Campanacci V, Cambillau C, Canard B, Ziebuhr J. 2006. Discovery of an RNA virus 3′→5′ exoribonuclease that is critically involved in coronavirus RNA synthesis. Proc Natl Acad Sci U S A 103:5108–5113. https://doi.org/10.1073/pnas.0508200103.
14. Smith EC, Blanc H, Surdel MC, Vignuzzi M, Denison MR. 2013. Coronaviruses lacking exoribonuclease activity are susceptible to lethal mutagenesis: evidence for proofreading and potential therapeutics. PLoS Pathog 9:e1003565. https://doi.org/10.1371/journal.ppat.1003565.
15. Ferron F, Subissi L, Silveira De Morais AT, Le NTT, Sevajol M, Gluais L, Decroly E, Vonrhein C, Bricogne G, Canard B, Imbert I. 2018. Structural and molecular basis of mismatch correction and ribavirin excision from coronavirus RNA. Proc Natl Acad Sci U S A 115:E162–E171. https://doi.org/10.1073/pnas.1718806115.

16. Wang Q, Wu J, Wang H, Gao Y, Liu Q, Mu A, Ji W, Yan L, Zhu Y, Zhu C, Fang X, Yang X, Huang Y, Gao H, Liu F, Ge J, Sun Q, Yang X, Xu W, Liu Z, Yang H, Lou Z, Jiang B, Guddat LW, Gong P, Rao Z. 2020. Structural basis for RNA replication by the SARS-CoV-2 polymerase. Cell 182:417–428. https://doi.org/10.1016/j.cell.2020.05.034.
17. Gao Y, Yan L, Huang Y, Liu F, Zhao Y, Cao L, Wang T, Sun Q, Ming Z, Zhang L, Ge J, Zheng L, Zhang Y, Wang H, Zhu Y, Zhu C, Hu T, Hua T, Zhang B, Yang X, Li J, Yang H, Liu Z, Xu W, Guddat LW, Wang Q, Lou Z, Rao Z. 2020. Structure of the RNA-dependent RNA polymerase from COVID-19 virus. Science 368:779–782. https://doi.org/10.1126/science.abb7498.
18. Hillen HS, Kokic G, Farnung L, Dienemann C, Tegunov D, Cramer P. 2020. Structure of replicating SARS-CoV-2 polymerase. Nature 584:154–156. https://doi.org/10.1038/s41586-020-2368-8.
19. Yin W, Mao C, Luan X, Shen D-D, Shen Q, Su H, Wang X, Zhou F, Zhao W, Gao M, Chang S, Xie Y-C, Tian G, Jiang H-W, Tao S-C, Shen J, Jiang Y, Jiang H, Xu Y, Zhang S, Zhang Y, Xu HE. 2020. Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by remdesivir. Science 368:1499–1504. https://doi.org/10.1126/science.abc1560.
20. Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L, Neville S, Carra E, Lew W, Ross B, Wang Q, Wolfe L, Jordan R, Soloveva V, Knox J, Perry J, Perron M, Stray KM, Barauskas O, Feng JY, Xu Y, Lee G, Rheingold AL, Ray AS, Bannister R, Strickley R, Swaminathan S, Lee WA, Bavari S, Cihlar T, Lo MK, Warren TK, Mackman RL. 2017. Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo[2,1-f][triazin-4-amino] adenine C-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses. J Med Chem 60:1648–1661. https://doi.org/10.1021/acs.jmedchem.6b01594.
21. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. 2020. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem 295:4773–4779. https://doi.org/10.1074/jbc.AC120.013056.
22. Gordon CJ, Tchesnokov EP, Woolner E, Perry JK, Feng JY, Porter DP, Götte M. 2020. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. J Biol Chem 295:6785–6797. https://doi.org/10.1074/jbc.RA120.013679.
23. Shannon A, Tuyet Le NT, Selisko B, Eydoux C, Alvarez K, Guillemot J-C, Decroly E, Peersen O, Ferron F, Canard B. 2020. Remdesivir and SARS-CoV-2: structural requirements at both nsp12 RdRp and nsp14 exonuclease active-sites. Antiviral Res 178:104793. https://doi.org/10.1016/j.antiviral.2020.104793.
24. Tchesnokov EP, Gordon CJ, Woolner E, Kocinkova D, Perry JK, Feng JY, Porter DP, Götte M. 2020. Template-dependent inhibition of coronavirus RNA-dependent RNA polymerase by remdesivir reveals a second mechanism of action. J Biol Chem 295:16156–16165. https://doi.org/10.1074/jbc.AC120.015720.
25. Kokic G, Hillen HS, Tegunov D, Dienemann C, Seitz F, Schmitzova J, Farnung L, Siewert A, Höbartner C, Cramer P. 2021. Mechanism of SARS-CoV-2 polymerase stalling by remdesivir. Nat Commun 12:279. https://doi.org/10.1038/s41467-020-20542-0.
26. Bravo JPK, Dangerfield TL, Taylor DW, Johnson KA. 2021. Remdesivir is a delayed translocation inhibitor of SARS-CoV-2 replication. Mol Cell 81:1548–1552.e4. https://doi.org/10.1016/j.molcel.2021.01.035.
27. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, Leist SR, Pyrc K, Feng JY, Trantcheva I, Bannister R, Park Y, Babusis D, Clarke MO, Mackman RL, Spahn JE, Palmiotti CA, Siegel D, Ray AS, Cihlar T, Jordan R, Denison MR, Baric RS. 2017. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 9:eaal3653. https://doi.org/10.1126/scitranslmed.aal3653.
28. Sheahan TP, Sims AC, Zhou S, Graham RL, Pruijssers AJ, Agostini ML, Leist SR, Schäfer A, Dinnon KH, Stevens LJ, Chappell JD, Lu X, Hughes TM, George AS, Hill CS, Montgomery SA, Brown AJ, Bluemling GR, Natchus MG, Saindane M, Kolykhalov AA, Painter G, Harcourt J, Tamin A, Thornburg NJ, Swanstrom R, Denison MR, Baric RS. 2020. An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. Sci Transl Med 12:eabb5883. https://doi.org/10.1126/scitranslmed.abb5883.
29. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, Smith EC, Case JB, Feng JY, Jordan R, Ray AS, Cihlar T, Siegel D, Mackman RL, Clarke MO, Baric RS, Denison MR. 2018. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. mBio 9:e00221-18. https://doi.org/10.1128/mBio.00221-18.
30. Pruijssers AJ, George AS, Schäfer A, Leist SR, Gralinksi LE, Dinnon KH, Yount BL, Agostini ML, Stevens LJ, Chappell JD, Lu X, Hughes TM, Gully K, Martinez DR, Brown AJ, Graham RL, Perry JK, Du Pont V, Pitts J, Ma B, Babusis D, Murakami E, Feng JY, Bilello JP, Porter DP, Cihlar T, Baric RS, Denison MR, Sheahan TP. 2020. Remdesivir inhibits SARS-CoV-2 in human lung cells and chimeric SARS-CoV expressing the SARS-CoV-2 RNA polymerase in mice. Cell Rep 32:107940. https://doi.org/10.1016/j.celrep.2020.107940.
31. Xu Y, Barauskas O, Kim C, Babusis D, Murakami E, Kornyeyev D, Lee G, Stepan G, Perron M, Bannister R, Schultz BE, Sakowicz R, Porter D, Cihlar T, Feng JY. 2021. Off-target in vitro profiling demonstrates that remdesivir is a highly selective antiviral agent. Antimicrob Agents Chemother 65:e02237-20. https://doi.org/10.1128/AAC.02237-20.
32. de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, Scott D, Cihlar T, Feldmann H. 2020. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A 117:6771–6776. https://doi.org/10.1073/pnas.1922083117.
33. Williamson BN, Feldmann F, Schwarz B, Meade-White K, Porter DP, Schulz J, van Doremalen N, Leighton I, Yinda CK, Pérez-Pérez L, Okumura A, Lovaglio J, Hanley PW, Saturday G, Bosio CM, Anzick S, Barbian K, Cihlar T, Martens C, Scott DP, Munster VJ, de Wit E. 2020. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. Nature 585:273–276. https://doi.org/10.1038/s41586-020-2423-5.
34. Wang Y, Chen L. 2020. Tissue distributions of antiviral drugs affect their capabilities of reducing viral loads in COVID-19 treatment. Eur J Pharmacol 889:173634. https://doi.org/10.1016/j.ejphar.2020.173634.
35. Sun D. 2020. Remdesivir for treatment of COVID-19: combination of pulmonary and IV administration may offer additional benefit. 22:77. https://doi.org/10.1208/s12248-020-00483-8.
36. Yan VC, Muller FL. 2020. Advantages of the parent nucleoside GS-441524 over remdesivir for COVID-19 treatment. ACS Med Chem Lett 11:1361–1366. https://doi.org/10.1021/acsmedchemlett.0c00316.
37. Yan VC, Khadka S, Arthur K, Ackroyd JJ, Georgiou DK, Muller FL. 2021. Pharmacokinetics of orally administered GS-441524 in dogs. bioRxiv https://www.biorxiv.org/content/10.1101/2021.02.04.429674v3.
38. Li Y, Cao L, Li G, Cong F, Li Y, Sun J, Luo Y, Chen G, Li G, Wang P, Xing F, Ji Y, Zhao J, Zhang Y, Guo D, Zhang X. 2021. Remdesivir metabolite GS-441524 effectively inhibits SARS-CoV-2 infection in mouse models. J Med Chem https://doi.org/10.1021/acs.jmedchem.0c01929.
39. Humeniuk R, Mathias A, Kirby BJ, Lutz JD, Cao H, Osinusi A, Babusis D, Porter D, Wei X, Ling J, Reddy YS, German P. 2021. Pharmacokinetic, pharmacodynamic, and drug-interaction profile of remdesivir, a SARS-CoV-2 replication inhibitor. Clin Pharmacokinet 60:569–583. https://doi.org/10.1007/s40262-021-00984-5.
40. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh M, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC. 2020. Remdesivir for the treatment of COVID-19: final report. N Engl J Med 383:1813–1826. https://doi.org/10.1056/NEJMoa2007764.
41. Pan H, Peto R, Henao-Restrepo A-M, Preziosi M-P, Sathiyamoorthy V, Abdool Karim Q, Alejandria MM, Hernández García C, Kieny M-P, Malekzadeh R, Murthy S, Reddy KS, Roses Periago M, Abi Hanna P, Ader F, Al-Bader AM, Alhasawi A, Allum E, Alotaibi A, Alvarez-Moreno CA, Appadoo S, Asiri A, Aukrust P, Barratt-Due A, Bellani S, Branca M, Cappel-Porter HBC, Cerrato N, Chow TS, Como N, Eustace J, García PJ, Godbole S, Gotuzzo E, Griskevicius L, Hamra R, Hassan M, Hassany M, Hutton D, Irmansyah I, Jancoriene L, Kirwan J, Kumar S, Lennon P, Lopardo G, Lydon P, Magrini N, Maguire T, Manevska S, Manuel O, WHO Solidarity Trial Consortium, et al. 2021. Repurposed antiviral drugs for COVID-19: interim WHO solidarity trial results. N Engl J Med 384:497–511. https://doi.org/10.1056/NEJMoa2023184.
42. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu Y, Luo G, Wang K, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang Y, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zhang Y, Cao L, Guo T, Wan Y, Qin H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B, Wang C. 2020. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet Lond Engl 395:1569–1578. https://doi.org/10.1016/S0140-6736(20)31022-9.
43. Spinner CD, Gottlieb RL, Criner GJ, López JRA, Cattelan AM, Viladomiu AS, Ogbuagu O, Malhotra P, Mullane KM, Castagna A, Chai LYA, Roestenberg M, Tsang OTY, Bernasconi E, Turnier PL, Chang S-C,

SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wang H, Gaggar A, Brainard DM, McPhail MJ, Bhagani S, Ahn MY, Sanyal AJ, Huhn G, Marty FM, GS-US-540–5774 Investigators. 2020. Effect of remdesivir versus standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA 324:1048–1057. https://doi.org/10.1001/jama.2020.16349.
44. Maves RC. 2021. Making sense of contradictory evidence in coronavirus disease 2019 trials. Clin Infect Dis https://doi.org/10.1093/cid/ciab012.
45. Kaka AS, MacDonald R, Greer N, Vela K, Duan-Porter W, Obley A, Wilt TJ. 2021. Major Update: remdesivir for adults with COVID-19: a living systematic review and meta-analysis for the American College of Physicians practice points. Ann Intern Med 174:663–672. https://doi.org/10.7326/M20-8148.
46. Rosenke K, Hansen F, Schwarz B, Feldmann F, Haddock E, Rosenke R, Barbian K, Meade-White K, Okumura A, Leventhal S, Hawman DW, Ricotta E, Bosio CM, Martens C, Saturday G, Feldmann H, Jarvis MA. 2021. Orally delivered MK-4482 inhibits SARS-CoV-2 replication in the Syrian hamster model. Nat Commun 12:2295. https://doi.org/10.1038/s41467-021-22580-8.
47. Gordon CJ, Tchesnokov EP, Schinazi RF, Götte M. 2021. Molnupiravir promotes SARS-CoV-2 mutagenesis via the RNA template. J Biol Chem 100770. https://doi.org/10.1016/j.jbc.2021.100770.
48. Zhou S, Hill CS, Sarkar S, Tse LV, Woodburn BMD, Schinazi RF, Sheahan TP, Baric RS, Heise MT, Swanstrom R. 2021. β-D-N4-hydroxycytidine (NHC) inhibits SARS-CoV-2 through lethal mutagenesis but is also mutagenic to mammalian cells. J Infect Dis https://doi.org/10.1093/infdis/jiab247.
49. Agostini ML, Pruijssers AJ, Chappell JD, Gribble J, Lu X, Andres EL, Bluemling GR, Lockwood MA, Sheahan TP, Sims AC, Natchus MG, Saindane M, Kolykhalov AA, Painter GR, Baric RS, Denison MR. 2019. Small-molecule antiviral β-D-N4-hydroxycytidine inhibits a proofreading-intact coronavirus with a high genetic barrier to resistance. J Virol 93:e01348-19. https://doi.org/10.1128/JVI.01348-19.
50. Wahl A, Gralinski LE, Johnson CE, Yao W, Kovarova M, Dinnon KH, Liu H, Madden VJ, Krzystek HM, De C, White KK, Gully K, Schäfer A, Zaman T, Leist SR, Grant PO, Bluemling GR, Kolykhalov AA, Natchus MG, Askin FB, Painter G, Browne EP, Jones CD, Pickles RJ, Baric RS, Garcia JV. 2021. SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801. Nature 591:451–457. https://doi.org/10.1038/s41586-021-03312-w.
51. Cox RM, Wolf JD, Plemper RK. 2021. Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. Nat Microbiol 6:11–18. https://doi.org/10.1038/s41564-020-00835-2.
52. Painter WP, Holman W, Bush JA, Almazedi F, Malik H, Eraut NCJE, Morin MJ, Szewczyk LJ, Painter GR. 2021. Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2. Antimicrob Agents Chemother 65:e02428-20. https://doi.org/10.1128/AAC.02428-20.
53. Khoo SH, FitzGerald R, Fletcher T, Ewings S, Jaki T, Lyon R, Downs N, Walker L, Tansley-Hancock O, Greenhalf W, Woods C, Reynolds H, Marwood E, Mozgunov P, Adams E, Bullock K, Holman W, Bula MD, Gibney JL, Saunders G, Corkhill A, Hale C, Thorne K, Chiong J, Condie S, Pertinez H, Painter W, Wrixon E, Johnson L, Yeats S, Mallard K, Radford M, Fines K, Shaw V, Owen A, Lalloo DG, Jacobs M, Griffiths G. 2021. Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a phase 1, dose-escalating, randomised controlled study. medRxiv https://www.medrxiv.org/content/10.1101/2021.05.03.21256309v1.
54. Zandi K, Amblard F, Musall K, Downs-Bowen J, Kleinbard R, Oo A, Cao D, Liang B, Russell OO, McBrayer T, Bassit L, Kim B, Schinazi RF. 2020. Repurposing nucleoside analogs for human coronaviruses. Antimicrob Agents Chemother 65:e01652-20. https://doi.org/10.1128/AAC.01652-20.
55. Good SS, Moussa A, Zhou X-J, Pietropaolo K, Sommadossi J-P. 2020. Preclinical evaluation of AT-527, a novel guanosine nucleotide prodrug with potent, pan-genotypic activity against hepatitis C virus. PLoS One 15:e0227104. https://doi.org/10.1371/journal.pone.0227104.
56. Berliba E, Bogus M, Vanhoutte F, Berghmans P-J, Good SS, Moussa A, Pietropaolo K, Murphy RL, Zhou X-J, Sommadossi J-P. 2019. Safety, pharmacokinetics, and antiviral activity of AT-527, a novel purine nucleotide prodrug, in HCV-infected subjects with and without cirrhosis. Antimicrob Agents Chemother 63:e01201-19. https://doi.org/10.1128/AAC.01201-19.
57. Good SS, Westover J, Jung KH, Zhou X-J, Moussa A, Colla PL, Collu G, Canard B, Sommadossi J-P. 2021. AT-527, a double prodrug of a guanosine nucleotide analog, is a potent inhibitor of SARS-CoV-2 *in vitro* and a promising oral antiviral for treatment of COVID-19. Antimicrob Agents Chemother 65:e02479-20. https://doi.org/10.1128/AAC.02479-20.
58. Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. 2013. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antiviral Res 100:446–454. https://doi.org/10.1016/j.antiviral.2013.09.015.
59. Delang L, Abdelnabi R, Neyts J. 2018. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. Antiviral Res 153:85–94. https://doi.org/10.1016/j.antiviral.2018.03.003.
60. Shannon A, Selisko B, Le N-T-T, Huchting J, Touret F, Piorkowski G, Fattorini V, Ferron F, Decroly E, Meier C, Coutard B, Peersen O, Canard B. 2020. Rapid incorporation of Favipiravir by the fast and permissive viral RNA polymerase complex results in SARS-CoV-2 lethal mutagenesis. Nat Commun 11:4682. https://doi.org/10.1038/s41467-020-18463-z.
61. Du Y-X, Chen X-P. 2020. Favipiravir: pharmacokinetics and concerns about clinical trials for 2019-nCoV infection. Clin Pharmacol Ther 108:242–247. https://doi.org/10.1002/cpt.1844.
62. Choy K-T, Yin-Lam Wong A, Kaewpreedee P, Sia S-F, Chen D, Yan Hui KP, Wing Chu DK, W, Chan MC, Pak-Hang Cheung P, Huang X, Peiris M, Yen H-L. 2020. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication *in vitro*. Antiviral Res 178:104786. https://doi.org/10.1016/j.antiviral.2020.104786.
63. Jeon S, Ko M, Lee J, Choi I, Byun SY, Park S, Shum D, Kim S. 2020. Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs. Antimicrob Agents Chemother 64:e00819-20. https://doi.org/10.1128/AAC.00819-20.
64. Xie X, Muruato AE, Zhang X, Lokugamage KG, Fontes-Garfias CR, Zou J, Liu J, Ren P, Balakrishnan M, Cihlar T, Tseng C-TK, Makino S, Menachery VD, Bilello JP, Shi P-Y. 2020. A nanoluciferase SARS-CoV-2 for rapid neutralization testing and screening of anti-infective drugs for COVID-19. Nat Commun 11:5214. https://doi.org/10.1038/s41467-020-19055-7.
65. Naydenova K, Muir KW, Wu L-F, Zhang Z, Coscia F, Peet MJ, Castro-Hartmann P, Qian P, Sader K, Dent K, Kimanius D, Sutherland JD, Löwe J, Barford D, Russo CJ. 2021. Structure of the SARS-CoV-2 RNA-dependent RNA polymerase in the presence of favipiravir-RTP. Proc Natl Acad Sci U S A 118:e2021946118. https://doi.org/10.1073/pnas.2021946118.
66. Kaptein SJF, Jacobs S, Langendries L, Seldeslachts L, Horst ter S, Liesenborghs L, Hens B, Vergote V, Heylen E, Barthelemy K, Maas E, Keyzer CD, Bervoets L, Rymenants J, Buyten TV, Zhang X, Abdelnabi R, Pang J, Williams R, Thibaut HJ, Dallmeier K, Boudewijns R, Wouters J, Augustijns P, Verougstraete N, Cawthorne C, Breuer J, Solas C, Weynand B, Annaert P, Spriet I, Velde GV, Neyts J, Rocha-Pereira J, Delang L. 2020. Favipiravir at high doses has potent antiviral activity in SARS-CoV-2-infected hamsters, whereas hydroxychloroquine lacks activity. Proc Natl Acad Sci U S A 117:26955–26965. https://doi.org/10.1073/pnas.2014441117.
67. Udwadia ZF, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, Kadam J, Wu W, Caracta CF, Tandon M. 2021. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: a randomized, comparative, open-label, multicenter, phase 3 clinical trial. Int J Infect Dis 103:62–71. https://doi.org/10.1016/j.ijid.2020.11.142.
68. Doi Y, Hibino M, Hase R, Yamamoto M, Kasamatsu Y, Hirose M, Mutoh Y, Homma Y, Terada M, Ogawa T, Kashizaki F, Yokoyama T, Koba H, Kasahara H, Yokota K, Kato H, Yoshida J, Kita T, Kato Y, Kamio T, Kodama N, Uchida Y, Ikeda N, Shinoda M, Nakagawa A, Nakatsumi H, Horiguchi T, Iwata M, Matsuyama A, Banno S, Koseki T, Teramachi M, Miyata M, Tajima S, Maeki T, Nakayama E, Taniguchi S, Lim CK, Saijo M, Imai T, Yoshida H, Kabata D, Shintani A, Yuzawa Y, Kondo M. 2020. A prospective, randomized, open-label trial of early versus late favipiravir therapy in hospitalized patients with COVID-19. Antimicrob Agents Chemother 64:e01897-20. https://doi.org/10.1128/AAC.01897-20.
69. Ivashchenko AA, Dmitriev KA, Vostokova NV, Azarova VN, Blinow AA, Egorova AN, Gordeev IG, Ilin AP, Karapetian RN, Kravchenko DV, Lomakin NV, Merkulova EA, Papazova NA, Pavlikova EP, Savchuk NP, Simakina EN, Sitdekov TA, Smolyarchuk EA, Tikhomolova EG, Yakubova EV, Ivachtchenko AV. 2020. AVIFAVIR for treatment of patients with moderate coronavirus disease 2019 (COVID-19): interim results of a phase II/III multicenter randomized clinical trial. Clin Infect Dis https://doi.org/10.1093/cid/ciaa1176.
70. Lou Y, Liu L, Yao H, Hu X, Su J, Xu K, Luo R, Yang X, He L, Lu X, Zhao Q, Liang T, Qiu Y. 2021. Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. Eur J Pharm Sci 157:105631. https://doi.org/10.1016/j.ejps.2020.105631.

71. Jockusch S, Tao C, Li X, Anderson TK, Chien M, Kumar S, Russo JJ, Kirchdoerfer RN, Ju J. 2020. A library of nucleotide analogues terminate RNA synthesis catalyzed by polymerases of coronaviruses that cause SARS and COVID-19. Antiviral Res 180:104857. https://doi.org/10.1016/j.antiviral.2020.104857.
72. Jockusch S, Tao C, Li X, Chien M, Kumar S, Morozova I, Kalachikov S, Russo JJ, Ju J. 2020. Sofosbuvir terminated RNA is more resistant to SARS-CoV-2 proofreader than RNA terminated by remdesivir. Sci Rep 10:16577. https://doi.org/10.1038/s41598-020-73641-9.
73. Chien M, Anderson TK, Jockusch S, Tao C, Li X, Kumar S, Russo JJ, Kirchdoerfer RN, Ju J. 2020. Nucleotide analogues as inhibitors of SARS-CoV-2 polymerase, a key drug target for COVID-19. J Proteome Res 19:4690–4697. https://doi.org/10.1021/acs.jproteome.0c00392.
74. Sacramento CQ, Fintelman-Rodrigues N, Temerozo JR, Da Silva A de PD, Gomeas Diaz SDS, da Silva C dos S, Ferreira AC, Mattos M, Pão CRR, de Freitas CS, Soares VC, Hoelz LVB, Fernandes TVA, Branco FSC, Bastos MM, Boechat N, Saraiva FB, Ferreira MA, Jockusch S, Wang X, Tao C, Chien M, Xie W, Patel D, Garzia A, Tuschl T, Russo JJ, Rajoli RKR, Pedrosa CSG, Vitória G, Souza LRQ, Goto-Silva L, Guimarães MZ, Rehen SK, Owen A, Bozza FA, Bou-Habib DC, Ju J, Bozza PT, Souza TML. 2021. *In vitro* antiviral activity of the anti-HCV drugs daclatasvir and sofosbuvir against SARS-CoV-2, the aetiological agent of COVID-19. J Antimicrob Chemother 76:1874–1885. https://doi.org/10.1093/jac/dkab072.
75. Simmons B, Wentzel H, Mobarak S, Eslami G, Sadeghi A, Ali Asgari A, Abbaspour Kasgari H, Tirgar Fakheri H, Merat S, Hill A. 2021. Sofosbuvir/daclatasvir regimens for the treatment of COVID-19: an individual patient data meta-analysis. J Antimicrob Chemother 76:286–291. https://doi.org/10.1093/jac/dkaa418.
76. Sacramento CQ, Fintelman-Rodrigues N, Temerozo JR, Dias S da SG, Ferreira AC, Mattos M, Pao CRR, de Freitas CS, Soares VC, Bozza FA, Bou-Habib DC, Bozza PT, Souza TML. 2020. The *in vitro* antiviral activity of the anti-hepatitis C virus (HCV) drugs daclatasvir and sofosbuvir against SARS-CoV-2. bioRxiv https://www.biorxiv.org/content/10.1101/2020.06.15.153411v2.
77. Day CW, Baric R, Cai SX, Frieman M, Kumaki Y, Morrey JD, Smee DF, Barnard DL. 2009. A new mouse-adapted strain of SARS-CoV as a lethal model for evaluating antiviral agents *in vitro* and *in vivo*. Virology 395:210–222. https://doi.org/10.1016/j.virol.2009.09.023.
78. Stockman LJ, Bellamy R, Garner P. 2006. SARS: systematic review of treatment effects. PLoS Med 3:e343. https://doi.org/10.1371/journal.pmed.0030343.
79. Falzarano D, de Wit E, Martellaro C, Callison J, Munster VJ, Feldmann H. 2013. Inhibition of novel β coronavirus replication by a combination of interferon-α2b and ribavirin. Sci Rep 3:1686. https://doi.org/10.1038/srep01686.
80. Cannalire R, Cerchia C, Beccari AR, Di Leva FS, Summa V. 2020. Targeting SARS-CoV-2 proteases and polymerase for COVID-19 treatment: state of the art and future opportunities. J Med Chem https://doi.org/10.1021/acs.jmedchem.0c01140.
81. Zhang L, Lin D, Sun X, Curth U, Drosten C, Sauerhering L, Becker S, Rox K, Hilgenfeld R. 2020. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. Science 368:409–412. https://doi.org/10.1126/science.abb3405.
82. Banerjee R, Perera L, Tillekeratne LMV. 2021. Potential SARS-CoV-2 main protease inhibitors. Drug Discov Today 26:804–816. https://doi.org/10.1016/j.drudis.2020.12.005.
83. Osipiuk J, Azizi S-A, Dvorkin S, Endres M, Jedrzejczak R, Jones KA, Kang S, Kathayat RS, Kim Y, Lisnyak VG, Maki SL, Nicolaescu V, Taylor CA, Tesar C, Zhang Y-A, Zhou Z, Randall G, Michalska K, Snyder SA, Dickinson BC, Joachimiak A. 2021. Structure of papain-like protease from SARS-CoV-2 and its complexes with non-covalent inhibitors. Nat Commun 12:743. https://doi.org/10.1038/s41467-021-21060-3.
84. Klemm T, Ebert G, Calleja DJ, Allison CC, Richardson LW, Bernardini JP, Lu BG, Kuchel NW, Grohmann C, Shibata Y, Gan ZY, Cooney JP, Doerflinger M, Au AE, Blackmore TR, van der Heden van Noort GJ, Geurink PP, Ovaa H, Newman J, Riboldi-Tunnicliffe A, Czabotar PE, Mitchell JP, Feltham R, Lechtenberg BC, Lowes KN, Dewson G, Pellegrini M, Lessene G, Komander D. 2020. Mechanism and inhibition of the papain-like protease, PLpro, of SARS-CoV-2. 39:e106275. https://doi.org/10.15252/embj.2020106275.
85. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO, Spahn JE, Bauer L, Sellers S, Porter D, Feng JY, Cihlar T, Jordan R, Denison MR, Baric RS. 2020. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 11:222. https://doi.org/10.1038/s41467-019-13940-6.
86. Fintelman-Rodrigues N, Sacramento CQ, Lima CR, da Silva FS, Ferreira AC, Mattos M, de Freitas CS, Soares VC, Dias S da SG, Temerozo JR, Miranda MD, Matos AR, Bozza FA, Carels N, Alves CR, Siqueira MM, Bozza PT, Souza TML. 2020. Atazanavir, alone or in combination with ritonavir, inhibits SARS-CoV-2 replication and proinflammatory cytokine production. Antimicrob Agents Chemother 64:e00825-20. https://doi.org/10.1128/AAC.00825-20.
87. De Meyer S, Bojkova D, Cinatl J, Van Damme E, Buyck C, Van Loock M, Woodfall B, Ciesek S. 2020. Lack of antiviral activity of darunavir against SARS-CoV-2. Int J Infect Dis 97:7–10. https://doi.org/10.1016/j.ijid.2020.05.085.
88. Park S-J, Yu K-M, Kim Y-I, Kim S-M, Kim E-H, Kim S-G, Kim EJ, Casel MAB, Rollon R, Jang S-G, Lee M-H, Chang J-H, Song M-S, Jeong HW, Choi Y, Chen W, Shin W-J, Jung JU, Choi YK. 2020. Antiviral efficacies of FDA-approved drugs against SARS-CoV-2 infection in ferrets. mBio 11:e01114-20. https://doi.org/10.1128/mBio.01114-20.
89. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, et al. 2020. A trial of lopinavir–ritonavir in adults hospitalized with severe COVID-19. N Engl J Med 382:1787–1799. https://doi.org/10.1056/NEJMoa2001282.
90. Arabi YM, Asiri AY, Assiri AM, Balkhy HH, Bshabshe AA, Jeraisy MA, Mandourah Y, Azzam MHA, Eshaq AMB, Johani SA, Harbi SA, Jokhdar HAA, Deeb AM, Memish ZA, Jose J, Ghazal S, Faraj SA, Mekhlafi GAA, Sherbeeni NM, Elzein FE, Al-Hameed F, Saedi AA, Alharbi NK, Fowler RA, Hayden FG, Al-Dawood A, Abdelzaher M, Bajhmom W, AlMutairi BM, Hussein MA, Alothman A, Saudi Critical Care Trials Group. 2020. Interferon β1b and lopinavir–ritonavir for Middle East respiratory syndrome. N Engl J Med 383:1645–1656. https://doi.org/10.1056/NEJMoa2015294.
91. Dai W, Zhang B, Jiang X-M, Su H, Li J, Zhao Y, Xie X, Jin Z, Peng J, Liu F, Li C, Li Y, Bai F, Wang H, Cheng X, Cen X, Hu S, Yang X, Wang J, Liu X, Xiao G, Jiang H, Rao Z, Zhang L-K, Xu Y, Yang H, Liu H. 2020. Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease. Science 368:1331–1335. https://doi.org/10.1126/science.abb4489.
92. Jin Z, Du X, Xu Y, Deng Y, Liu M, Zhao Y, Zhang B, Li X, Zhang L, Peng C, Duan Y, Yu J, Wang L, Yang K, Liu F, Jiang R, Yang X, You T, Liu X, Yang X, Bai F, Liu H, Liu X, Guddat LW, Xu W, Xiao G, Qin C, Shi Z, Jiang H, Rao Z, Yang H. 2020. Structure of M pro from SARS-CoV-2 and discovery of its inhibitors. Nature 582:289–293. https://doi.org/10.1038/s41586-020-2223-y.
93. Lockbaum GJ, Reyes AC, Lee JM, Tilvawala R, Nalivaika EA, Ali A, Kurt Yilmaz N, Thompson PR, Schiffer CA. 2021. Crystal structure of SARS-CoV-2 main protease in complex with the non-covalent inhibitor ML188. Viruses 13:174. https://doi.org/10.3390/v13020174.
94. Hattori S, Higshi-Kuwata N, Raghavaiah J, Das D, Bulut H, Davis DA, Takamatsu Y, Matsuda K, Takamune N, Kishimoto N, Okamura T, Misumi S, Yarchoan R, Maeda K, Ghosh AK, Mitsuya H. 2020. GRL-0920, an indole chloropyridinyl ester, completely blocks SARS-CoV-2 infection. mBio 11:e01833-20. https://doi.org/10.1128/mBio.01833-20.
95. Hattori S, Higashi-Kuwata N, Hayashi H, Allu SR, Raghavaiah J, Bulut H, Das D, Anson BJ, Lendy EK, Takamatsu Y, Takamune N, Kishimoto N, Murayama K, Hasegawa K, Li M, Davis DA, Kodama EN, Yarchoan R, Wlodawer A, Misumi S, Mesecar AD, Ghosh AK, Mitsuya H. 2021. A small molecule compound with an indole moiety inhibits the main protease of SARS-CoV-2 and blocks virus replication. Nat Commun 12:668. https://doi.org/10.1038/s41467-021-20900-6.
96. Hoffman RL, Kania RS, Brothers MA, Davies JF, Ferre RA, Gajiwala KS, He M, Hogan RJ, Kozminski K, Li LY, Lockner JW, Lou J, Marra MT, Mitchell LJ, Murray BW, Nieman JA, Noell S, Planken SP, Rowe T, Ryan K, Smith GJ, Solowiej JE, Steppan CM, Taggart B. 2020. Discovery of ketone-based covalent inhibitors of coronavirus 3CL proteases for the potential therapeutic treatment of COVID-19. J Med Chem 63:12725–12747. https://doi.org/10.1021/acs.jmedchem.0c01063.
97. Kneller DW, Galanie S, Phillips G, O'Neill HM, Coates L, Kovalevsky A. 2020. Malleability of the SARS-CoV-2 3CL Mpro active-site cavity facilitates binding of clinical antivirals. Structure 28:1313–1320. https://doi.org/10.1016/j.str.2020.10.007.
98. Steuten K, Kim H, Widen JC, Babin BM, Onguka O, Lovell S, Bolgi O, Cerikan B, Neufeldt CJ, Cortese M, Muir RK, Bennett JM, Geiss-Friedlander R, Peters C, Bartenschlager R, Bogyo M. 2021. Challenges for targeting SARS-CoV-2

proteases as a therapeutic strategy for COVID-19. ACS Infect Dis 7:1457–1468. https://doi.org/10.1021/acsinfecdis.0c00815.
99. Vandyck K, Abdelnabi R, Gupta K, Jochmans D, Jekle A, Deval J, Misner D, Bardiot D, Foo CS, Liu C, Ren S, Beigelman L, Blatt LM, Boland S, Vangeel L, Dejonghe S, Chaltin P, Marchand A, Serebryany V, Stoycheva A, Chanda S, Symons JA, Raboisson P, Neyts J. 2021. ALG-097111, a potent and selective SARS-CoV-2 3-chymotrypsin-like cysteine protease inhibitor exhibits *in vivo* efficacy in a Syrian hamster model. Biochem Biophys Res Commun 555:134–139. https://doi.org/10.1016/j.bbrc.2021.03.096.
100. de Vries M, Mohamed AS, Prescott RA, Valero-Jimenez AM, Desvignes L, O'Connor R, Steppan C, Devlin JC, Ivanova E, Herrera A, Schinlever A, Loose P, Ruggles K, Koralov SB, Anderson AS, Binder J, Dittmann M. 2021. A comparative analysis of SARS-CoV-2 antivirals characterizes 3CLpro inhibitor PF-00835231 as a potential new treatment for COVID-19. J Virol 95:e01819-20. https://doi.org/10.1128/JVI.01819-20.
101. Boras B, Jones RM, Anson BJ, Arenson D, Aschenbrenner L, Bakowski MA, Beutler N, Binder J, Chen E, Eng H, Hammond J, Hoffman R, Kadar EP, Kania R, Kimoto E, Kirkpatrick MG, Lanyon L, Lendy EK, Lillis JR, Luthra SA, Ma C, Noell S, Obach RS, O'Brien MN, O'Connor R, Ogilvie K, Owen D, Pettersson M, Reese MR, Rogers T, Rossulek MI, Sathish JG, Steppan C, Ticehurst M, Updyke LW, Zhu Y, Wang J, Chatterjee AK, Mesecar AD, Anderson AS, Allerton C. 2020. Discovery of a novel inhibitor of coronavirus 3CL protease as a clinical candidate for the potential treatment of COVID-19. bioRxiv https://www.biorxiv.org/content/10.1101/2020.09.12.293498v3.
102. Menéndez CA, Byléhn F, Perez-Lemus GR, Alvarado W, de Pablo JJ. 2020. Molecular characterization of ebselen binding activity to SARS-CoV-2 main protease. Sci Adv 6:eabd0345. https://doi.org/10.1126/sciadv.abd0345.
103. Zmudzinski M, Rut W, Olech K, Granda J, Giurg M, Burda-Grabowska M, Zhang L, Sun X, Lv Z, Nayak D, Kesik-Brodacka M, Olsen SK, Hilgenfeld R, Drag M. 2020. Ebselen derivatives are very potent dual inhibitors of SARS-CoV-2 proteases: PL^{pro} and M^{pro} in *in vitro* studies. bioRxiv https://www.biorxiv.org/content/10.1101/2020.08.30.273979v1.
104. Weglarz-Tomczak E, Tomczak JM, Talma M, Burda-Grabowska M, Giurg M, Brul S. 2021. Identification of ebselen and its analogues as potent covalent inhibitors of papain-like protease from SARS-CoV-2. Sci Rep 11:3640. https://doi.org/10.1038/s41598-021-83229-6.
105. Kim Y, Liu H, Galasiti Kankanamalage AC, Weerasekara S, Hua DH, Groutas WC, Chang K-O, Pedersen NC. 2016. Reversal of the progression of fatal coronavirus infection in cats by a broad-spectrum coronavirus protease inhibitor. PLoS Pathog 12:e1005531. https://doi.org/10.1371/journal.ppat.1005531.
106. Kim Y, Lovell S, Tiew K-C, Mandadapu SR, Alliston KR, Battaile KP, Groutas WC, Chang K-O. 2012. Broad-spectrum antivirals against 3C or 3C-like proteases of picornaviruses, noroviruses, and coronaviruses. J Virol 86:11754–11762. https://doi.org/10.1128/JVI.01348-12.
107. Ma C, Sacco MD, Hurst B, Townsend JA, Hu Y, Szeto T, Zhang X, Tarbet B, Marty MT, Chen Y, Wang J. 2020. Boceprevir, GC-376, and calpain inhibitors II, XII inhibit SARS-CoV-2 viral replication by targeting the viral main protease. Cell Res 30:678–692. https://doi.org/10.1038/s41422-020-0356-z.
108. Vuong W, Khan MB, Fischer C, Arutyunova E, Lamer T, Shields J, Saffran HA, McKay RT, van Belkum MJ, Joyce MA, Young HS, Tyrrell DL, Vederas JC, Lemieux MJ. 2020. Feline coronavirus drug inhibits the main protease of SARS-CoV-2 and blocks virus replication. Nat Commun 11:4282. https://doi.org/10.1038/s41467-020-18096-2.
109. Luan X, Shang W, Wang Y, Yin W, Jiang Y, Feng S, Wang Y, Liu M, Zhou R, Zhang Z, Wang F, Cheng W, Gao M, Wang H, Wu W, Tian R, Tian Z, Jin Y, Jiang H, Zhang L, Xu HE, Zhang S. 2020. Structure basis for inhibition of SARS-CoV-2 by the feline drug GC376. bioRxiv https://www.biorxiv.org/content/10.1101/2020.06.07.138677v1.
110. Fu L, Ye F, Feng Y, Yu F, Wang Q, Wu Y, Zhao C, Sun H, Huang B, Niu P, Song H, Shi Y, Li X, Tan W, Qi J, Gao GF. 2020. Both Boceprevir and GC376 efficaciously inhibit SARS-CoV-2 by targeting its main protease. Nat Commun 11:4417. https://doi.org/10.1038/s41467-020-18233-x.
111. Galasiti Kankanamalage AC, Kim Y, Damalanka VC, Rathnayake AD, Fehr AR, Mehzabeen N, Battaile KP, Lovell S, Lushington GH, Perlman S, Chang K-O, Groutas WC. 2018. Structure-guided design of potent and permeable inhibitors of MERS coronavirus 3CL protease that utilize a piperidine moiety as a novel design element. Eur J Med Chem 150:334–346. https://doi.org/10.1016/j.ejmech.2018.03.004.
112. Iketani S, Forouhar F, Liu H, Hong SJ, Lin F-Y, Nair MS, Zask A, Huang Y, Xing L, Stockwell BR, Chavez A, Ho DD. 2021. Lead compounds for the development of SARS-CoV-2 3CL protease inhibitors. Nat Commun 12:2016. https://doi.org/10.1038/s41467-021-22362-2.
113. Sacco MD, Ma C, Lagarias P, Gao A, Townsend JA, Meng X, Dube P, Zhang X, Hu Y, Kitamura N, Hurst B, Tarbet B, Marty MT, Kolocouris A, Xiang Y, Chen Y, Wang J. 2020. Structure and inhibition of the SARS-CoV-2 main protease reveals strategy for developing dual inhibitors against Mpro and cathepsin L. Sci Adv 6:eabe0751. https://doi.org/10.1126/sciadv.abe0751.
114. Ghahremanpour MM, Tirado-Rives J, Deshmukh M, Ippolito JA, Zhang C-H, Cabeza de Vaca I, Liosi M-E, Anderson KS, Jorgensen WL. 2020. Identification of 14 known drugs as inhibitors of the main protease of SARS-CoV-2. ACS Med Chem Lett 11:2526–2533. https://doi.org/10.1021/acsmedchemlett.0c00521.
115. Qiao J, Li Y-S, Zeng R, Liu F-L, Luo R-H, Huang C, Wang Y-F, Zhang J, Quan B, Shen C, Mao X, Liu X, Sun W, Yang W, Ni X, Wang K, Xu L, Duan Z-L, Zou Q-C, Zhang H-L, Qu W, Long Y-H-P, Li M-H, Yang R-C, Liu X, You J, Zhou Y, Yao R, Li W-P, Liu J-M, Chen P, Liu Y, Lin G-F, Yang X, Zou J, Li L, Hu Y, Lu G-W, Li W-M, Wei Y-Q, Zheng Y-T, Lei J, Yang S. 2021. SARS-CoV-2 Mpro inhibitors with antiviral activity in a transgenic mouse model. Science 371:1374–1378. https://doi.org/10.1126/science.abf1611.
116. Walls AC, Park Y-J, Tortorici MA, Wall A, McGuire AT, Veesler D. 2020. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 181:281–292. https://doi.org/10.1016/j.cell.2020.02.058.
117. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, Graham BS, McLellan JS. 2020. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 367:1260–1263. https://doi.org/10.1126/science.abb2507.
118. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, Zhang Q, Shi X, Wang Q, Zhang L, Wang X. 2020. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature 581:215–220. https://doi.org/10.1038/s41586-020-2180-5.
119. Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, Lu G, Qiao C, Hu Y, Yuen K-Y, Wang Q, Zhou H, Yan J, Qi J. 2020. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell 181:894–904. https://doi.org/10.1016/j.cell.2020.03.045.
120. Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H, Geng Q, Auerbach A, Li F. 2020. Structural basis of receptor recognition by SARS-CoV-2. Nature 581:221–224. https://doi.org/10.1038/s41586-020-2179-y.
121. Xu C, Wang Y, Liu C, Zhang C, Han W, Hong X, Wang Y, Hong Q, Wang S, Zhao Q, Wang Y, Yang Y, Chen K, Zheng W, Kong L, Wang F, Zuo Q, Huang Z, Cong Y. 2021. Conformational dynamics of SARS-CoV-2 trimeric spike glycoprotein in complex with receptor ACE2 revealed by cryo-EM. Sci Adv 7:eabe5575. https://doi.org/10.1126/sciadv.abe5575.
122. Cai Y, Zhang J, Xiao T, Peng H, Sterling SM, Walsh RM, Rawson S, Rits-Volloch S, Chen B. 2020. Distinct conformational states of SARS-CoV-2 spike protein. Science 369:1586–1592. https://doi.org/10.1126/science.abd4251.
123. Millet JK, Whittaker GR. 2015. Host cell proteases: critical determinants of coronavirus tropism and pathogenesis. Virus Res 202:120–134. https://doi.org/10.1016/j.virusres.2014.11.021.
124. Tortorici MA, Veesler D. 2019. Structural insights into coronavirus entry. Adv Virus Res 105:93–116. https://doi.org/10.1016/bs.aivir.2019.08.002.
125. Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, Decroly E. 2020. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res 176:104742. https://doi.org/10.1016/j.antiviral.2020.104742.
126. Benton DJ, Wrobel AG, Xu P, Roustan C, Martin SR, Rosenthal PB, Skehel JJ, Gamblin SJ. 2020. Receptor binding and priming of the spike protein of SARS-CoV-2 for membrane fusion. Nature 588:327–330. https://doi.org/10.1038/s41586-020-2772-0.
127. Cheng Y-W, Chao T-L, Li C-L, Chiu M-F, Kao H-C, Wang S-H, Pang Y-H, Lin C-H, Tsai Y-M, Lee W-H, Tao M-H, Ho T-C, Wu P-Y, Jang L-T, Chen P-J, Chang S-Y, Yeh S-H. 2020. Furin inhibitors block SARS-CoV-2 spike protein cleavage to suppress virus production and cytopathic effects. Cell Rep 33:108254. https://doi.org/10.1016/j.celrep.2020.108254.
128. Johnson BA, Xie X, Bailey AL, Kalveram B, Lokugamage KG, Muruato A, Zou J, Zhang X, Juelich T, Smith JK, Zhang L, Bopp N, Schindewolf C, Vu M, Vanderheiden A, Winkler ES, Swetnam D, Plante JA, Aguilar P, Plante KS, Popov V, Lee B, Weaver SC, Suthar MS, Routh AL, Ren P, Ku Z, An Z, Debbink K, Diamond MS, Shi PY, Freiberg AN, Menachery VD. 2021. Loss of furin cleavage site attenuates SARS-CoV-2 pathogenesis. Nature 591:293–299. https://doi.org/10.1038/s41586-021-03237-4.
129. Hoffmann M, Kleine-Weber H, Pöhlmann S. 2020. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of

human lung cells. Mol Cell 78:779–784. https://doi.org/10.1016/j.molcel.2020.04.022.
130. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu N-H, Nitsche A, Müller MA, Drosten C, Pöhlmann S. 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181:271–280. https://doi.org/10.1016/j.cell.2020.02.052.
131. Bestle D, Heindl MR, Limburg H, Van TVL, Pilgram O, Moulton H, Stein DA, Hardes K, Eickmann M, Dolnik O, Rohde C, Klenk H-D, Garten W, Steinmetzer T, Böttcher-Friebertshäuser E. 2020. TMPRSS2 and furin are both essential for proteolytic activation of SARS-CoV-2 in human airway cells. Life Sci Alliance 3:e202000786. https://doi.org/10.26508/lsa.202000786.
132. Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, Guo L, Guo R, Chen T, Hu J, Xiang Z, Mu Z, Chen X, Chen J, Hu K, Jin Q, Wang J, Qian Z. 2020. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun 11:1620. https://doi.org/10.1038/s41467-020-15562-9.
133. Shirato K, Kawase M, Matsuyama S. 2018. Wild-type human coronaviruses prefer cell-surface TMPRSS2 to endosomal cathepsins for cell entry. Virology 517:9–15. https://doi.org/10.1016/j.virol.2017.11.012.
134. Simmons G, Gosalia DN, Rennekamp AJ, Reeves JD, Diamond SL, Bates P. 2005. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. Proc Natl Acad Sci U S A 102:11876–11881. https://doi.org/10.1073/pnas.0505577102.
135. Tang T, Bidon M, Jaimes JA, Whittaker GR, Daniel S. 2020. Coronavirus membrane fusion mechanism offers a potential target for antiviral development. Antiviral Res 178:104792. https://doi.org/10.1016/j.antiviral.2020.104792.
136. Wang X, Xia S, Zhu Y, Lu L, Jiang S. 2021. Pan-coronavirus fusion inhibitors as the hope for today and tomorrow. Protein Cell 12:84–88. https://doi.org/10.1007/s13238-020-00806-7.
137. Battles MB, McLellan JS. 2019. Respiratory syncytial virus entry and how to block it. 4. Nat Rev Microbiol 17:233–245. https://doi.org/10.1038/s41579-019-0149-x.
138. Luna MS, Manzoni P, Paes B, Baraldi E, Cossey V, Kugelman A, Chawla R, Dotta A, Rodríguez Fernández R, Resch B, Carbonell-Estrany X. 2020. Expert consensus on palivizumab use for respiratory syncytial virus in developed countries. Paediatr Respir Rev 33:35–44. https://doi.org/10.1016/j.prrv.2018.12.001.
139. Sedeyn K, Saelens X. 2019. New antibody-based prevention and treatment options for influenza. Antiviral Res 170:104562. https://doi.org/10.1016/j.antiviral.2019.104562.
140. Mulangu S, Dodd LE, Davey RT, Tshiani Mbaya O, Proschan M, Mukadi D, Lusakibanza Manzo M, Nzolo D, Tshomba Oloma A, Ibanda A, Ali R, Coulibaly S, Levine AC, Grais R, Diaz J, Lane HC, Muyembe-Tamfum J-J, Sivahera B, Camara M, Kojan R, Walker R, Dighero-Kemp B, Cao H, Mukumbayi P, Mbala-Kingebeni P, Ahuka S, Albert S, Bonnett T, Crozier I, Duvenhage M, Proffitt C, Teitelbaum M, Moench T, Aboulhab J, Barrett K, Cahill K, Cone K, Eckes R, Hensley L, Herpin B, Higgs E, Ledgerwood J, Pierson J, Smolskis M, Sow Y, Tierney J, Sivapalasingam S, Holman W, Gettinger N, Vallée D, PALM Consortium Study Team/PALM Writing Group, et al. 2019. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med 381:2293–2303. https://doi.org/10.1056/NEJMoa1910993.
141. Sivapalasingam S, Saviolakis GA, Kulcsar K, Nakamura A, Conrad T, Hassanein M, Sumner G, Elango C, Kamal MA, Eng S, Kyratsous CA, Musser BJ, Frieman M, Kantrowitz J, Weinreich DM, Yancopoulos G, Stahl N, Lipsich L. 2021. Human monoclonal antibody cocktail for the treatment or prophylaxis of Middle East respiratory syndrome coronavirus. J Infect Dis https://doi.org/10.1093/infdis/jiab036.
142. Chandrashekar A, Liu J, Martinot AJ, McMahan K, Mercado NB, Peter L, Tostanoski LH, Yu J, Maliga Z, Nekorchuk M, Busman-Sahay K, Terry M, Wrijil LM, Ducat S, Martinez DR, Atyeo C, Fischinger S, Burke JS, Slein MD, Pessaint L, Van Ry A, Greenhouse J, Taylor T, Blade K, Cook A, Finneyfrock B, Brown R, Teow E, Velasco J, Zahn R, Wegmann F, Abbink P, Bondzie EA, Dagotto G, Gebre MS, He X, Jacob-Dolan C, Kordana N, Li Z, Lifton MA, Mahrokhian SH, Maxfield LF, Nityanandam R, Nkolola JP, Schmidt AG, Miller AD, Baric RS, Alter G, Sorger PK, Estes JD, Andersen H, Lewis MG, Barouch DH. 2020. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. Science 369:812–817. https://doi.org/10.1126/science.abc4776.
143. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J, Khetan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T, COVE Study Group. 2021. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 384:403–416. https://doi.org/10.1056/NEJMoa2035389.
144. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC, C4591001 Clinical Trial Group. 2020. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 383:2603–2615. https://doi.org/10.1056/NEJMoa2034577.
145. Walsh EE, Frenck RW, Falsey AR, Kitchin N, Absalon J, Gurtman A, Lockhart S, Neuzil K, Mulligan MJ, Bailey R, Swanson KA, Li P, Koury K, Kalina W, Cooper D, Fontes-Garfias C, Shi P-Y, Türeci Ö, Tompkins KR, Lyke KE, Raabe V, Dormitzer PR, Jansen KU, Şahin U, Gruber WC. 2020. Safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. N Engl J Med 383:2439–2450. https://doi.org/10.1056/NEJMoa2027906.
146. Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, Baum A, Pascal K, Quandt J, Maurus D, Brachtendorf S, Lörks V, Sikorski J, Hilker R, Becker D, Eller A-K, Grützner J, Boesler C, Rosenbaum C, Kühnle M-C, Luxemburger U, Kemmer-Brück A, Langer D, Bexon M, Bolte S, Karikó K, Palanche T, Fischer B, Schultz A, Shi P-Y, Fontes-Garfias C, Perez JL, Swanson KA, Loschko J, Scully IL, Cutler M, Kalina W, Kyratsous CA, Cooper D, Dormitzer PR, Jansen KU, Türeci Ö. 2020. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature 586:594–599. https://doi.org/10.1038/s41586-020-2814-7.
147. Atyeo C, Fischinger S, Zohar T, Slein MD, Burke J, Loos C, McCulloch DJ, Newman KL, Wolf C, Yu J, Shuey K, Feldman J, Hauser BM, Caradonna T, Schmidt AG, Suscovich TJ, Linde C, Cai Y, Barouch D, Ryan ET, Charles RC, Lauffenburger D, Chu H, Alter G. 2020. Distinct early serological signatures track with SARS-CoV-2 survival. Immunity 53:524–532. https://doi.org/10.1016/j.immuni.2020.07.020.
148. Garcia-Beltran WF, Lam EC, Astudillo MG, Yang D, Miller TE, Feldman J, Hauser BM, Caradonna TM, Clayton KL, Nitido AD, Murali MR, Alter G, Charles RC, Dighe A, Branda JA, Lennerz JK, Lingwood D, Schmidt AG, Iafrate AJ, Balazs AB. 2021. COVID-19-neutralizing antibodies predict disease severity and survival. Cell 184:476–488. https://doi.org/10.1016/j.cell.2020.12.015.
149. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, Musser BJ, Soo Y, Rofail D, Im J, Perry C, Pan C, Hosain R, Mahmood A, Davis JD, Turner KC, Hooper AT, Hamilton JD, Baum A, Kyratsous CA, Kim Y, Cook A, Kampman W, Kohli A, Sachdeva Y, Graber X, Kowal B, DiCioccio T, Stahl N, Lipsich L, Braunstein N, Herman G, Yancopoulos GD, Trial Investigators. 2021. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med 384:238–251. https://doi.org/10.1056/NEJMoa2035002.
150. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, Subbarao K, Kent SJ, Triccas JA, Davenport MP. 2021. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med https://doi.org/10.1038/s41591-021-01377-8.
151. Long Q-X, Liu B-Z, Deng H-J, Wu G-C, Deng K, Chen Y-K, Liao P, Qiu J-F, Lin Y, Cai X-F, Wang D-Q, Hu Y, Ren J-H, Tang N, Xu Y-Y, Yu L-H, Mo Z, Gong F, Zhang X-L, Tian W-G, Hu L, Zhang X-X, Xiang J-L, Du H-X, Liu H-W, Lang C-H, Luo X-H, Wu S-B, Cui X-P, Zhou Z, Zhu M-M, Wang J, Xue C-J, Li X-F, Wang L, Li Z-J, Wang K, Niu C-C, Yang Q-J, Tang X-J, Zhang Y, Liu X-M, Li J-J, Zhang D-C, Zhang F, Liu P, Yuan J, Li Q, Hu J-L, Chen J, et al. 2020. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med 26:845–848. https://doi.org/10.1038/s41591-020-0897-1.
152. Robbiani DF, Gaebler C, Muecksch F, Lorenzi JCC, Wang Z, Cho A, Agudelo M, Barnes CO, Gazumyan A, Finkin S, Hägglöf T, Oliveira TY, Viant C, Hurley A, Hoffmann H-H, Millard KG, Kost RG, Cipolla M, Gordon K, Bianchini F, Chen ST, Ramos V, Patel R, Dizon J, Shimeliovich I, Mendoza P, Hartweger H, Nogueira L, Pack M, Horowitz J, Schmidt F, Weisblum Y, Michailidis E, Ashbrook AW, Waltari E, Pak JE, Huey-Tubman KE, Koranda N, Hoffman PR, West AP, Rice CM, Hatziioannou T, Bjorkman PJ, Bieniasz PD, Caskey M, Nussenzweig MC. 2020. Convergent antibody responses to SARS-CoV-2 in convalescent individuals. Nature 584:437–442. https://doi.org/10.1038/s41586-020-2456-9.
153. Chirathaworn C, Sripramote M, Chalongviriyalert P, Jirajariyavej S, Kiatpanabhikul P, Saiyarin J, Soudon C, Thienfaidee O, Palakawong Na Ayuthaya T, Brukesawan C, Chaiwanichsiri D, Intharasongkroh D, Wanlapakorn N, Chansaenroj J, Puenpa J, Yorsaeng R, Thitithanyanont

A, Kitphati R, Mungaomklang A, Nagavajara P, Poovorawan Y. 2020. SARS-CoV-2 RNA shedding in recovered COVID-19 cases and the presence of antibodies against SARS-CoV-2 in recovered COVID-19 cases and close contacts, Thailand, April-June 2020. PLoS One 15:e0236905. https://doi.org/10.1371/journal.pone.0236905.
154. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, Wang X, Yuan J, Li T, Li J, Qian S, Hong C, Wang F, Liu Y, Wang Z, He Q, Li Z, He B, Zhang T, Fu Y, Ge S, Liu L, Zhang J, Xia N, Zhang Z. 2020. Antibody responses to SARS-CoV-2 in patients with novel coronavirus disease 2019. Clin Infect Dis off Publ Infect Dis Soc Am 71:2027–2034. https://doi.org/10.1093/cid/ciaa344.
155. Zohar T, Alter G. 2020. Dissecting antibody-mediated protection against SARS-CoV-2. 7. Nat Rev Immunol 20:392–394. https://doi.org/10.1038/s41577-020-0359-5.
156. Secchi M, Bazzigaluppi E, Brigatti C, Marzinotto I, Tresoldi C, Rovere-Querini P, Poli A, Castagna A, Scarlatti G, Zangrillo A, Ciceri F, Piemonti L, Lampasona V. 2020. COVID-19 survival associates with the immunoglobulin response to the SARS-CoV-2 spike receptor binding domain. J Clin Invest 130:6366–6378. https://doi.org/10.1172/JCI142804.
157. Lucas C, Klein J, Sundaram ME, Liu F, Wong P, Silva J, Mao T, Oh JE, Mohanty S, Huang J, Tokuyama M, Lu P, Venkataraman A, Park A, Israelow B, Vogels CBF, Muenker MC, Chang C-H, Casanovas-Massana A, Moore AJ, Zell J, Fournier JB, Wyllie AL, Campbell M, Lee A, Chun HJ, Grubaugh ND, Schulz WL, Farhadian S, Cruz CD, Ring AM, Shaw AC, Wisnewski AV, Yildirim I, Ko AI, Omer S, Iwasaki A. 2021. Delayed production of neutralizing antibodies correlates with fatal COVID-19. Nat Med https://doi.org/10.1038/s41591-021-01355-0.
158. Premkumar L, Segovia-Chumbez B, Jadi R, Martinez DR, Raut R, Markmann A, Cornaby C, Bartelt L, Weiss S, Park Y, Edwards CE, Weimer E, Scherer EM, Rouphael N, Edupuganti S, Weiskopf D, Tse LV, Hou YJ, Margolis D, Sette A, Collins MH, Schmitz J, Baric RS, de Silva AM. 2020. The receptor binding domain of the viral spike protein is an immunodominant and highly specific target of antibodies in SARS-CoV-2 patients. Sci Immunol 5:eabc8413. https://doi.org/10.1126/sciimmunol.abc8413.
159. Piccoli L, Park Y-J, Tortorici MA, Czudnochowski N, Walls AC, Beltramello M, Silacci-Fregni C, Pinto D, Rosen LE, Bowen JE, Acton OJ, Jaconi S, Guarino B, Minola A, Zatta F, Sprugasci N, Bassi J, Peter A, De Marco A, Nix JC, Mele F, Jovic S, Rodriguez BF, Gupta SV, Jin F, Piumatti G, Lo Presti G, Pellanda AF, Biggiogero M, Tarkowski M, Pizzuto MS, Cameroni E, Havenar-Daughton C, Smithey M, Hong D, Lepori V, Albanese E, Ceschi A, Bernasconi E, Elzi L, Ferrari P, Garzoni C, Riva A, Snell G, Sallusto F, Fink K, Virgin HW, Lanzavecchia A, Corti D, Veesler D. 2020. Mapping neutralizing and immunodominant sites on the SARS-CoV-2 spike receptor-binding domain by structure-guided high-resolution serology. Cell 183:1024–1042.e21. https://doi.org/10.1016/j.cell.2020.09.037.
160. Greaney AJ, Loes AN, Crawford KHD, Starr TN, Malone KD, Chu HY, Bloom JD. 2021. Comprehensive mapping of mutations in the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human plasma antibodies. Cell Host Microbe 29:463–476.e6. https://doi.org/10.1016/j.chom.2021.02.003.
161. Harvey WT, Carabelli AM, Jackson B, Gupta RK, Thomson EC, Harrison EM, Ludden C, Reeve R, Rambaut A, Peacock SJ, Robertson DL, COVID-19 Genomics UK (COG-UK) Consortium. 2021. SARS-CoV-2 variants, spike mutations, and immune escape. Nat Rev Microbiol 19:409–424. https://doi.org/10.1038/s41579-021-00573-0.
162. Raybould MIJ, Kovaltsuk A, Marks C, Deane CM. 2021. CoV-AbDab: the coronavirus antibody database. Bioinformatics 37:734–735. https://doi.org/10.1093/bioinformatics/btaa739.
163. Taylor PC, Adams AC, Hufford MM, de la Torre I, Winthrop K, Gottlieb RL. 2021. Neutralizing monoclonal antibodies for treatment of COVID-19. Nat Rev Immunol 21:382–393. https://doi.org/10.1038/s41577-021-00542-x.
164. Yuan M, Liu H, Wu NC, Wilson IA. 2021. Recognition of the SARS-CoV-2 receptor binding domain by neutralizing antibodies. Biochem Biophys Res Commun 538:192–203. https://doi.org/10.1016/j.bbrc.2020.10.012.
165. Barnes CO, Jette CA, Abernathy ME, Dam K-MA, Esswein SR, Gristick HB, Malyutin AG, Sharaf NG, Huey-Tubman KE, Lee YE, Robbiani DF, Nussenzweig MC, West AP, Bjorkman PJ. 2020. SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies. Nature 588:682–687. https://doi.org/10.1038/s41586-020-2852-1.
166. Finkelstein MT, Mermelstein AG, Parker Miller E, Seth PC, Stancofski E-SD, Fera D. 2021. Structural analysis of neutralizing epitopes of the SARS-CoV-2 spike to guide therapy and vaccine design strategies. Viruses 13:134. https://doi.org/10.3390/v13010134.
167. Wang C, Li W, Drabek D, Okba NMA, van Haperen R, Osterhaus ADME, van Kuppeveld FJM, Haagmans BL, Grosveld F, Bosch B-J. 2020. A human monoclonal antibody blocking SARS-CoV-2 infection. Nat Commun 11:2251. https://doi.org/10.1038/s41467-020-16256-y.
168. Yuan M, Wu NC, Zhu X, Lee C-CD, So RTY, Lv H, Mok CKP, Wilson IA. 2020. A highly conserved cryptic epitope in the receptor-binding domains of SARS-CoV-2 and SARS-CoV. Science 368:630–633. https://doi.org/10.1126/science.abb7269.
169. Zhou D, Duyvesteyn HME, Chen C-P, Huang C-G, Chen T-H, Shih S-R, Lin Y-C, Cheng C-Y, Cheng S-H, Huang Y-C, Lin T-Y, Ma C, Huo J, Carrique L, Malinauskas T, Ruza RR, Shah PNM, Tan TK, Rijal P, Donat RF, Godwin K, Buttigieg KR, Tree JA, Radecke J, Paterson NG, Supasa P, Mongkolsapaya J, Screaton GR, Carroll MW, Gilbert-Jaramillo J, Knight ML, James W, Owens RJ, Naismith JH, Townsend AR, Fry EE, Zhao Y, Ren J, Stuart DI, Huang K-YA. 2020. Structural basis for the neutralization of SARS-CoV-2 by an antibody from a convalescent patient. Nat Struct Mol Biol 27:950–958. https://doi.org/10.1038/s41594-020-0480-y.
170. Wec AZ, Wrapp D, Herbert AS, Maurer DP, Haslwanter D, Sakharkar M, Jangra RK, Dieterle ME, Lilov A, Huang D, Tse LV, Johnson NV, Hsieh C-L, Wang N, Nett JH, Champney E, Burnina I, Brown M, Lin S, Sinclair M, Johnson C, Pudi S, Bortz R, Wirchnianski AS, Laudermilch E, Florez C, Fels JM, O'Brien CM, Graham BS, Nemazee D, Burton DR, Baric RS, Voss JE, Chandran K, Dye JM, McLellan JS, Walker LM. 2020. Broad neutralization of SARS-related viruses by human monoclonal antibodies. Science 369:731–736. https://doi.org/10.1126/science.abc7424.
171. Pinto D, Park Y-J, Beltramello M, Walls AC, Tortorici MA, Bianchi S, Jaconi S, Culap K, Zatta F, De Marco A, Peter A, Guarino B, Spreafico R, Cameroni E, Case JB, Chen RE, Havenar-Daughton C, Snell G, Telenti A, Virgin HW, Lanzavecchia A, Diamond MS, Fink K, Veesler D, Corti D. 2020. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. Nature 583:290–295. https://doi.org/10.1038/s41586-020-2349-y.
172. Chi X, Yan R, Zhang J, Zhang G, Zhang Y, Hao M, Zhang Z, Fan P, Dong Y, Yang Y, Chen Z, Guo Y, Zhang J, Li Y, Song X, Chen Y, Xia L, Fu L, Hou L, Xu J, Yu C, Li J, Zhou Q, Chen W. 2020. A neutralizing human antibody binds to the N-terminal domain of the Spike protein of SARS-CoV-2. Science 369:650–655. https://doi.org/10.1126/science.abc6952.
173. Liu L, Wang P, Nair MS, Yu J, Rapp M, Wang Q, Luo Y, Chan JF-W, Sahi V, Figueroa A, Guo XV, Cerutti G, Bimela J, Gorman J, Zhou T, Chen Z, Yuen K-Y, Kwong PD, Sodroski JG, Yin MT, Sheng Z, Huang Y, Shapiro L, Ho DD. 2020. Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike. Nature 584:450–456. https://doi.org/10.1038/s41586-020-2571-7.
174. Hansen J, Baum A, Pascal KE, Russo V, Giordano S, Wloga E, Fulton BO, Yan Y, Koon K, Patel K, Chung KM, Hermann A, Ullman E, Cruz J, Rafique A, Huang T, Fairhurst J, Libertiny C, Malbec M, Lee W, Welsh R, Farr G, Pennington S, Deshpande D, Cheng J, Watty A, Bouffard P, Babb R, Levenkova N, Chen C, Zhang B, Hernandez AR, Saotome K, Zhou Y, Franklin M, Sivapalasingam S, Lye DC, Weston S, Logue J, Haupt R, Frieman M, Chen G, Olson W, Murphy AJ, Stahl N, Yancopoulos GD, Kyratsous CA. 2020. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. Science 369:1010–1014. https://doi.org/10.1126/science.abd0827.
175. Baum A, Ajithdoss D, Copin R, Zhou A, Lanza K, Negron N, Ni M, Wei Y, Mohammadi K, Musser B, Atwal GS, Oyejide A, Goez-Gazi Y, Dutton J, Clemmons E, Staples HM, Bartley C, Klaffke B, Alfson K, Gazi M, Gonzalez O, Dick E, Carrion R, Pessaint L, Porto M, Cook A, Brown R, Ali V, Greenhouse J, Taylor T, Andersen H, Lewis MG, Stahl N, Murphy AJ, Yancopoulos GD, Kyratsous CA. 2020. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. Science 370:1110–1115. https://doi.org/10.1126/science.abe2402.
176. Baum A, Fulton BO, Wloga E, Copin R, Pascal KE, Russo V, Giordano S, Lanza K, Negron N, Ni M, Wei Y, Atwal GS, Murphy AJ, Stahl N, Yancopoulos GD, Kyratsous CA. 2020. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science 369:1014–1018. https://doi.org/10.1126/science.abd0831.
177. Jones BE, Brown-Augsburger PL, Corbett KS, Westendorf K, Davies J, Cujec TP, Wiethoff CM, Blackbourne JL, Heinz BA, Foster D, Higgs RE, Balasubramaniam D, Wang L, Zhang Y, Yang ES, Bidshahri R, Kraft L, Hwang Y, Žentelis S, Jepson KR, Goya R, Smith MA, Collins DW, Hinshaw SJ, Tycho SA, Pellacani D, Xiang P, Muthuraman K, Sobhanifar S, Piper MH, Triana FJ, Hendle J, Pustilnik A, Adams AC, Berens SJ, Baric RS, Martinez DR, Cross RW,

Geisbert TW, Borisevich V, Abiona O, Belli HM, de Vries M, Mohamed A, Dittmann M, Samanovic MI, Mulligan MJ, Goldsmith JA, Hsieh C-L, Johnson NV, et al. 2021. The neutralizing antibody, LY-CoV555, protects against SARS-CoV-2 infection in non-human primates. Sci Transl Med 13:eabf1906. https://doi.org/10.1126/scitranslmed.abf1906.

178. Shi R, Shan C, Duan X, Chen Z, Liu P, Song J, Song T, Bi X, Han C, Wu L, Gao G, Hu X, Zhang Y, Tong Z, Huang W, Liu WJ, Wu G, Zhang B, Wang L, Qi J, Feng H, Wang F-S, Wang Q, Gao GF, Yuan Z, Yan J. 2020. A human neutralizing antibody targets the receptor binding site of SARS-CoV-2. Nature 584:120–124. https://doi.org/10.1038/s41586-020-2381-y.
179. Zost SJ, Gilchuk P, Case JB, Binshtein E, Chen RE, Nkolola JP, Schäfer A, Reidy JX, Trivette A, Nargi RS, Sutton RE, Suryadevara N, Martinez DR, Williamson LE, Chen EC, Jones T, Day S, Myers L, Hassan AO, Kafai NM, Winkler ES, Fox JM, Shrihari S, Mueller BK, Meiler J, Chandrashekar A, Mercado NB, Steinhardt JJ, Ren K, Loo Y-M, Kallewaard NL, McCune BT, Keeler SP, Holtzman MJ, Barouch DH, Gralinski LE, Baric RS, Thackray LB, Diamond MS, Carnahan RH, Crowe JE. 2020. Potently neutralizing and protective human antibodies against SARS-CoV-2. Nature 584:443–449. https://doi.org/10.1038/s41586-020-2548-6.
180. Kim C, Ryu D-K, Lee J, Kim Y-I, Seo J-M, Kim Y-G, Jeong J-H, Kim M, Kim J-I, Kim P, Bae JS, Shim EY, Lee MS, Kim MS, Noh H, Park G-S, Park JS, Son D, An Y, Lee JN, Kwon K-S, Lee J-Y, Lee H, Yang J-S, Kim K-C, Kim SS, Woo H-M, Kim J-W, Park M-S, Yu K-M, Kim S-M, Kim E-H, Park S-J, Jeong ST, Yu CH, Song Y, Gu SH, Oh H, Koo B-S, Hong JJ, Ryu C-M, Park WB, Oh M, Choi YK, Lee S-Y. 2021. A therapeutic neutralizing antibody targeting receptor binding domain of SARS-CoV-2 spike protein. Nat Commun 12:288. https://doi.org/10.1038/s41467-020-20602-5.
181. Yang L, Liu W, Yu X, Wu M, Reichert JM, Ho M. 2020. COVID-19 antibody therapeutics tracker: a global online database of antibody therapeutics for the prevention and treatment of COVID-19. Antib Ther 3:205–212. https://doi.org/10.1093/abt/tbaa020.
182. Tuccori M, Ferraro S, Convertino I, Cappello E, Valdiserra G, Blandizzi C, Maggi F, Focosi D. 2020. Anti-SARS-CoV-2 neutralizing monoclonal antibodies: clinical pipeline. mAbs 12:1854149. https://doi.org/10.1080/19420862.2020.1854149.
183. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, Huhn G, Cardona J, Mocherla B, Stosor V, Shawa I, Adams AC, Van Naarden J, Custer KL, Shen L, Durante M, Oakley G, Schade AE, Sabo J, Patel DR, Klekotka P, Skovronsky DM, BLAZE-1 Investigators. 2021. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. N Engl J Med 384:229–237. https://doi.org/10.1056/NEJMoa2029849.
184. Lundgren JD, Grund B, Barkauskas CE, Holland TL, Gottlieb RL, Sandkovsky U, Brown SM, Knowlton KU, Self WH, Files DC, Jain MK, Benfield T, Bowdish ME, Leshnower BG, Baker JV, Jensen J-U, Gardner EM, Ginde AA, Harris ES, Johansen IS, Markowitz N, Matthay MA, Østergaard L, Chang CC, Davey VJ, Goodman A, Higgs ES, Murray DD, Murray TA, Paredes R, Parmar MKB, Phillips AN, Reilly C, Sharma S, Dewar RL, Teitelbaum M, Wentworth D, Cao H, Klekotka P, Babiker AG, Gelijns AC, Kan VL, Polizzotto MN, Thompson BT, Lane HC, Neaton JD, ACTIV-3/TICO LY-CoV555 Study Group. 2021. A neutralizing monoclonal antibody for hospitalized patients with Covid-19. N Engl J Med 384:905–914. https://doi.org/10.1056/NEJMoa2033130.
185. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, Huhn G, Cardona J, Mocherla B, Stosor V, Shawa I, Kumar P, Adams AC, Van Naarden J, Custer KL, Durante M, Oakley G, Schade AE, Holzer TR, Ebert PJ, Higgs RE, Kallewaard NL, Sabo J, Patel DR, Klekotka P, Shen L, Skovronsky DM. 2021. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA 325:632–644. https://doi.org/10.1001/jama.2021.0202.
186. Dougan M, Nirula A, Gottlieb R, Azizad M, Mocherla B, Chen P, Huhn G, Adams A, Schade A, Sabo J, Patel D, Klekotka P, Shen L, Skovronsky D, BLAZE-1 Investigators. 2021. Bamlanivimab+Etesevimab for the treatment of COVID-19 in high-risk ambulatory patients, abstr 122. 28th Conference on Retroviruses and Opportunistic Infections, 6 to 10 March 2021. https://www.croiconference.org/abstract/bamlanivimabetesevimab-for-treatment-of-covid-19-in-high-risk-ambulatory-patients/.
187. Cohen MS, Nirula A, Mulligan MJ, Novak RM, Marovich M, Yen C, Stemer A, Mayer SM, Wohl D, Brengle B, Montague BT, Frank I, McCulloh RJ, Fichtenbaum CJ, Lipson B, Gabra N, Ramirez JA, Thai C, Chege W, Gomez Lorenzo MM, Sista N, Farrior J, Clement ME, Brown ER, Custer KL, Van Naarden J, Adams AC, Schade AE, Dabora MC, Knorr J, Price KL, Sabo J, Tuttle JL, Klekotka P, Shen L, Skovronsky DM, for the BLAZE-2 Investigators. 2021. Effect of bamlanivimab vs placebo on incidence of COVID-19 among residents and staff of skilled nursing and assisted living facilities: a randomized clinical trial. JAMA. 326:46–55. https://doi.org/10.1001/jama.2021.8828.
188. O'Brien MP, Forleo-Neto E, Musser BJ, Isa F, Chan K-C, Sarkar N, Bar KJ, Barnabas RV, Barouch DH, Cohen MS, Hurt CB, Burwen DR, Marovich MA, Hou P, Heirman I, Davis JD, Turner KC, Ramesh D, Mahmood A, Hooper AT, Hamilton JD, Kim Y, Purcell LA, Baum A, Kyratsous CA, Krainson J, Perez-Perez R, Mohseni R, Kowal B, DiCioccio AT, Stahl N, Lipsich L, Braunstein N, Herman G, Yancopoulos GD, Weinreich DM, for the Covid-19 Phase 3 Prevention Trial Team 2021. Subcutaneous REGEN-COV antibody combination for Covid-19 prevention. medRxiv. https://doi.org/10.1101/2021.06.14.21258567
189. Weinreich D, Sivapalasingam S, Norton TD, Ali S, Gao H, Bhore R, Xiao J, Hooper AT, Hamilton JD, Musser BJ, Rofail D, Hussein M, Im J, Atmodjo DY, Perry C, Pan C, Mahmood A, Hosain R, Davis JD, Turner KC, Baum A, Kyratsous CA, Kim Y, Cook A, Kampman W, Roque-Guerrero L, Acloque G, Aazami H, Cannon K, Simon-Campos JA, Bocchini JA, Kowal B, DiCioccio T, Soo Y, Stahl N, Lipsich L, Braunstein N, Herman G, Yancopoulos GD, Investigators T. 2021. REGEN-COV antibody cocktail clinical outcomes study in COVID-19 outpatients. medRxiv https://www.medrxiv.org/content/10.1101/2021.05.19.21257469v2.
190. Gupta A, Gonzalez-Rojas Y, Juarez E, Casal MC, Moya J, Falci DR, Sarkis E, Solis J, Zheng H, Scott N, Cathcart AL, Hebner CM, Sager J, Mogalian E, Tipple C, Peppercorn A, Alexander E, Pang PS, Free A, Brinson C, Aldinger M, Shapiro AE. 2021. Early Covid-19 treatment with SARS-CoV-2 neutralizing antibody sotrovimab. medRxiv https://www.medrxiv.org/content/10.1101/2021.05.27.21257096v1.
191. Dejnirattisai W, Zhou D, Supasa P, Liu C, Mentzer AJ, Ginn H, Zhao Y, Duyvesteyn HME, Tuekprakhon A, Nutalai R, Wang B, Paesen GC, Lopez-Camacho C, Slon-Campos J, Walter T, Skelly D, Clemens SAC, Naveca FG, Nascimento V, Nascimento F, da Costa CF, Dold C, Levin R, Dong T, Pollard AJ, Knight JC, Crook D, Lambe T, Clutterbuck E, Bibi S, Flaxman A, Bittaye M, Belij-Rammerstorfer S, Gilbert S, Carroll MW, Klenerman P, Barnes E, Dunachie SJ, Paterson NG, Williams MA, Hall DR, Hulswit R, Bowden TA, Fry EE, Mongkolsapaya J, Ren J, Stuart DI, Screaton GR. 2021. Antibody evasion by the Brazilian P.1 strain of SARS-CoV-2. bioRxiv https://www.biorxiv.org/content/10.1101/2021.03.12.435194v2.
192. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, Wang M, Yu J, Zhang B, Kwong PD, Graham BS, Mascola JR, Chang JY, Yin MT, Sobieszczyk M, Kyratsous CA, Shapiro L, Sheng Z, Huang Y, Ho DD. 2021. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. Nature 593:130–135. https://doi.org/10.1038/s41586-021-03398-2.
193. Hoffmann M, Hofmann-Winkler H, Krueger N, Kempf A, Nehlmeier I, Graichen L, Sidarovich A, Moldenhauer A-S, Winkler MS, Schulz S, Jaeck H-M, Stankov MV, Behrens GMN, Poehlmann S. 2021. SARS-CoV-2 variant B.1.617 is resistant to bamlanivimab and evades antibodies induced by infection and vaccination. bioRxiv https://www.biorxiv.org/content/10.1101/2021.05.04.442663v1.
194. Copin R, Baum A, Wloga E, Pascal KE, Giordano S, Fulton BO, Zhou A, Negron N, Lanza K, Chan N, Coppola A, Chiu J, Ni M, Atwal GS, Hernandez AR, Saotome K, Zhou Y, Franklin MC, Hooper AT, McCarthy S, Hamon S, Hamilton JD, Staples HM, Alfson K, Carrion R, Ali S, Norton T, Somersan-Karakaya S, Sivapalasingam S, Herman GA, Weinreich DM, Lipsich L, Stahl N, Murphy AJ, Yancopoulos GD, Kyratsous CA. 2021. REGEN-COV protects against viral escape in preclinical and human studies. bioRxiv https://www.biorxiv.org/content/10.1101/2021.03.10.434834v4.
195. Cathcart AL, Havenar-Daughton C, Lempp FA, Ma D, Schmid M, Agostini ML, Guarino B, Iulio JD, Rosen L, Tucker H, Dillen J, Subramanian S, Sloan B, Bianchi S, Wojcechowskyj J, Zhou J, Kaiser H, Chase A, Montiel-Ruiz M, Czudnochowski N, Cameroni E, Ledoux S, Colas C, Soriaga L, Telenti A, Hwang S, Snell G, Virgin HW, Corti D, Hebner CM. 2021. The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent *in vitro* and *in vivo* activity against SARS-CoV-2. bioRxiv https://www.biorxiv.org/content/10.1101/2021.03.09.434607v4.
196. McCallum M, Bassi J, Marco AD, Chen A, Walls AC, Iulio JD, Tortorici MA, Navarro M-J, Silacci-Fregni C, Saliba C, Agostini M, Pinto D, Culap K, Bianchi S, Jaconi S, Cameroni E, Bowen JE, Tiles SW, Pizzuto MS, Guastalla SB, Bona G, Pellanda AF, Garzoni C, Voorhis WCV, Rosen LE, Snell GC, Telenti A, Virgin HW, Piccoli L, Corti D, Veesler D. 2021. SARS-CoV-2 immune evasion by variant B.1.427/B.1.429. bioRxiv https://www.biorxiv.org/content/10.1101/2021.03.31.437925v1.
197. Shen X, Tang H, McDanal C, Wagh K, Fischer W, Theiler J, Yoon H, Li D, Haynes BF, Sanders KO, Gnanakaran S, Hengartner N, Pajon R, Smith G, Glenn GM, Korber B, Montefiori DC. 2021. SARS-CoV-2 variant B.1.1.7 is

susceptible to neutralizing antibodies elicited by ancestral spike vaccines. Cell Host Microbe 29:529–539.e3. https://doi.org/10.1016/j.chom.2021.03.002.
198. Wu Y, Jiang S, Ying T. 2017. Single-domain antibodies as therapeutics against human viral diseases. Front Immunol 8:1802. https://doi.org/10.3389/fimmu.2017.01802.
199. Czajka TF, Vance DJ, Mantis NJ. 2021. Slaying SARS-CoV-2 one (single-domain) antibody at a time. Trends Microbiol 29:195–203. https://doi.org/10.1016/j.tim.2020.12.006.
200. Wrapp D, De Vlieger D, Corbett KS, Torres GM, Wang N, Van Breedam W, Roose K, van Schie L, Hoffmann M, Pöhlmann S, Graham BS, Callewaert N, Schepens B, Saelens X, McLellan JS, VIB-CMB COVID-19 Response Team. 2020. Structural basis for potent neutralization of betacoronaviruses by single-domain camelid antibodies. Cell 181:1004–1015. https://doi.org/10.1016/j.cell.2020.04.031.
201. Schoof M, Faust B, Saunders RA, Sangwan S, Rezelj V, Hoppe N, Boone M, Billesbølle CB, Puchades C, Azumaya CM, Kratochvil HT, Zimanyi M, Deshpande I, Liang J, Dickinson S, Nguyen HC, Chio CM, Merz GE, Thompson MC, Diwanji D, Schaefer K, Anand AA, Dobzinski N, Zha BS, Simoneau CR, Leon K, White KM, Chio US, Gupta M, Jin M, Li F, Liu Y, Zhang K, Bulkley D, Sun M, Smith AM, Rizo AN, Moss F, Brilot AF, Pourmal S, Trenker R, Pospiech T, Gupta S, Barsi-Rhyne B, Belyy V, Barile-Hill AW, Nock S, Liu Y, Krogan NJ, Ralston CY, Consortium4‡ QSB, et al. 2020. An ultrapotent synthetic nanobody neutralizes SARS-CoV-2 by stabilizing inactive Spike. Science 370:1473–1479. https://doi.org/10.1126/science.abe3255.
202. Custódio TF, Das H, Sheward DJ, Hanke L, Pazicky S, Pieprzyk J, Sorgenfrei M, Schroer MA, Gruzinov AY, Jeffries CM, Graewert MA, Svergun DI, Dobrev N, Remans K, Seeger MA, McInerney GM, Murrell B, Hällberg BM, Löw C. 2020. Selection, biophysical and structural analysis of synthetic nanobodies that effectively neutralize SARS-CoV-2. 1. Nat Commun 11:5588. https://doi.org/10.1038/s41467-020-19204-y.
203. Hanke L, Vidakovics Perez L, Sheward DJ, Das H, Schulte T, Moliner-Morro A, Corcoran M, Achour A, Karlsson Hedestam GB, Hällberg BM, Murrell B, McInerney GM. 2020. An alpaca nanobody neutralizes SARS-CoV-2 by blocking receptor interaction. Nat Commun 11:4420. https://doi.org/10.1038/s41467-020-18174-5.
204. Bracken CJ, Lim SA, Solomon P, Rettko NJ, Nguyen DP, Zha BS, Schaefer K, Byrnes JR, Zhou J, Lui I, Liu J, Pance K, Zhou XX, Leung KK, Wells JA, QCRG Structural Biology Consortium. 2021. Bi-paratopic and multivalent VH domains block ACE2 binding and neutralize SARS-CoV-2. Nat Chem Biol 17:113–121. https://doi.org/10.1038/s41589-020-00679-1.
205. Xiang Y, Nambulli S, Xiao Z, Liu H, Sang Z, Duprex WP, Schneidman-Duhovny D, Zhang C, Shi Y. 2020. Versatile and multivalent nanobodies efficiently neutralize SARS-CoV-2. Science 370:1479–1484. https://doi.org/10.1126/science.abe4747.
206. Huo J, Le Bas A, Ruza RR, Duyvesteyn HME, Mikolajek H, Malinauskas T, Tan TK, Rijal P, Dumoux M, Ward PN, Ren J, Zhou D, Harrison PJ, Weckener M, Clare DK, Vogirala VK, Radecke J, Moynié L, Zhao Y, Gilbert-Jaramillo J, Knight ML, Tree JA, Buttigieg KR, Coombes N, Elmore MJ, Carroll MW, Carrique L, Shah PNM, James W, Townsend AR, Stuart DI, Owens RJ, Naismith JH. 2020. Neutralizing nanobodies bind SARS-CoV-2 spike RBD and block interaction with ACE2. Nat Struct Mol Biol 27:846–854. https://doi.org/10.1038/s41594-020-0469-6.
207. Wu Y, Li C, Xia S, Tian X, Kong Y, Wang Z, Gu C, Zhang R, Tu C, Xie Y, Yang Z, Lu L, Jiang S, Ying T. 2020. Identification of human single-domain antibodies against SARS-CoV-2. Cell Host Microbe 27:891–898. https://doi.org/10.1016/j.chom.2020.04.023.
208. Li W, Chen C, Drelich A, Martinez DR, Gralinski LE, Sun Z, Schäfer A, Kulkarni SS, Liu X, Leist SR, Zhelev DV, Zhang L, Kim Y-J, Peterson EC, Conard A, Mellors JW, Tseng C-TK, Falzarano D, Baric RS, Dimitrov DS. 2020. Rapid identification of a human antibody with high prophylactic and therapeutic efficacy in three animal models of SARS-CoV-2 infection. Proc Natl Acad Sci U S A 117:29832–29838. https://doi.org/10.1073/pnas.2010197117.
209. Koenig P-A, Das H, Liu H, Kümmerer BM, Gohr FN, Jenster L-M, Schiffelers LDJ, Tesfamariam YM, Uchima M, Wuerth JD, Gatterdam K, Ruetalo N, Christensen MH, Fandrey CI, Normann S, Tödtmann JMP, Pritzl S, Hanke L, Boos J, Yuan M, Zhu X, Schmid-Burgk JL, Kato H, Schindler M, Wilson IA, Geyer M, Ludwig KU, Hällberg BM, Wu NC, Schmidt FI. 2021. Structure-guided multivalent nanobodies block SARS-CoV-2 infection and suppress mutational escape. Science 371:eabe6230. https://doi.org/10.1126/science.abe6230.
210. Li W, Schäfer A, Kulkarni SS, Liu X, Martinez DR, Chen C, Sun Z, Leist SR, Drelich A, Zhang L, Ura ML, Berezuk A, Chittori S, Leopold K, Mannar D, Srivastava SS, Zhu X, Peterson EC, Tseng C-T, Mellors JW, Falzarano D, Subramaniam S, Baric RS, Dimitrov DS. 2020. High potency of a bivalent human VH domain in SARS-CoV-2 animal models. Cell 183:429–441.e16. https://doi.org/10.1016/j.cell.2020.09.007.
211. Pymm P, Adair A, Chan L-J, Cooney JP, Mordant FL, Allison CC, Lopez E, Haycroft ER, O'Neill MT, Tan LL, Dietrich MH, Drew D, Doerflinger M, Dengler MA, Scott NE, Wheatley AK, Gherardin NA, Venugopal H, Cromer D, Davenport MP, Pickering R, Godfrey DI, Purcell DFJ, Kent SJ, Chung AW, Subbarao K, Pellegrini M, Glukhova A, Tham W-H. 2021. Nanobody cocktails potently neutralize SARS-CoV-2 D614G N501Y variant and protect mice. Proc Natl Acad Sci U S A 118:e2101918118. https://doi.org/10.1073/pnas.2101918118.
212. Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, Wiggins CC, Bruno KA, Klompas AM, Lesser ER, Kunze KL, Sexton MA, Diaz Soto JC, Baker SE, Shepherd JRA, van Helmond N, Verdun NC, Marks P, van Buskirk CM, Winters JL, Stubbs JR, Rea RF, Hodge DO, Herasevich V, Whelan ER, Clayburn AJ, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Paneth NS, Fairweather D, Wright RS, Casadevall A. 2021. Convalescent plasma antibody levels and the risk of death from COVID-19. N Engl J Med 384:1015–1027. https://doi.org/10.1056/NEJMoa2031893.
213. Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, Savoy N, Giunta DH, Pérez LG, Sánchez M del L, Gamarnik AV, Ojeda DS, Santoro DM, Camino PJ, Antelo S, Rainero K, Vidiella GP, Miyazaki EA, Cornistein W, Trabadelo OA, Ross FM, Spotti M, Funtowicz G, Scordo WE, Losso MH, Ferniot I, Pardo PE, Rodriguez E, Rucci P, Pasquali J, Fuentes NA, Esperatti M, Speroni GA, Nannini EC, Matteaccio A, Michelangelo HG, Follmann D, Lane HC, Belloso WH, PlasmAr Study Group. 2021. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. N Engl J Med 384:619–629. https://doi.org/10.1056/NEJMoa2031304.
214. Piechotta V, Chai KL, Valk SJ, Doree C, Monsef I, Wood EM, Lamikanra A, Kimber C, McQuilten Z, So-Osman C, Estcourt LJ, Skoetz N. 2020. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev 7:CD013600.
215. Libster R, Pérez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, Esteban I, Caballero MT, Wood C, Berrueta M, Rondan A, Lescano G, Cruz P, Ritou Y, Fernández Viña V, Álvarez Paggi D, Esperante S, Ferreti A, Ofman G, Ciganda Á, Rodriguez R, Lantos J, Valentini R, Itcovici N, Hintze A, Oyarvide ML, Etchegaray C, Neira A, Name I, Alfonso J, López Castelo R, Caruso G, Rapelius S, Alvez F, Etchenique F, Dimase F, Alvarez D, Aranda SS, Sánchez Yanotti C, De Luca J, Jares Baglivo S, Laudanno S, Nowogrodzki F, Larrea R, Silveyra M, Leberzstein G, Debonis A, Molinos J, González M, Perez E, Fundación INFANT–COVID-19 Group, et al. 2021. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. N Engl J Med 384:610–618. https://doi.org/10.1056/NEJMoa2033700.
216. Focosi D, Tuccori M, Franchini M. 2021. The road towards polyclonal anti-SARS-CoV-2 immunoglobulins (hyperimmune serum) for passive immunization in COVID-19. Life 11:144. https://doi.org/10.3390/life11020144.
217. Tang J, Lee Y, Ravichandran S, Grubbs G, Huang C, Stauft C, Wang T, Golding B, Golding H, Khurana S. 2021. Reduced neutralization of SARS-CoV-2 variants by convalescent plasma and hyperimmune intravenous immunoglobulins for treatment of COVID-19. bioRxiv https://www.biorxiv.org/content/10.1101/2021.03.19.436183v1.
218. Lopardo G, Belloso WH, Nannini E, Colonna M, Sanguineti S, Zylberman V, Muñoz L, Dobarro M, Lebersztein G, Farina J, Vidiella G, Bertetti A, Crudo F, Alzogaray MF, Barcelona L, Teijeiro R, Lambert S, Scublinsky D, Iacono M, Stanek V, Solari R, Cruz P, Casas MM, Abusamra L, Luciardi HL, Cremona A, Caruso D, de Miguel B, Lloret SP, Millán S, Kilstein Y, Pereiro A, Sued O, Cahn P, Spatz L, Goldbaum F, INM005 Study Group. 2021. RBD-specific polyclonal F(ab¨)2 fragments of equine antibodies in patients with moderate to severe COVID-19 disease: a randomized, multicenter, double-blind, placebo-controlled, adaptive phase 2/3 clinical trial. EClinicalMedicine 34:100843. https://doi.org/10.1016/j.eclinm.2021.100843.
219. Gaborit B, Dailly E, Vanhove B, Josien R, Lacombe K, Dubee V, Ferre V, Brouard S, Ader F, Vibet M-A, Thuaut AL, Danger R, Omnes AO, Berly L, Chiffoleau A, Jobert A, Duvaux O, Raffi F. 2021. Pharmacokinetics and safety of XAV-19, a swine glyco-humanized polyclonal anti-SARS-CoV-2 antibody, for COVID-19-related moderate pneumonia: a randomized, double-blind, placebo-controlled, phase IIa study. medRxiv https://www.medrxiv.org/content/10.1101/2021.04.15.21255549v1.

220. Beigel JH, Voell J, Kumar P, Raviprakash K, Wu H, Jiao J-A, Sullivan E, Luke T, Davey RT. 2018. Safety and tolerability of a novel, polyclonal human anti-MERS coronavirus antibody produced from transchromosomic cattle: a phase 1 randomised, double-blind, single-dose-escalation study. Lancet Infect Dis 18:410–418. https://doi.org/10.1016/S1473-3099(18)30002-1.
221. Yuan K, Yi L, Chen J, Qu X, Qing T, Rao X, Jiang P, Hu J, Xiong Z, Nie Y, Shi X, Wang W, Ling C, Yin X, Fan K, Lai L, Ding M, Deng H. 2004. Suppression of SARS-CoV entry by peptides corresponding to heptad regions on spike glycoprotein. Biochem Biophys Res Commun 319:746–752. https://doi.org/10.1016/j.bbrc.2004.05.046.
222. Channappanavar R, Lu L, Xia S, Du L, Meyerholz DK, Perlman S, Jiang S. 2015. Protective effect of intranasal regimens containing peptidic Middle East respiratory syndrome coronavirus fusion inhibitor against MERS-CoV infection. J Infect Dis 212:1894–1903. https://doi.org/10.1093/infdis/jiv325.
223. Lu L, Liu Q, Zhu Y, Chan K-H, Qin L, Li Y, Wang Q, Chan JF-W, Du L, Yu F, Ma C, Ye S, Yuen K-Y, Zhang R, Jiang S. 2014. Structure-based discovery of Middle East respiratory syndrome coronavirus fusion inhibitor. Nat Commun 5:3067. https://doi.org/10.1038/ncomms4067.
224. Wang C, Zhao L, Xia S, Zhang T, Cao R, Liang G, Li Y, Meng G, Wang W, Shi W, Zhong W, Jiang S, Liu K. 2018. *De novo* design of α-helical lipopeptides targeting viral fusion proteins: a promising strategy for relatively broad-spectrum antiviral drug discovery. J Med Chem 61:8734–8745. https://doi.org/10.1021/acs.jmedchem.8b00890.
225. Xia S, Yan L, Xu W, Agrawal AS, Algaissi A, Tseng C-TK, Wang Q, Du L, Tan W, Wilson IA, Jiang S, Yang B, Lu L. 2019. A pan-coronavirus fusion inhibitor targeting the HR1 domain of human coronavirus spike. Sci Adv 5:eaav4580. https://doi.org/10.1126/sciadv.aav4580.
226. Zhu Y, Yu D, Yan H, Chong H, He Y. 2020. Design of potent membrane fusion inhibitors against SARS-CoV-2, an emerging coronavirus with high fusogenic activity. J Virol 94:e00635-20. https://doi.org/10.1128/JVI.00635-20.
227. Xia S, Liu M, Wang C, Xu W, Lan Q, Feng S, Qi F, Bao L, Du L, Liu S, Qin C, Sun F, Shi Z, Zhu Y, Jiang S, Lu L. 2020. Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion. Cell Res 30:343–355. https://doi.org/10.1038/s41422-020-0305-x.
228. Chong H, Xue J, Xiong S, Cong Z, Ding X, Zhu Y, Liu Z, Chen T, Feng Y, He L, Guo Y, Wei Q, Zhou Y, Qin C, He Y. 2017. A lipopeptide HIV-1/2 fusion inhibitor with highly potent *in vitro*, *ex vivo*, and *in vivo* antiviral activity. J Virol 91:e00288-17. https://doi.org/10.1128/JVI.00288-17.
229. Outlaw VK, Bovier FT, Mears MC, Cajimat MN, Zhu Y, Lin MJ, Addetia A, Lieberman NAP, Peddu v, xie x, shi p-y, greninger al, gellman sh, bente da, moscona a, porotto m. 2020. inhibition of coronavirus entry *in vitro* and *ex vivo* by a lipid-conjugated peptide derived from the SARS-CoV-2 spike glycoprotein HRC domain. mBio 11:e01935-20. https://doi.org/10.1128/mBio.01935-20.
230. de Vries RD, Schmitz KS, Bovier FT, Predella C, Khao J, Noack D, Haagmans BL, Herfst S, Stearns KN, Drew-Bear J, Biswas S, Rockx B, McGill G, Dorrello NV, Gellman SH, Alabi CA, de Swart RL, Moscona A, Porotto M. 2021. Intranasal fusion inhibitory lipopeptide prevents direct-contact SARS-CoV-2 transmission in ferrets. Science 371:1379–1382. https://doi.org/10.1126/science.abf4896.
231. Imai Y, Kuba K, Penninger JM. 2007. Angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Cell Mol Life Sci 64:2006–2012. https://doi.org/10.1007/s00018-007-6228-6.
232. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM. 2005. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 11:875–879. https://doi.org/10.1038/nm1267.
233. Khan A, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, Hall R, Poirier G, Ronco JJ, Tidswell M, Hardes K, Powley WM, Wright TJ, Siederer SK, Fairman DA, Lipson DA, Bayliffe AI, Lazaar AL. 2017. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care 21:234. https://doi.org/10.1186/s13054-017-1823-x.
234. Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, Leopoldi A, Garreta E, Hurtado del Pozo C, Prosper F, Romero JP, Wirnsberger G, Zhang H, Slutsky AS, Conder R, Montserrat N, Mirazimi A, Penninger JM. 2020. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell 181:905–913. https://doi.org/10.1016/j.cell.2020.04.004.
235. Haschke M, Schuster M, Poglitsch M, Loibner H, Salzberg M, Bruggisser M, Penninger J, Krähenbühl S. 2013. Pharmacokinetics and pharmacodynamics of recombinant human angiotensin-converting enzyme 2 in healthy human subjects. Clin Pharmacokinet 52:783–792. https://doi.org/10.1007/s40262-013-0072-7.
236. Hofmann H, Geier M, Marzi A, Krumbiegel M, Peipp M, Fey GH, Gramberg T, Pöhlmann S. 2004. Susceptibility to SARS coronavirus S protein-driven infection correlates with expression of angiotensin converting enzyme 2 and infection can be blocked by soluble receptor. Biochem Biophys Res Commun 319:1216–1221. https://doi.org/10.1016/j.bbrc.2004.05.114.
237. Apeiron Biologics. 2021. Apeiron's APN01 shows clinical benefits for severely ill COVID-19 patients in phase 2 trial. Apeiron Biologics, Vienna, Austria.
238. Lei C, Qian K, Li T, Zhang S, Fu W, Ding M, Hu S. 2020. Neutralization of SARS-CoV-2 spike pseudotyped virus by recombinant ACE2-Ig. Nat Commun 11:2070. https://doi.org/10.1038/s41467-020-16048-4.
239. Curreli F, Victor SMB, Ahmed S, Drelich A, Tong X, Tseng C-TK, Hillyer CD, Debnath AK. 2020. Stapled peptides based on human angiotensin-converting enzyme 2 (ACE2) potently inhibit SARS-CoV-2 infection *in vitro*. mBio 11:e02451-20. https://doi.org/10.1128/mBio.02451-20.
240. Glasgow A, Glasgow J, Limonta D, Solomon P, Lui I, Zhang Y, Nix MA, Rettko NJ, Zha S, Yamin R, Kao K, Rosenberg OS, Ravetch JV, Wiita AP, Leung KK, Lim SA, Zhou XX, Hobman TC, Kortemme T, Wells JA. 2020. Engineered ACE2 receptor traps potently neutralize SARS-CoV-2. Proc Natl Acad Sci U S A 117:28046–28055. https://doi.org/10.1073/pnas.2016093117.
241. Xiao T, Lu J, Zhang J, Johnson RI, McKay LGA, Storm N, Lavine CL, Peng H, Cai Y, Rits-Volloch S, Lu S, Quinlan BD, Farzan M, Seaman MS, Griffiths A, Chen B. 2021. A trimeric human angiotensin-converting enzyme 2 as an anti-SARS-CoV-2 agent. Nat Struct Mol Biol 28:202–209. https://doi.org/10.1038/s41594-020-00549-3.
242. Chan KK, Tan TJC, Narayanan KK, Procko E. 2021. An engineered decoy receptor for SARS-CoV-2 broadly binds protein S sequence variants. Sci Adv 7:eabf1738. https://doi.org/10.1126/sciadv.abf1738.
243. Chan KK, Dorosky D, Sharma P, Abbasi SA, Dye JM, Kranz DM, Herbert AS, Procko E. 2020. Engineering human ACE2 to optimize binding to the spike protein of SARS coronavirus 2. Science 369:1261–1265. https://doi.org/10.1126/science.abc0870.
244. Linsky TW, Vergara R, Codina N, Nelson JW, Walker MJ, Su W, Barnes CO, Hsiang T-Y, Esser-Nobis K, Yu K, Reneer ZB, Hou YJ, Priya T, Mitsumoto M, Pong A, Lau UY, Mason ML, Chen J, Chen A, Berrocal T, Peng H, Clairmont NS, Castellanos J, Lin Y-R, Josephson-Day A, Baric RS, Fuller DH, Walkey CD, Ross TM, Swanson R, Bjorkman PJ, Gale M, Blancas-Mejia LM, Yen H-L, Silva D-A. 2020. *De novo* design of potent and resilient hACE2 decoys to neutralize SARS-CoV-2. Science 370:1208–1214. https://doi.org/10.1126/science.abe0075.
245. Han DP, Penn-Nicholson A, Cho MW. 2006. Identification of critical determinants on ACE2 for SARS-CoV entry and development of a potent entry inhibitor. Virology 350:15–25. https://doi.org/10.1016/j.virol.2006.01.029.
246. Cao L, Goreshnik I, Coventry B, Case JB, Miller L, Kozodoy L, Chen RE, Carter L, Walls AC, Park Y-J, Strauch E-M, Stewart L, Diamond MS, Veesler D, Baker D. 2020. *De novo* design of picomolar SARS-CoV-2 miniprotein inhibitors. Science 370:426–431. https://doi.org/10.1126/science.abd9909.
247. Stumpp MT, Dawson KM, Binz HK. 2020. Beyond antibodies: the DARPin drug platform. BioDrugs 34:423–433. https://doi.org/10.1007/s40259-020-00429-8.
248. Walser M, Rothenberger S, Hurdiss DL, Schlegel A, Calabro V, Fontaine S, Villemagne D, Paladino M, Hospodarsch T, Neculcea A, Cornelius A, Schildknecht P, Matzner M, Haenggi M, Franchini M, Kaufmann Y, Schlegel I, Iss C, Loser T, Mangold S, Herzog C, Schiegg D, Reichen C, Radom F, Bosshart A, Lehmann A, Haeuptle MA, Zuercher A, Vagt T, Sigrist G, Straumann M, Proba K, Veitonmaki N, Dawson KM, Zitt C, Mayor J, Ryter S, Lyoo H, Wang C, Li W, Drulyte I, Binz HK, de Waal L, Stittelaar KJ, Lewis S, Steiner D, van Kuppeveld FJM, Engler O, Bosch B-J, Stumpp MT, et al. 2020. Highly potent anti-SARS-CoV-2 multi-DARPin therapeutic candidates. bioRxiv https://www.biorxiv.org/content/10.1101/2020.08.25.256339v2.
249. Lang J, Yang N, Deng J, Liu K, Yang P, Zhang G, Jiang C. 2011. Inhibition of SARS pseudovirus cell entry by lactoferrin binding to heparan sulfate proteoglycans. PLoS One 6:e23710. https://doi.org/10.1371/journal.pone.0023710.

250. Clausen TM, Sandoval DR, Spliid CB, Pihl J, Perrett HR, Painter CD, Narayanan A, Majowicz SA, Kwong EM, McVicar RN, Thacker BE, Glass CA, Yang Z, Torres JL, Golden GJ, Bartels PL, Porell RN, Garretson AF, Laubach L, Feldman J, Yin X, Pu Y, Hauser BM, Caradonna TM, Kellman BP, Martino C, Gordts PLSM, Chanda SK, Schmidt AG, Godula K, Leibel SL, Jose J, Corbett KD, Ward AB, Carlin AF, Esko JD. 2020. SARS-CoV-2 infection depends on cellular heparan sulfate and ACE2. Cell 183:1043–1057. https://doi.org/10.1016/j.cell.2020.09.033.
251. Chang R, Ng TB, Sun W-Z. 2020. Lactoferrin as potential preventative and treatment for COVID-19. Int J Antimicrob Agents 56:106118. https://doi.org/10.1016/j.ijantimicag.2020.106118.
252. Hu Y, Meng X, Zhang F, Xiang Y, Wang J. 2021. The *in vitro* antiviral activity of lactoferrin against common human coronaviruses and SARS-CoV-2 is mediated by targeting the heparan sulfate coreceptor. Emerg Microbes Infect 10:317–330. https://doi.org/10.1080/22221751.2021.1888660.
253. Tandon R, Sharp JS, Zhang F, Pomin VH, Ashpole NM, Mitra D, McCandless MG, Jin W, Liu H, Sharma P, Linhardt RJ. 2021. Effective inhibition of SARS-CoV-2 entry by heparin and enoxaparin derivatives. J Virol 95:e01987-20. https://doi.org/10.1128/JVI.01987-20.
254. Mycroft-West CJ, Su D, Pagani I, Rudd TR, Elli S, Gandhi NS, Guimond SE, Miller GJ, Meneghetti MCZ, Nader HB, Li Y, Nunes QM, Procter P, Mancini N, Clementi M, Bisio A, Forsyth NR, Ferro V, Turnbull JE, Guerrini M, Fernig DG, Vicenzi E, Yates EA, Lima MA, Skidmore MA. 2020. Heparin inhibits cellular invasion by SARS-CoV-2: structural dependence of the interaction of the spike S1 receptor-binding domain with heparin. Thromb Haemost 120:1700–1715. https://doi.org/10.1055/s-0040-1721319.
255. Kim SY, Jin W, Sood A, Montgomery DW, Grant OC, Fuster MM, Fu L, Dordick JS, Woods RJ, Zhang F, Linhardt RJ. 2020. Characterization of heparin and severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) spike glycoprotein binding interactions. Antiviral Res 181:104873. https://doi.org/10.1016/j.antiviral.2020.104873.
256. Sallard E, Lescure F-X, Yazdanpanah Y, Mentre F, Peiffer-Smadja N. 2020. Type 1 interferons as a potential treatment against COVID-19. Antiviral Res 178:104791. https://doi.org/10.1016/j.antiviral.2020.104791.
257. McNab F, Mayer-Barber K, Sher A, Wack A, O'Garra A. 2015. Type I interferons in infectious disease. Nat Rev Immunol 15:87–103. https://doi.org/10.1038/nri3787.
258. Park A, Iwasaki A. 2020. Type I and type III interferons: induction, signaling, evasion, and application to combat COVID-19. Cell Host Microbe 27:870–878. https://doi.org/10.1016/j.chom.2020.05.008.
259. Lazear HM, Schoggins JW, Diamond MS. 2019. Shared and distinct functions of type I and type III interferons. Immunity 50:907–923. https://doi.org/10.1016/j.immuni.2019.03.025.
260. de Wit E, van Doremalen N, Falzarano D, Munster VJ. 2016. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 14:523–534. https://doi.org/10.1038/nrmicro.2016.81.
261. Totura AL, Baric RS. 2012. SARS coronavirus pathogenesis: host innate immune responses and viral antagonism of interferon. Curr Opin Virol 2:264–275. https://doi.org/10.1016/j.coviro.2012.04.004.
262. Ribero MS, Jouvenet N, Dreux M, Nisole S. 2020. Interplay between SARS-CoV-2 and the type I interferon response. PLoS Pathog 16:e1008737. https://doi.org/10.1371/journal.ppat.1008737.
263. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann H-H, Zhang Y, Dorgham K, Philippot Q, Rosain J, Béziat V, Manry J, Shaw E, Haljasmägi L, Peterson P, Lorenzo L, Bizien L, Trouillet-Assant S, Dobbs K, de Jesus AA, Belot A, Kallaste A, Catherinot E, Tandjaoui-Lambiotte Y, Pen JL, Kerner G, Bigio B, Seeleuthner Y, Yang R, Bolze A, Spaan AN, Delmonte OM, et al. 2020. Auto-antibodies against type I IFNs in patients with life-threatening COVID-19. Science 370:eabd4585. https://doi.org/10.1126/science.abd4585.
264. Blanco-Melo D, Nilsson-Payant BE, Liu W-C, Uhl S, Hoagland D, Møller R, Jordan TX, Oishi K, Panis M, Sachs D, Wang TT, Schwartz RE, Lim JK, Albrecht RA, tenOever BR. 2020. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 181:1036–1045.e9. https://doi.org/10.1016/j.cell.2020.04.026.
265. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, Péré H, Charbit B, Bondet V, Chenevier-Gobeaux C, Breillat P, Carlier N, Gauzit R, Morbieu C, Pène F, Marin N, Roche N, Szwebel T-A, Merkling SH, Treluyer J-M, Veyer D, Mouthon L, Blanc C, Tharaux P-L, Rozenberg F, Fischer A, Duffy D, Rieux-Laucat F, Kernéis S, Terrier B. 2020. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science 369:718–724. https://doi.org/10.1126/science.abc6027.
266. Zhou Z, Ren L, Zhang L, Zhong J, Xiao Y, Jia Z, Guo L, Yang J, Wang C, Jiang S, Yang D, Zhang G, Li H, Chen F, Xu Y, Chen M, Gao Z, Yang J, Dong J, Liu B, Zhang X, Wang W, He K, Jin Q, Li M, Wang J. 2020. Heightened innate immune responses in the respiratory tract of COVID-19 patients. Cell Host Microbe 27:883–890.e2. https://doi.org/10.1016/j.chom.2020.04.017.
267. Ziegler CGK, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, Cao Y, Yousif AS, Bals J, Hauser BM, Feldman J, Muus C, Wadsworth MH, Kazer SW, Hughes TK, Doran B, Gatter GJ, Vukovic M, Taliaferro F, Mead BE, Guo Z, Wang JP, Gras D, Plaisant M, Ansari M, Angelidis I, Adler H, Sucre JMS, Taylor CJ, Lin B, Waghray A, Mitsialis V, Dwyer DF, Buchheit KM, Boyce JA, Barrett NA, Laidlaw TM, Carroll SL, Colonna L, Tkachev V, Peterson CW, Yu A, Zheng HB, Gideon HP, Winchell CG, Lin PL, Bingle CD, Snapper SB, Kropski JA, Theis FJ, Schiller HB, Zaragosi L-E, Barbry P, Leslie A, Kiem H-P, Flynn JL, HCA Lung Biological Network, et al. 2020. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. Cell 181:1016–1035. https://doi.org/10.1016/j.cell.2020.04.035.
268. Lokugamage KG, Hage A, de Vries M, Valero-Jimenez AM, Schindewolf C, Dittmann M, Rajsbaum R, Menachery VD. 2020. Type I interferon susceptibility distinguishes SARS-CoV-2 from SARS-CoV. J Virol 94:e01410-20. https://doi.org/10.1128/JVI.01410-20.
269. Mantlo E, Bukreyeva N, Maruyama J, Paessler S, Huang C. 2020. Antiviral activities of type I interferons to SARS-CoV-2 infection. Antiviral Res 179:104811. https://doi.org/10.1016/j.antiviral.2020.104811.
270. Felgenhauer U, Schoen A, Gad HH, Hartmann R, Schaubmar AR, Failing K, Drosten C, Weber F. 2020. Inhibition of SARS-CoV-2 by type I and type III interferons. J Biol Chem 295:13958–13964. https://doi.org/10.1074/jbc.AC120.013788.
271. Vanderheiden A, Ralfs P, Chirkova T, Upadhyay AA, Zimmerman MG, Bedoya S, Aoued H, Tharp GM, Pellegrini KL, Manfredi C, Sorscher E, Mainou B, Lobby JL, Kohlmeier JE, Lowen AC, Shi P-Y, Menachery VD, Anderson LJ, Grakoui A, Bosinger SE, Suthar MS. 2020. Type I and type III interferons restrict SARS-CoV-2 infection of human airway epithelial cultures. J Virol 94:e00985-20. https://doi.org/10.1128/JVI.00985-20.
272. Busnadiego I, Fernbach S, Pohl MO, Karakus U, Huber M, Trkola A, Stertz S, Hale BG. 2020. Antiviral activity of type I, II, and III interferons counterbalances ACE2 inducibility and restricts SARS-CoV-2. mBio 11:e01928-20. https://doi.org/10.1128/mBio.01928-20.
273. Barnard DL, Day CW, Bailey K, Heiner M, Montgomery R, Lauridsen L, Chan PKS, Sidwell RW. 2006. Evaluation of immunomodulators, interferons and known *in vitro* SARS-coV inhibitors for inhibition of SARS-coV replication in BALB/c mice. Antivir Chem Chemother 17:275–284. https://doi.org/10.1177/095632020601700505.
274. Kumaki Y, Ennis J, Rahbar R, Turner JD, Wandersee MK, Smith AJ, Bailey KW, Vest ZG, Madsen JR, Li JK-K, Barnard DL. 2011. Single-dose intranasal administration with mDEF201 (adenovirus vectored mouse interferon-alpha) confers protection from mortality in a lethal SARS-CoV BALB/c mouse model. Antiviral Res 89:75–82. https://doi.org/10.1016/j.antiviral.2010.11.007.
275. Haagmans BL, Kuiken T, Martina BE, Fouchier RAM, Rimmelzwaan GF, van Amerongen G, van Riel D, de Jong T, Itamura S, Chan K-H, Tashiro M, Osterhaus ADME. 2004. Pegylated interferon-alpha protects type 1 pneumocytes against SARS coronavirus infection in macaques. Nat Med 10:290–293. https://doi.org/10.1038/nm1001.
276. Smits SL, de Lang A, van den Brand JMA, Leijten LM, van IJcken WF, Eijkemans MJC, van Amerongen G, Kuiken T, Andeweg AC, Osterhaus ADME, Haagmans BL. 2010. Exacerbated innate host response to SARS-CoV in aged non-human primates. PLoS Pathog 6:e1000756. https://doi.org/10.1371/journal.ppat.1000756.
277. Dinnon KH, Leist SR, Schäfer A, Edwards CE, Martinez DR, Montgomery SA, West A, Yount BL, Hou YJ, Adams LE, Gully KL, Brown AJ, Huang E, Bryant MD, Choong IC, Glenn JS, Gralinski LE, Sheahan TP, Baric RS. 2020. A mouse-adapted model of SARS-CoV-2 to test COVID-19 countermeasures. Nature 586:560–566. https://doi.org/10.1038/s41586-020-2708-8.
278. Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, Perlman S. 2016. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe 19:181–193. https://doi.org/10.1016/j.chom.2016.01.007.
279. Channappanavar R, Fehr AR, Zheng J, Wohlford-Lenane C, Abrahante JE, Mack M, Sompallae R, McCray PB, Meyerholz DK, Perlman S. 2019. IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. J Clin Invest 129:3625–3639. https://doi.org/10.1172/JCI126363.

280. Monk PD, Marsden RJ, Tear VJ, Brookes J, Batten TN, Mankowski M, Gabbay FJ, Davies DE, Holgate ST, Ho L-P, Clark T, Djukanovic R, Wilkinson TMA, Crooks MG, Dosanjh DP, Siddiqui S, Rahman NM, Smith JA, Horsley A, Harrison TW, Saralaya D, McGarvey L, Watson A, Foster E, Fleet A, Singh D, Hemmings S, Aitken S, Dudley S, Beegan R, Thompson A, Rodrigues PM, Inhaled Interferon Beta COVID-19 Study Group. 2021. Safety and efficacy of inhaled nebulized interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med 9:196–206. https://doi.org/10.1016/S2213-2600(20)30511-7.
281. Jagannathan P, Andrews JR, Bonilla H, Hedlin H, Jacobson KB, Balasubramanian V, Purington N, Kamble S, de Vries CR, Quintero O, Feng K, Ley C, Winslow D, Newberry J, Edwards K, Hislop C, Choong I, Maldonado Y, Glenn J, Bhatt A, Blish C, Wang T, Khosla C, Pinsky BA, Desai M, Parsonnet J, Singh U. 2021. Peginterferon lambda-1a for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial. 1. Nat Commun 12:1967. https://doi.org/10.1038/s41467-021-22177-1.
282. Feld JJ, Kandel C, Biondi MJ, Kozak RA, Zahoor MA, Lemieux C, Borgia SM, Boggild AK, Powis J, McCready J, Tan DHS, Chan T, Coburn B, Kumar D, Humar A, Chan A, O'Neil B, Noureldin S, Booth J, Hong R, Smookler D, Aleyadeh W, Patel A, Barber B, Casey J, Hiebert R, Mistry H, Choong I, Hislop C, Santer DM, Lorne Tyrrell D, Glenn JS, Gehring AJ, Janssen HLA, Hansen BE. 2021. Peginterferon lambda for the treatment of outpatients with COVID-19: a phase 2, placebo-controlled randomised trial. Lancet Respir Med 9:498–510. https://doi.org/10.1016/S2213-2600(20)30566-X.
283. Davoudi-Monfared E, Rahmani H, Khalili H, Hajiabdolbaghi M, Salehi M, Abbasian L, Kazemzadeh H, Yekaninejad MS. 2020. Efficacy and safety of interferon β-1a in treatment of severe COVID-19: a randomized clinical trial. Antimicrob Agents Chemother 64:e01061-20. https://doi.org/10.1128/AAC.01061-20.
284. Zheng F, Zhou Y, Zhou Z, Ye F, Huang B, Huang Y, Ma J, Zuo Q, Tan X, Xie J, Niu P, Wang W, Xu Y, Peng F, Zhou N, Cai C, Tang W, Xiao X, Li Y, Zhou Z, Jiang Y, Xie Y, Tan W, Gong G. 2020. SARS-CoV-2 clearance in COVID-19 patients with novaferon treatment: a randomized, open-label, parallel group trial. Int J Infect Dis 99:84–91. https://doi.org/10.1016/j.ijid.2020.07.053.
285. Hung IF-N, Lung K-C, Tso EY-K, Liu R, Chung TW-H, Chu M-Y, Ng Y-Y, Lo J, Chan J, Tam AR, Shum H-P, Chan V, Wu AK-L, Sin K-M, Leung W-S, Law W-L, Lung DC, Sin S, Yeung P, Yip CC-Y, Zhang RR, Fung AY-F, Yan EY-W, Leung K-H, Ip JD, Chu AW-H, Chan W-M, Ng AC-K, Lee R, Fung K, Yeung A, Wu T-C, Chan JW-M, Yan W-W, Chan W-M, Chan JF-W, Lie AK-W, Tsang OT-Y, Cheng VC-C, Que T-L, Lau C-S, Chan K-H, To KK-W, Yuen K-Y. 2020. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet Lond Engl 395:1695–1704. https://doi.org/10.1016/S0140-6736(20)31042-4.
286. Kawase M, Shirato K, van der Hoek L, Taguchi F, Matsuyama S. 2012. Simultaneous treatment of human bronchial epithelial cells with serine and cysteine protease inhibitors prevents severe acute respiratory syndrome coronavirus entry. J Virol 86:6537–6545. https://doi.org/10.1128/JVI.00094-12.
287. Yamamoto M, Kiso M, Sakai-Tagawa Y, Iwatsuki-Horimoto K, Imai M, Takeda M, Kinoshita N, Ohmagari N, Gohda J, Semba K, Matsuda Z, Kawaguchi Y, Kawaoka Y, Inoue J-I. 2020. The anticoagulant nafamostat potently inhibits SARS-CoV-2 S protein-mediated fusion in a cell fusion assay system and viral infection *in vitro* in a cell-type-dependent manner. Viruses 12:629. https://doi.org/10.3390/v12060629.
288. Hoffmann M, Hofmann-Winkler H, Smith JC, Krüger N, Arora P, Sørensen LK, Søgaard OS, Hasselstrøm JB, Winkler M, Hempel T, Raich L, Olsson S, Danov O, Jonigk D, Yamazoe T, Yamatsuta K, Mizuno H, Ludwig S, Noé F, Kjolby M, Braun A, Sheltzer JM, Pöhlmann S. 2021. Camostat mesylate inhibits SARS-CoV-2 activation by TMPRSS2-related proteases and its metabolite GBPA exerts antiviral activity. EBioMedicine 65:103255. https://doi.org/10.1016/j.ebiom.2021.103255.
289. Shrimp JH, Kales SC, Sanderson PE, Simeonov A, Shen M, Hall MD. 2020. An enzymatic TMPRSS2 assay for assessment of clinical candidates and discovery of inhibitors as potential treatment of COVID-19. ACS Pharmacol Transl Sci 3:997–1007. https://doi.org/10.1021/acsptsci.0c00106.
290. Hoffmann M, Schroeder S, Kleine-Weber H, Müller MA, Drosten C, Pöhlmann S. 2020. Nafamostat mesylate blocks activation of SARS-CoV-2: new treatment option for COVID-19. Antimicrob Agents Chemother 64:e00754-20. https://doi.org/10.1128/AAC.00754-20.
291. Bojkova D, McGreig JE, McLaughlin K-M, Masterson SG, Antczak M, Widera M, Krähling V, Ciesek S, Wass MN, Michaelis M, Cinatl J, Jr. 2021. Differentially conserved amino acid positions may reflect differences in SARS-CoV-2 and SARS-CoV behaviour. Bioinformatics https://doi.org/10.1093/bioinformatics/btab094.
292. Zhou Y, Vedantham P, Lu K, Agudelo J, Carrion R, Nunneley JW, Barnard D, Pöhlmann S, McKerrow JH, Renslo AR, Simmons G. 2015. Protease inhibitors targeting coronavirus and filovirus entry. Antiviral Res 116:76–84. https://doi.org/10.1016/j.antiviral.2015.01.011.
293. Kitagawa J, Arai H, Iida H, Mukai J, Furukawa K, Ohtsu S, Nakade S, Hikima T, Haranaka M, Uemura N. 2021. A phase I study of high dose camostat mesylate in healthy adults provides a rationale to repurpose the TMPRSS2 inhibitor for the treatment of COVID-19. Clin Transl Sci https://doi.org/10.1111/cts.13052.
294. Gunst JD, Staerke NB, Pahus MH, Kristensen LH, Bodilsen J, Lohse N, Dalgaard LS, Brønnum D, Fröbert O, Hønge B, Johansen IS, Monrad I, Erikstrup C, Rosendal R, Vilstrup E, Mariager T, Bove DG, Offersen R, Shakar S, Cajander S, Jørgensen NP, Sritharan SS, Breining P, Jespersen S, Mortensen KL, Jensen ML, Kolte L, Frattari GS, Larsen CS, Storgaard M, Nielsen LP, Tolstrup M, Sædder EA, Østergaard LJ, Ngo HTT, Jensen MH, Højen JF, Kjolby M, Søgaard OS. 2021. Efficacy of the TMPRSS2 inhibitor camostat mesilate in patients hospitalized with Covid-19-a double-blind randomized controlled trial. EClinicalMedicine 35:100849. https://doi.org/10.1016/j.eclinm.2021.100849.
295. Okajima M, Takahashi Y, Kaji T, Ogawa N, Mouri H. 2020. Nafamostat mesylate-induced hyperkalemia in critically ill patients with COVID-19: four case reports. World J Clin Cases 8:5320–5325. https://doi.org/10.12998/wjcc.v8.i21.5320.
296. Azouz NP, Klingler AM, Callahan V, Akhrymuk IV, Elez K, Raich L, Henry BM, Benoit JL, Benoit SW, Noé F, Kehn-Hall K, Rothenberg ME. 2021. Alpha 1 antitrypsin is an Inhibitor of the SARS-CoV-2-priming protease TMPRSS2. Pathog Immun 6:55–74. https://doi.org/10.20411/pai.v6i1.408.
297. Oguntuyo KY, Stevens CS, Siddiquey MN, Schilke RM, Woolard MD, Zhang H, Acklin JA, Ikegame S, Hung C, Lim JK, Cross RW, Geisbert TW, Ivanov SS, Kamil JP, Lee B. 2020. In plain sight: the role of alpha-1-antitrypsin in COVID-19 pathogenesis and therapeutics. bioRxiv https://www.biorxiv.org/content/10.1101/2020.08.14.248880v1.
298. Wettstein L, Weil T, Conzelmann C, Müller JA, Gross R, Hirschenberger M, Seidel A, Klute S, Zech F, Prelli Bozzo C, Preising N, Fois G, Lochbaum R, Knaff PM, Mailänder V, Ständker L, Thal DR, Schumann C, Stenger S, Kleger A, Lochnit G, Mayer B, Ruiz-Blanco YB, Hoffmann M, Sparrer KMJ, Pöhlmann S, Sanchez-Garcia E, Kirchhoff F, Frick M, Münch J. 2021. Alpha-1 antitrypsin inhibits TMPRSS2 protease activity and SARS-CoV-2 infection. Nat Commun 12:1726. https://doi.org/10.1038/s41467-021-21972-0.
299. Bojkova D, Bechtel M, McLaughlin K-M, McGreig JE, Klann K, Bellinghausen C, Rohde G, Jonigk D, Braubach P, Ciesek S, Münch C, Wass MN, Michaelis M, Cinatl J. 2020. Aprotinin inhibits SARS-CoV-2 replication. Cells 9:2377. https://doi.org/10.3390/cells9112377.
300. Yang C, Chapman KR, Wong A, Liu M. 2021. α1-Antitrypsin deficiency and the risk of COVID-19: an urgent call to action. Lancet Respir Med 9:337–339. https://doi.org/10.1016/S2213-2600(21)00018-7.
301. Lucas JM, Heinlein C, Kim T, Hernandez SA, Malik MS, True LD, Morrissey C, Corey E, Montgomery B, Mostaghel E, Clegg N, Coleman I, Brown CM, Schneider EL, Craik C, Simon JA, Bedalov A, Nelson PS. 2014. The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. Cancer Discov 4:1310–1325. https://doi.org/10.1158/2159-8290.CD-13-1010.
302. Hörnich BF, Grosskopf AK, Schlagowski S, Tenbusch M, Kleine-Weber H, Neipel F, Stahl-Hennig C, Hahn AS. 2021. SARS-CoV-2 and SARS-CoV spike-mediated cell-cell fusion differ in the requirements for receptor expression and proteolytic activation. J Virol 95:e00002-21. https://doi.org/10.1128/JVI.00002-21.
303. Ansarin K, Tolouian R, Ardalan M, Taghizadieh A, Varshochi M, Teimouri S, Vaezi T, Valizadeh H, Saleh P, Safiri S, Chapman KR. 2020. Effect of bromhexine on clinical outcomes and mortality in COVID-19 patients: a randomized clinical trial. BioImpacts BI 10:209–215. https://doi.org/10.34172/bi.2020.27.
304. Coelho AR, Oliveira PJ. 2020. Dihydroorotate dehydrogenase inhibitors in SARS-CoV-2 infection. Eur J Clin Invest 50:e13366. https://doi.org/10.1111/eci.13366.

305. Xiong R, Zhang L, Li S, Sun Y, Ding M, Wang Y, Zhao Y, Wu Y, Shang W, Jiang X, Shan J, Shen Z, Tong Y, Xu L, Chen Y, Liu Y, Zou G, Lavillete D, Zhao Z, Wang R, Zhu L, Xiao G, Lan K, Li H, Xu K. 2020. Novel and potent inhibitors targeting DHODH are broad-spectrum antivirals against RNA viruses including newly-emerged coronavirus SARS-CoV-2. Protein Cell 11:723–739. https://doi.org/10.1007/s13238-020-00768-w.
306. Wang M, Zhao Y, Hu W, Zhao D, Zhang Y, Wang T, Zheng Z, Li X, Zeng S, Liu Z, Lu L, Wan Z, Hu K. 2020. Treatment of COVID-19 patients with prolonged postsymptomatic viral shedding with leflunomide: a single-center, randomized, controlled clinical trial. Clin Infect Dis https://doi.org/10.1093/cid/ciaa1417.
307. Luban J, Sattler RA, Mühlberger E, Graci JD, Cao L, Weetall M, Trotta C, Colacino JM, Bavari S, Strambio-De-Castillia C, Suder EL, Wang Y, Soloveva V, Cintron-Lue K, Naryshkin NA, Pykett M, Welch EM, O'Keefe K, Kong R, Goodwin E, Jacobson A, Paessler S, Peltz SW. 2021. The DHODH inhibitor PTC299 arrests SARS-CoV-2 replication and suppresses induction of inflammatory cytokines. Virus Res 292:198246. https://doi.org/10.1016/j.virusres.2020.198246.
308. Hahn F, Wangen C, Häge S, Peter AS, Dobler G, Hurst B, Julander J, Fuchs J, Ruzsics Z, Überla K, Jäck H-M, Ptak R, Muehler A, Gröppel M, Vitt D, Peelen E, Kohlhof H, Marschall M. 2020. IMU-838, a developmental DHODH inhibitor in phase II for autoimmune disease, shows anti-SARS-CoV-2 and broad-spectrum antiviral efficacy *in vitro*. Viruses 12:1394. https://doi.org/10.3390/v12121394.
309. White KM, Rosales R, Yildiz S, Kehrer T, Miorin L, Moreno E, Jangra S, Uccellini MB, Rathnasinghe R, Coughlan L, Martinez-Romero C, Batra J, Rojc A, Bouhaddou M, Fabius JM, Obernier K, Dejosez M, Guillén MJ, Losada A, Avilés P, Schotsaert M, Zwaka T, Vignuzzi M, Shokat KM, Krogan NJ, García-Sastre A. 2021. Plitidepsin has potent preclinical efficacy against SARS-CoV-2 by targeting the host protein eEF1A. Science 371:926–931. https://doi.org/10.1126/science.abf4058.
310. Varona JF, Landete P, Lopez-Martin JA, Estrada V, Paredes R, Guisado-Vasco P, de Orueta LF, Torralba M, Fortun J, Vates R, Barberan J, Clotet B, Ancochea J, Carnevali D, Cabello N, Porras L, Gijon P, Monereo A, Abad D, Zuñiga S, Sola I, Rodon J, Izquierdo-Useros N, Fudio S, Pontes MJ, de Rivas B, de Velasco PG, Sopesen B, Nieto A, Gomez J, Aviles P, Lubomirov R, White KM, Rosales R, Yildiz S, Reuschl A-K, Thorne LG, Jolly C, Towers GJ, Zuliani-Alvarez L, Bouhaddou M, Obernier K, Enjuanes L, Fernandez-Sousa JM, Group PCS, Krogan NJ, Jimeno JM, Garcia-Sastre A. 2021. Plitidepsin has a positive therapeutic index in adult patients with COVID-19 requiring hospitalization. medRxiv https://www.medrxiv.org/content/10.1101/2021.05.25.21257505v1.
311. Kang Y-L, Chou Y, Rothlauf PW, Liu Z, Soh TK, Cureton D, Case JB, Chen RE, Diamond MS, Whelan SPJ, Kirchhausen T. 2020. Inhibition of PIKfyve kinase prevents infection by Zaire ebolavirus and SARS-CoV-2. Proc Natl Acad Sci U S A 117:20803–20813. https://doi.org/10.1073/pnas.2007837117.
312. Riva L, Yuan S, Yin X, Martin-Sancho L, Matsunaga N, Pache L, Burgstaller-Muehlbacher S, De Jesus PD, Teriete P, Hull MV, Chang MW, Chan JF-W, Cao J, Poon VK-M, Herbert KM, Cheng K, Nguyen T-TH, Rubanov A, Pu Y, Nguyen C, Choi A, Rathnasinghe R, Schotsaert M, Miorin L, Dejosez M, Zwaka TP, Sit K-Y, Martinez-Sobrido L, Liu W-C, White KM, Chapman ME, Lendy EK, Glynne RJ, Albrecht R, Ruppin E, Mesecar AD, Johnson JR, Benner C, Sun R, Schultz PG, Su AI, García-Sastre A, Chatterjee AK, Yuen K-Y, Chanda SK. 2020. Discovery of SARS-CoV-2 antiviral drugs through large-scale compound repurposing. Nature 586:113–119. https://doi.org/10.1038/s41586-020-2577-1.
313. Bouhaddou M, Memon D, Meyer B, White KM, Rezelj VV, Correa Marrero M, Polacco BJ, Melnyk JE, Ulferts S, Kaake RM, Batra J, Richards AL, Stevenson E, Gordon DE, Rojc A, Obernier K, Fabius JM, Soucheray M, Miorin L, Moreno E, Koh C, Tran QD, Hardy A, Robinot R, Vallet T, Nilsson-Payant BE, Hernandez-Armenta C, Dunham A, Weigang S, Knerr J, Modak M, Quintero D, Zhou Y, Dugourd A, Valdeolivas A, Patil T, Li Q, Hüttenhain R, Cakir M, Muralidharan M, Kim M, Jang G, Tutuncuoglu B, Hiatt J, Guo JZ, Xu J, Bouhaddou S, Mathy CJP, Gaulton A, Manners EJ, Félix E, Shi Y, Goff M, Lim JK, McBride T, O'Neal MC, Cai Y, Chang JCJ, Broadhurst DJ, Klippsten S, De wit E, Leach AR, Kortemme T, Shoichet B, Ott M, Saez-Rodriguez J, tenOever BR, Mullins RD, Fischer ER, Kochs G, Grosse R, García-Sastre A, Vignuzzi M, Johnson JR, Shokat KM, Swaney DL, Beltrao P, Krogan NJ. 2020. The global phosphorylation landscape of SARS-CoV-2 infection. Cell 182:685–712. https://doi.org/10.1016/j.cell.2020.06.034.
314. Baranov MV, Bianchi F, van den Bogaart G. 2020. The PIKfyve inhibitor apilimod: a double-edged sword against COVID-19. Cells 10:30. https://doi.org/10.3390/cells10010030.
315. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. 2003. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis 3:722–727. https://doi.org/10.1016/S1473-3099(03)00806-5.
316. Burkard C, Verheije MH, Wicht O, van Kasteren SI, van Kuppeveld FJ, Haagmans BL, Pelkmans L, Rottier PJM, Bosch BJ, de Haan CAM. 2014. Coronavirus cell entry occurs through the endo-/lysosomal pathway in a proteolysis-dependent manner. PLoS Pathog 10:e1004502. https://doi.org/10.1371/journal.ppat.1004502.
317. Dyall J, Coleman CM, Hart BJ, Venkataraman T, Holbrook MR, Kindrachuk J, Johnson RF, Olinger GG, Jahrling PB, Laidlaw M, Johansen LM, Lear-Rooney CM, Glass PJ, Hensley LE, Frieman MB. 2014. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. Antimicrob Agents Chemother 58:4885–4893. https://doi.org/10.1128/AAC.03036-14.
318. de Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, van Nieuwkoop S, Bestebroer TM, van den Hoogen BG, Neyts J, Snijder EJ. 2014. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob Agents Chemother 58:4875–4884. https://doi.org/10.1128/AAC.03011-14.
319. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, Seidah NG, Nichol ST. 2005. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2:69. https://doi.org/10.1186/1743-422X-2-69.
320. Keyaerts E, Vijgen L, Maes P, Neyts J, Van Ranst M. 2004. *In vitro* inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun 323:264–268. https://doi.org/10.1016/j.bbrc.2004.08.085.
321. Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, Wiselka M, Ustianowski A, Elmahi E, Prudon B, Whitehouse T, Felton T, Williams J, Faccenda J, Underwood J, Baillie JK, Chappell LC, Faust SN, Jaki T, Jeffery K, Lim WS, Montgomery A, Rowan K, Tarning J, Watson JA, White NJ, Juszczak E, Haynes R, Landray MJ, RECOVERY Collaborative Group. 2020. Effect of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 383:2030–2040. https://doi.org/10.1056/NEJMoa2022926.
322. Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, Williams DA, Okafor EC, Pullen MF, Nicol MR, Nascene AA, Hullsiek KH, Cheng MP, Luke D, Lother SA, MacKenzie LJ, Drobot G, Kelly LE, Schwartz IS, Zarychanski R, McDonald EG, Lee TC, Rajasingham R, Boulware DR. 2020. Hydroxychloroquine in nonhospitalized adults with early COVID-19. A Randomized Trial Ann Intern Med 173:623–631. https://doi.org/10.7326/M20-4207.
323. Axfors C, Schmitt AM, Janiaud P, van't Hooft J, Abd-Elsalam S, Abdo EF, Abella BS, Akram J, Amaravadi RK, Angus DC, Arabi YM, Azhar S, Baden LR, Baker AW, Belkhir L, Benfield T, Berrevoets MAH, Chen C-P, Chen T-C, Cheng S-H, Cheng C-Y, Chung W-S, et al. 2021. Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials. Nat Commun 12:2349. https://doi.org/10.1038/s41467-021-22446-z.
324. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, Damiani LP, Marcadenti A, Kawano-Dourado L, Lisboa T, Junqueira DLM, Silva PGM, de B, Tramujas L, Abreu-Silva EO, Laranjeira LN, Soares AT, Echenique LS, Pereira AJ, Freitas FGR, Gebara OCE, Dantas VCS, Furtado RHM, Milan EP, Golin NA, Cardoso FF, Maia IS, Filho CRH, Kormann APM, Amazonas RB, de Oliveira MFB, Serpa-Neto A, Falavigna M, Lopes RD, Machado FR, Berwanger O. 2020. Hydroxychloroquine with or without azithromycin in mild-to-moderate COVID-19. N Engl J Med 383:2041–2052. https://doi.org/10.1056/NEJMoa2019014.
325. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, Wu Y, Xiao W, Liu S, Chen E, Chen W, Wang X, Yang J, Lin J, Zhao Q, Yan Y, Xie Z, Li D, Yang Y, Liu L, Qu J, Ning G, Shi G, Xie Q. 2020. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 369:m1849. https://doi.org/10.1136/bmj.m1849.
326. Mitjà O, Corbacho-Monné M, Ubals M, Tebe C, Peñafiel J, Tobias A, Ballana E, Alemany A, Riera-Martí N, Pérez CA, Suñer C, Laporte P, Admella P, Mitjà J, Clua M, Bertran L, Sarquella M, Gavilán S, Ara J, Argimon JM, Casabona J, Cuatrecasas G, Cañadas P, Elizalde-Torrent A, Fabregat R, Farré M, Forcada A, Flores-Mateo G, Muntada E, Nadal N, Narejos S, Gil-Ortega AN, Prat N, Puig J, Quiñones C, Reyes-Ureña J, Ramírez-Viaplana F, Ruiz L, Riveira-Muñoz E, Sierra A, Velasco C, Vivanco-Hidalgo RM, Sentís A, G-Beiras C, Clotet B, Vall-Mayans M. 2020. Hydroxychloroquine for early treatment of adults with mild Covid-19: a randomized-controlled trial. Clin Infect Dis https://doi.org/10.1093/cid/ciaa1009.

327. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, Skipper CP, Nascene AA, Nicol MR, Abassi M, Engen NW, Cheng MP, LaBar D, Lother SA, MacKenzie LJ, Drobot G, Marten N, Zarychanski R, Kelly LE, Schwartz IS, McDonald EG, Rajasingham R, Lee TC, Hullsiek KH. 2020. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med 383:517–525. https://doi.org/10.1056/NEJMoa2016638.
328. Mitjà O, Corbacho-Monné M, Ubals M, Alemany A, Suñer C, Tebé C, Tobias A, Peñafiel J, Ballana E, Pérez CA, Admella P, Riera-Martí N, Laporte P, Mitjà J, Clua M, Bertran L, Sarquella M, Gavilán S, Ara J, Argimon JM, Cuatrecasas G, Cañadas P, Elizalde-Torrent A, Fabregat R, Farré M, Forcada A, Flores-Mateo G, López C, Muntada E, Nadal N, Narejos S, Nieto A, Prat N, Puig J, Quiñones C, Ramírez-Viaplana F, Reyes-Urueña J, Riveira-Muñoz E, Ruiz L, Sanz S, Sentís A, Sierra A, Velasco C, Vivanco-Hidalgo RM, Zamora J, Casabona J, Vall-Mayans M, González-Beiras C, Clotet B, BCN-PEP-CoV2 Research Group. 2021. A cluster-randomized trial of hydroxychloroquine for prevention of Covid-19. N Engl J Med 384:417–427. https://doi.org/10.1056/NEJMoa2021801.
329. Hoffmann M, Mösbauer K, Hofmann-Winkler H, Kaul A, Kleine-Weber H, Krüger N, Gassen NC, Müller MA, Drosten C, Pöhlmann S. 2020. Chloroquine does not inhibit infection of human lung cells with SARS-CoV-2. Nature 585:588–590. https://doi.org/10.1038/s41586-020-2575-3.
330. Xu J, Shi P-Y, Li H, Zhou J. 2020. Broad spectrum antiviral agent niclosamide and its therapeutic potential. ACS Infect Dis 6:909–915. https://doi.org/10.1021/acsinfecdis.0c00052.
331. Chen W, Mook RA, Premont RT, Wang J. 2018. Niclosamide: beyond an antihelminthic drug. Cell Signal 41:89–96. https://doi.org/10.1016/j.cellsig.2017.04.001.
332. Braga L, Ali H, Secco I, Chiavacci E, Neves G, Goldhill D, Penn R, Jimenez-Guardeño JM, Ortega-Prieto AM, Bussani R, Cannatà A, Rizzari G, Collesi C, Schneider E, Arosio D, Shah AM, Barclay WS, Malim MH, Burrone J, Giacca M. 2021. Drugs that inhibit TMEM16 proteins block SARS-CoV-2 Spike-induced syncytia. Nature 594:88–93. https://doi.org/10.1038/s41586-021-03491-6.
333. Wu C-J, Jan J-T, Chen C-M, Hsieh H-P, Hwang D-R, Liu H-W, Liu C-Y, Huang H-W, Chen S-C, Hong C-F, Lin R-K, Chao Y-S, Hsu JTA. 2004. Inhibition of severe acute respiratory syndrome coronavirus replication by niclosamide. Antimicrob Agents Chemother 48:2693–2696. https://doi.org/10.1128/AAC.48.7.2693-2696.2004.
334. Wen C-C, Kuo Y-H, Jan J-T, Liang P-H, Wang S-Y, Liu H-G, Lee C-K, Chang S-T, Kuo C-J, Lee S-S, Hou C-C, Hsiao P-W, Chien S-C, Shyur L-F, Yang N-S. 2007. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. J Med Chem 50:4087–4095. https://doi.org/10.1021/jm070295s.
335. Brunaugh AD, Seo H, Warnken Z, Ding L, Seo SH, Smyth HDC. 2021. Development and evaluation of inhalable composite niclosamide-lysozyme particles: a broad-spectrum, patient-adaptable treatment for coronavirus infections and sequalae. 16:e0246803. https://doi.org/10.1371/journal.pone.0246803.
336. Backer V, Sjöbring U, Sonne J, Weiss A, Hostrup M, Johansen HK, Becker V, Sonne DP, Balchen T, Jellingsø M, Sommer MOA. 2021. A randomized, double-blind, placebo-controlled phase 1 trial of inhaled and intranasal niclosamide: a broad spectrum antiviral candidate for treatment of COVID-19. Lancet Reg Health Eur 4:100084. https://doi.org/10.1016/j.lanepe.2021.100084.
337. Xiao X, Wang C, Chang D, Wang Y, Dong X, Jiao T, Zhao Z, Ren L, Dela Cruz CS, Sharma L, Lei X, Wang J. 2020. Identification of potent and safe antiviral therapeutic candidates against SARS-CoV-2. Front Immunol 11:586572. https://doi.org/10.3389/fimmu.2020.586572.
338. Yuan S, Yin X, Meng X, Chan JF-W, Ye Z-W, Riva L, Pache L, Chan CC-Y, Lai P-M, Chan CC-S, Poon VK-M, Lee AC-Y, Matsunaga N, Pu Y, Yuen C-K, Cao J, Liang R, Tang K, Sheng L, Du Y, Xu W, Lau C-Y, Sit K-Y, Au W-K, Wang R, Zhang Y-Y, Tang Y-D, Clausen TM, Pihl J, Oh J, Sze K-H, Zhang AJ, Chu H, Kok K-H, Wang D, Cai X-H, Esko JD, Hung IF-N, Li RA, Chen H, Sun H, Jin D-Y, Sun R, Chanda SK, Yuen K-Y. 2021. Clofazimine broadly inhibits coronaviruses including SARS-CoV-2. Nature 593:418–423. https://doi.org/10.1038/s41586-021-03431-4.
339. Rossignol J-F. 2016. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. J Infect Public Health 9:227–230. https://doi.org/10.1016/j.jiph.2016.04.001.
340. Riccio A, Santopolo S, Rossi A, Piacentini S, Rossignol J-F, Santoro MG. 2021. Impairment of SARS-CoV-2 spike glycoprotein maturation and fusion activity by the broad-spectrum anti-infective drug nitazoxanide. bioRxiv https://www.biorxiv.org/content/10.1101/2021.04.12.439201v1.
341. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. 2020. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. Cell Res 30:269–271. https://doi.org/10.1038/s41422-020-0282-0.
342. Sales-Medina DF, Ferreira LRP, Romera LMD, Goncalves KR, Guido RVC, Courtemanche G, Buckeridge MS, Durigon EL, Moraes CB, Junior LF. 2020. Discovery of clinically approved drugs capable of inhibiting SARS-CoV-2 *in vitro* infection using a phenotypic screening strategy and network-analysis to predict their potential to treat COVID-19. bioRxiv https://www.biorxiv.org/content/10.1101/2020.07.09.196337v2.
343. Rocco PRM, Silva PL, Cruz FF, Junior MACM, Tierno P, Moura MA, De Oliveira LFG, Lima CC, Dos Santos EA, Junior WF, Fernandes APSM, Franchini KG, Magri E, de Moraes NF, Gonçalves JMJ, Carbonieri MN, Dos Santos IS, Paes NF, Maciel PVM, Rocha RP, de Carvalho AF, Alves PA, Modena JLP, Cordeiro AT, Trivella DBB, Marques RE, Luiz RR, Pelosi P, Lapa e Silva JR. 2020. Early use of nitazoxanide in mild Covid-19 disease: randomised, placebo-controlled trial. Eur Respir J https://doi.org/10.1183/13993003.03725-2020.
344. Rossignol J-F, Bardin MC, Oaks JB, Bostick BG, Vora KN, Fulgencio J, Mogelnicki D, Brechot C. 2021. Early treatment with nitazoxanide prevents worsening of mild and moderate COVID-19 and subsequent hospitalization. medRxiv https://www.medrxiv.org/content/10.1101/2021.04.19.21255441v1.
345. Shen L, Niu J, Wang C, Huang B, Wang W, Zhu N, Deng Y, Wang H, Ye F, Cen S, Tan W. 2019. High-throughput screening and identification of potent broad-spectrum inhibitors of coronaviruses. J Virol 93:e00023-19. https://doi.org/10.1128/JVI.00023-19.
346. Ko M, Chang SY, Byun SY, Ianevski A, Choi I, Pham Hung d'Alexandry d'Orengiani A-L, Ravlo E, Wang W, Bjørås M, Kainov DE, Shum D, Min J-Y, Windisch MP. 2021. Screening of FDA-approved drugs using a MERS-CoV clinical isolate from South Korea identifies potential therapeutic options for COVID-19. Viruses 13:651. https://doi.org/10.3390/v13040651.
347. Bleasel MD, Peterson GM. 2020. Emetine, ipecac, ipecac alkaloids, and analogues as potential antiviral agents for coronaviruses. Pharm Basel Switz 13:51.
348. Yang SNY, Atkinson SC, Wang C, Lee A, Bogoyevitch MA, Borg NA, Jans DA. 2020. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. Antiviral Res 177:104760. https://doi.org/10.1016/j.antiviral.2020.104760.
349. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. 2020. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. Antiviral Res 178:104787. https://doi.org/10.1016/j.antiviral.2020.104787.
350. Chaccour C, Hammann F, Ramón-García S, Rabinovich NR. 2020. Ivermectin and novel coronavirus disease (COVID-19): keeping rigor in times of urgency. Am J Trop Med Hyg 102:1156–1157. https://doi.org/10.4269/ajtmh.20-0271.
351. Schmith VD, Zhou JJ, Lohmer LRL. 2020. The approved dose of ivermectin alone is not the ideal dose for the treatment of COVID-19. Clin Pharmacol Ther 108:762–765. https://doi.org/10.1002/cpt.1889.
352. Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter J-J. 2021. Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: The ICON Study. Chest 159:85–92. https://doi.org/10.1016/j.chest.2020.10.009.
353. Kirti R, Roy R, Pattadar C, Raj R, Agarwal N, Biswas B, Manjhi PK, RD, Kumar Shyama S, Kumar A, Sarfaraz A. 2021. Ivermectin as a potential treatment for mild to moderate COVID-19: a double blind randomized placebo-controlled trial. medRxiv https://www.medrxiv.org/content/10.1101/2021.01.05.21249310v1.
354. López-Medina E, López P, Hurtado IC, Dávalos DM, Ramirez O, Martínez E, Díazgranados JA, Oñate JM, Chavarriaga H, Herrera S, Parra B, Libreros G, Jaramillo R, Avendaño AC, Toro DF, Torres M, Lesmes MC, Rios CA, Caicedo I. 2021. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. JAMA 325:1426–1435. https://doi.org/10.1001/jama.2021.3071.
355. Roman YM, Burela PA, Pasupuleti V, Piscoya A, Vidal JE, Hernandez AV. 2021. Ivermectin for the treatment of COVID-19: a systematic review and meta-analysis of randomized controlled trials. medRxiv https://www.medrxiv.org/content/10.1101/2021.05.21.21257595v2.
356. Matsuyama S, Kawase M, Nao N, Shirato K, Ujike M, Kamitani W, Shimojima M, Fukushi S. 2020. The inhaled steroid ciclesonide blocks SARS-CoV-2 RNA replication by targeting the viral replication-transcription complex in cultured cells. J Virol 95:e01648-20. https://doi.org/10.1128/JVI.01648-20.

357. Ko M, Chang SY, Byun SY, Choi I, Shum D, Min J-Y, Windisch MP, d'Orengiani A, d'Alexandry LPH. 2020. Screening of FDA-approved drugs using a MERS-CoV clinical isolate from South Korea identifies potential therapeutic options for COVID-19. bioRxiv https://www.biorxiv.org/content/10.1101/2020.02.25.965582v3.
358. Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, O'Meara MJ, Rezelj VV, Guo JZ, Swaney DL, Tummino TA, Huettenhain R, Kaake RM, Richards AL, Tutuncuoglu B, Foussard H, Batra J, Haas K, Modak M, Kim M, Haas P, Polacco BJ, Braberg H, Fabius JM, et al. 2020. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 583:459–468. https://doi.org/10.1038/s41586-020-2286-9.
359. Gordon DE, Hiatt J, Bouhaddou M, Rezelj VV, Ulferts S, Braberg H, Jureka AS, Obernier K, Guo JZ, Batra J, Kaake RM, Weckstein AR, Owens TW, Gupta M, Pourmal S, Titus EW, Cakir M, Soucheray M, McGregor M, Cakir Z, Jang G, O'Meara MJ, Tummino TA, Zhang Z, Foussard H, , et al. 2020. Comparative host-coronavirus protein interaction networks reveal pan-viral disease mechanisms. Science 370:eabe9403. https://doi.org/10.1126/science.abe9403.
360. Sukhatme VP, Reiersen AM, Vayttaden SJ, Sukhatme VV. 2021. Fluvoxamine: a review of its mechanism of action and its role in COVID-19. Front Pharmacol 12:652688. https://doi.org/10.3389/fphar.2021.652688.
361. Rosen DA, Seki SM, Fernández-Castañeda A, Beiter RM, Eccles JD, Woodfolk JA, Gaultier A. 2019. Modulation of the sigma-1 receptor–IRE1 pathway is beneficial in preclinical models of inflammation and sepsis. Sci Transl Med 11:eaau5266. https://doi.org/10.1126/scitranslmed.aau5266.
362. Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, Miller JP, Yang L, Yingling M, Avidan MS, Reiersen AM. 2020. Fluvoxamine versus placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. JAMA 324:2292–2300. https://doi.org/10.1001/jama.2020.22760.
363. Halpern SD, Karlawish JHT, Berlin JA. 2002. The continuing unethical conduct of underpowered clinical trials. JAMA 288:358–362. https://doi.org/10.1001/jama.288.3.358.
364. Grobler JA, Anderson AS, Fernandes P, Diamond MS, Colvis CM, Menetski JP, Alvarez RM, Young JAT, Carter KL. 2020. Accelerated preclinical paths to support rapid development of COVID-19 therapeutics. Cell Host Microbe 28:638–645. https://doi.org/10.1016/j.chom.2020.09.017.
365. Galindez G, Matschinske J, Rose TD, Sadegh S, Salgado-Albarrán M, Späth J, Baumbach J, Pauling JK. 2021. Lessons from the COVID-19 pandemic for advancing computational drug repurposing strategies. Nat Comput Sci 1:33–41. https://doi.org/10.1038/s43588-020-00007-6.
366. Sadegh S, Matschinske J, Blumenthal DB, Galindez G, Kacprowski T, List M, Nasirigerdeh R, Oubounyt M, Pichlmair A, Rose TD, Salgado-Albarrán M, Späth J, Stukalov A, Wenke NK, Yuan K, Pauling JK, Baumbach J. 2020. Exploring the SARS-CoV-2 virus-host-drug interactome for drug repurposing. Nat Commun 11:3518. https://doi.org/10.1038/s41467-020-17189-2.
367. Bojkova D, Klann K, Koch B, Widera M, Krause D, Ciesek S, Cinatl J, Münch C. 2020. Proteomics of SARS-CoV-2-infected host cells reveals therapy targets. Nature 583:469–472. https://doi.org/10.1038/s41586-020-2332-7.
368. Plackett B. 2020. Why big pharma has abandoned antibiotics. Nature 586:S50–S52. https://doi.org/10.1038/d41586-020-02884-3.
369. Viasus D, Paño-Pardo JR, Pachón J, Riera M, López-Medrano F, Payeras A, Fariñas MC, Moreno A, Rodríguez-Baño J, Oteo JA, Ortega L, Torre-Cisneros J, Segura F, Carratalà J, Novel Influenza A(H1N1) Study Group of the Spanish Network for Research in Infectious Diseases (REIPI). 2011. Timing of oseltamivir administration and outcomes in hospitalized adults with pandemic 2009 influenza A(H1N1) virus infection. Chest 140:1025–1032. https://doi.org/10.1378/chest.10-2792.
370. Aoki FY, Macleod MD, Paggiaro P, Carewicz O, El Sawy A, Wat C, Griffiths M, Waalberg E, Ward P, on behalf of the IMPACT Study Group. 2003. Early administration of oral oseltamivir increases the benefits of influenza treatment. J Antimicrob Chemother 51:123–129. https://doi.org/10.1093/jac/dkg007.
371. Fischer WA, Eron JJ, Jr, Holman W, Cohen MS, Fang L, Szewczyk LJ, Sheahan TP, Baric RS, Mollan KR, Wolfe CR, Duke ER, Azizad MM, Borroto-Esoda K, Wohl DA, Loftis AJ, Alabanza P, Lipansky F, Painter WP, 2021. Molnupiravir, an oral antiviral treatment for COVID-19. medRxiv. https://doi.org/10.1101/2021.06.17.21258639.
372. Horby PW, Mafham M, Peto L, Campbell M, Pessoa-Amorim G, Spata E, Staplin N, Emberson JR, Prudon B, Hine P, Brown T, Green CA, Sarkar R, Desai P, Yates B, Bewick T, Tiberi S, Felton T, Baillie JK, Buch MH, Chappell LC, Day JN, Faust SN, Jaki T, Jeffery K, Juszczak E, Lim WS, Montgomery A, Mumford A, Rowan K, Thwaites G, Weinreich DM, Haynes R, Landray MJ, 2021. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. medRxiv. https://doi.org/10.1101/2021.06.15.21258542.

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