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Review

Insights into biological therapeutic strategies for COVID-19

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ABSTRACT

The worldwide pandemic of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged in late December 2019 requires the urgent development of therapeutic options. So far, numerous studies have investigated and uncovered the underlying epidemiology and clinical characteristics of COVID-19 infections in order to develop effective drugs. Compared with antiviral small-molecule inhibitors, biotherapeutics have unique advantages such as fewer side effects by virtue of their high specificity, and thus can be rapidly developed for promising treatments of COVID-19. Here, we summarize potential biotherapeutics and their mechanisms of action, including convalescent plasma, therapeutic antibodies, peptides, engineered ACE2, interferons, cytokine inhibitors, and RNAi-based therapeutics, and discuss in depth the advancements and precautions for each type of biotherapeutics in the treatment of COVID-19.

1. Introduction

In late December 2019, a previously undetermined acute respiratory disease called coronavirus disease 2019 (COVID-19) emerged, which is caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) [1]. By March 11, 2020, COVID-19 was declared a pandemic by the World Health Organization, and at the time of this publication, resulted in over 44,000,000 infections and more than 1100,000 deaths worldwide (http://covid19.who.int) [2]. SARS-CoV-2 is an enveloped positive-sense RNA virus and belongs to the lineage B betacoronavirus that also includes the highly pathogenic coronaviruses MERS-CoV and SARS-CoV. Based on the phylogenetic analysis, SARS-CoV-2 shares high sequence identity with that of SARS-like coronaviruses (89.1% nucleotide similarity) and SARS-CoV (79% nucleotide similarity) [3, 4]. Like other coronaviruses, the structure of SARS-CoV-2 is composed of 16 nonstructural proteins (Nsps) (Nsp1–16), 5–8 accessory proteins, and 4 structural proteins including the spike (S), membrane (M), envelope (E) and nucleocapsid (N) proteins (Fig. 1a, b) [5]. The S protein is a heavily glycosylated type I membrane protein and uniformly arranged as trimers anchored in the viral membrane [6]. The trimeric S protein consists of two fragments: the receptor-binding fragment S1 and the fusion fragment S2 (Fig. 1a) [7], and is crucial for viral fusion, entry, and transmission.

The critical step for SARS-CoV-2 entering host cells and establishing infection is receptor binding and membrane fusion. The receptor-binding domain (RBD) of S1 interacts directly with angiotensin converting enzyme 2 (ACE2) on the surface of host cells [8]. The S protein is naturally in a closed conformation while the helices in the S2 component are capped by the neighboring RBD. Following cleavage by furin between the S1 and S2 domains, S trimers are able to accommodate the RBD in an open, ACE2-binding conformation [9]. Binding of the ACE2 receptor to open the RBD leads to a more open trimer conformation. Then, the S2 fusion region is exposed and inserted into the host cell membrane [10, 11], priming the internalization of SARS-CoV-2 into host cells by receptor mediated endocytosis [12]. Once inside the host cell endosomal compartment, there is an increase in H^+ influx into the endosome which activates cathepsin L to facilitate viral membrane fusion and release of RNA out of the endosome. Alternatively, following recognition by ACE2, proteolytic cleavage of the S protein by type II transmembrane serine protease (TMPRSS2) on the surface of host cell can induce direct fusion of the viral and plasma membranes leading to release of the viral RNA into the cytoplasm [13]. Next, polyproteins, such as pp1a and pp1ab, are translated, and cleaved by the Papain-like protease (Pl pro) and 3C-like protease (3CL pro) to form functional Nsps as a helicase or the RNA replicase-transcriptase complex (RdRp) [14]. Using these viral replicative enzymes, the viral RNA acts as a messenger RNA (mRNA) and then generates new RNA and the mRNAs for SARS-CoV-2 genome replication. RNA polymerization also relies on the RdRp. Subsequently, structure proteins of SARS-CoV-2 are translated by RdRp [15], and fuse with the virus precursor which is then transported from the endoplasmic reticulum through the Golgi apparatus to the cell surface via small vesicles. Finally, SARS-CoV-2 is released from the infected cell through exocytosis and can infect other host cells (Fig. 2) [13]. Noteworthily, increasing mutations occurring within the S protein-encoded genome have been detected. Among them, D614G shows fitness advantage and increases infectivity of the SARS-CoV-2, but not with disease severity [16]. Double mutations containing not only D614G but also P1263L,

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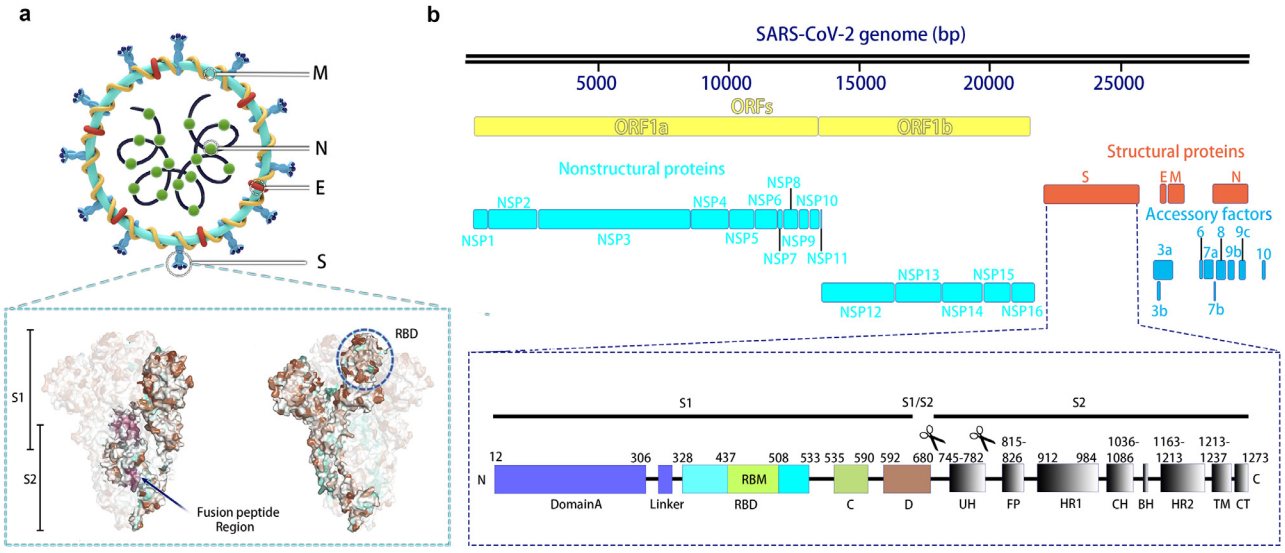

Fig. 1. Schematic representation of SARS-CoV-2 and construct of the spike protein. (a) Structure of SARS-CoV-2. (b) SARS-CoV-2 genome annotation. The regions of genome encoding 16 nonstructural proteins (cyan), 4 structural proteins (red), and 9 accessory factors (blue), as well as subunits contained in the S protein are displayed in proportion.

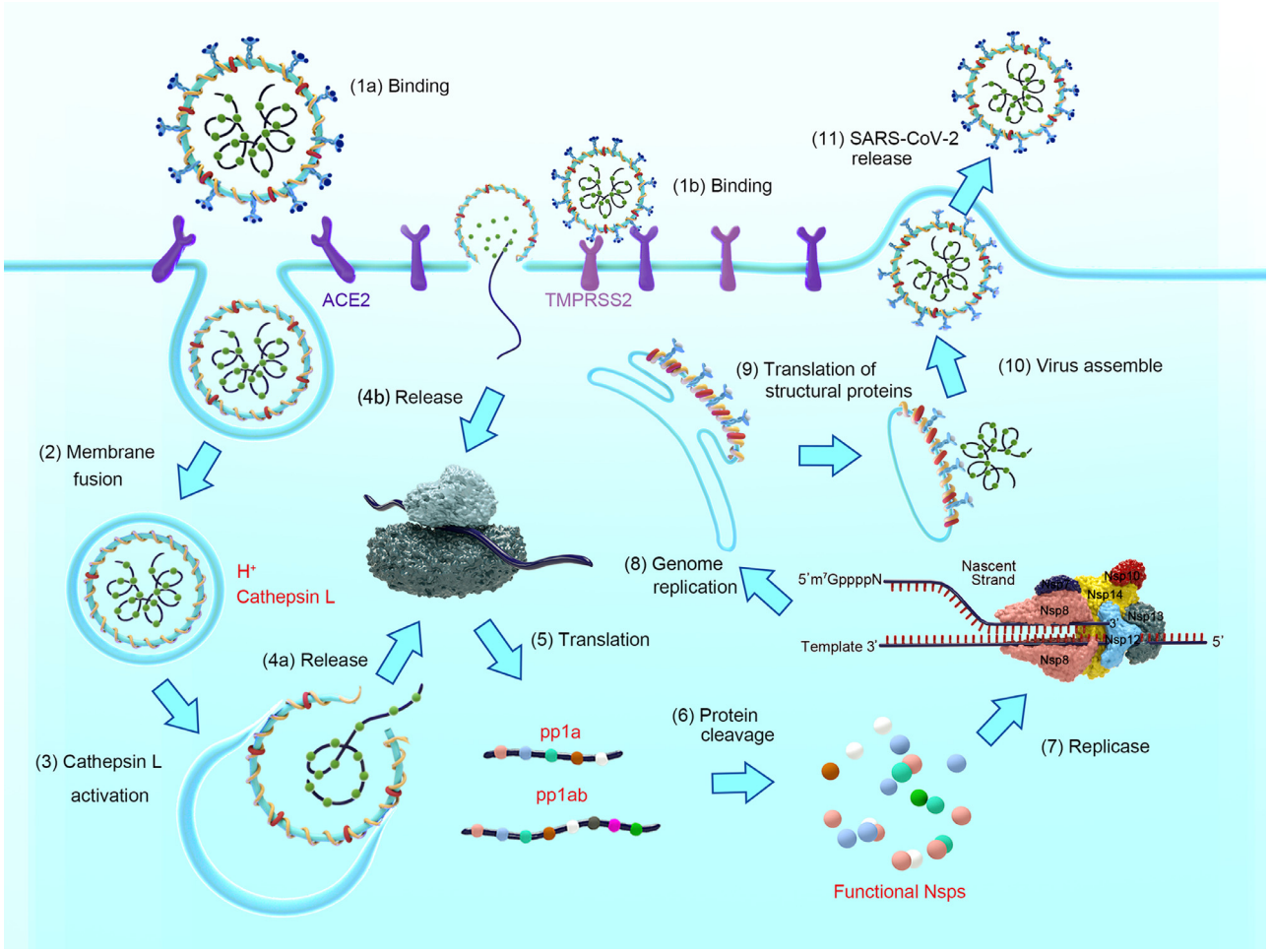

Fig. 2. Life cycle of SARS-CoV-2. For SARS-CoV-2 entering host cells and establishing infection, the S1 subunit of spike protein firstly binds to the ACE2 receptor (1a). Through conformational change, the virus is then internalized by receptor mediated endocytosis (2). Subsequently, increasing H^+ influx activates cathepsin L (3), which facilitates viral membrane fusion and release of RNA out of the endosome (4a). Alternatively, following recognition by ACE2, proteolytic cleavage of the spike protein by TMPRSS2 on the surface of the host cell (1b) induces direct fusion of the viral and cellular membranes and then leads to release of the viral RNA into the cytoplasm (4b). The viral RNA is then translated to produce the polyproteins pp1a and pp1ab (5), which are cleaved (6) to yield the 16 NSPs that form the RNA replicase-transcriptase complex (7) for the genome replication (8). The viral mRNA encoding structural proteins is then transcribed (9) for the final virus assemble (10). In the end, the new virion is released (11).

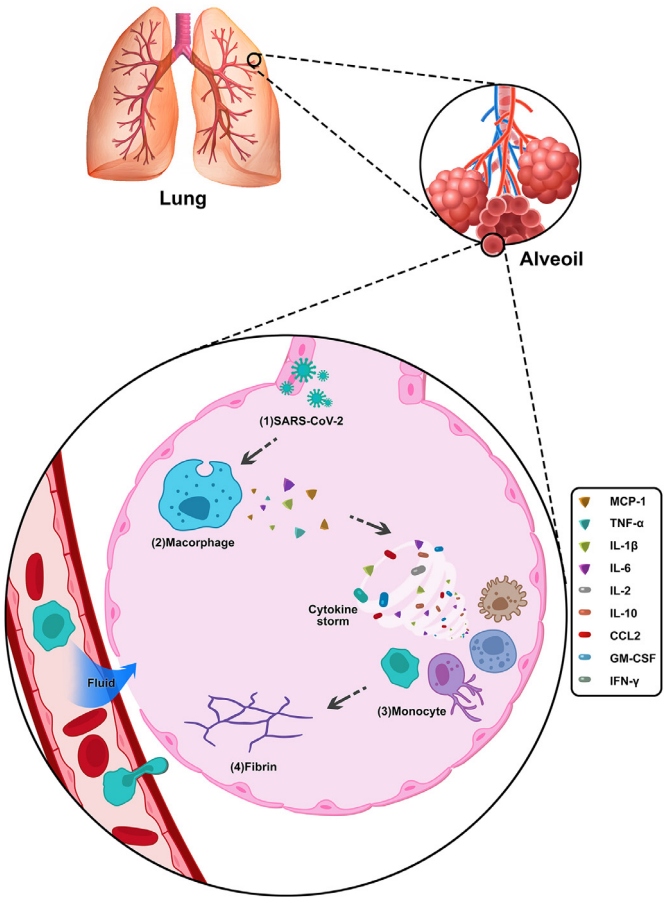

Fig. 3. Cytokine storm induced by SARS-CoV-2. The infection of SARS-CoV-2 in the lung (1) induces increased plasma concentrations of inflammatory cytokines and chemokines, secreted by immune cells, such as macrophages (2), T-lymphocytes and dendritic cells (3), and ultimately leads to the inflammatory cytokine storm (4).

S943T, S939F, D936F, I472V, K458R, V341I, or L5F, as well as the single mutation A520S are also significantly more infectious, whereas most variants with amino acid change at RBD are less infectious, and V341I and investigational glycosylation mutant (N331Q+N343Q) have no infectivity [17].

SARS-CoV-2 infection in humans can be asymptomatic or result in a range of mild to fatal disease [18]. Generally, COVID-19 patients with pneumonia present with fever, fatigue, dyspnea and a cough [19]. During infection, a local immune response is triggered by damaged lung cells. Clinical reports revealed that $CD4^+$ T cells are rapidly activated to form pathogenic T helper (Th) 1 cells and produce granulocyte-macrophage colony-stimulating factor (GM-CSF). In most COVID-19 infections, increased plasma concentrations of inflammatory cytokines, such as interleukins (IL-2, IL-7, IL-10), chemokine CCL2 and TNF-α, are found, especially in critically ill patients [20–22]. Moreover, these cytokines contribute to $CD14^+$ and $CD16^+$ monocyte recruitment and IL-6 secretion, which further aggravate the inflammatory response (Fig. 3) [23]. In severe COVID-19 infections, the overreactive immune response results in cytokine storm and development of severe acute respiratory distress syndrome (ARDS), which can cause respiratory failure, multi-organ failure, and death [2].

As an airborne virus, SARS-CoV-2 is transmitted through respiratory droplets and aerosols [24]. Moreover, SARS-CoV-2 infection can be asymptomatic, particularly in the younger population [25], and highly contagious before symptom onset [26]. These altogether contribute to the spread of SARS-CoV-2 worldwide and make it more challenging to curb SARS-CoV-2 transmission compared to other respiratory viruses [27,28]. Current clinical management of COVID-19 largely relies on infection prevention and supportive care. Epidemiological research showed that universal masking, extending social distancing and timely identification of infected individuals are the most effective preventive strategies in reducing the spread of COVID-19 [29]. Generally, 80% of patients with COVID-19 recover within 1 to 3 weeks without specific treatment. However, ~20% of patients rapidly deteriorate within ~7 to 10 days after symptom onset, and a small proportion (~5%) develop severe illness such as ARDS, ultimately resulting in death even under proper supportive care, which constitute a significant health and economic burden [30]. Thus, there is a critical need to develop vaccines and drugs to protect against and treat COVID-19.

Antifibrotic therapy is deemed to be effective in attenuating the progress of fibrosis and the progressive decline of lung function in COVID-19 patients when used early in SARS-CoV-2 infection [31]. A phase III trial showed that pirfenidone, an antifibrotic drug, reduced disease progression in patients with idiopathic pulmonary fibrosis, yet with no significant differences in dyspnea scores or rates of death when compared with the placebo group (NCT01366209). As an agonist of angiotensin II receptor type 2 that had been proved for inhibiting experimental acute lung injury and IL-6 expression [32], C21 has been approved for a phase II study in COVID-19 (EudraCT 2017–004923–63). Corticosteroid compound, a type of anti-inflammatory drug, has also been suggested as a potential drug against the COVID-19, in light of that ciclesonide suppressed SARS-CoV-2 replication in cultured cells [33] and COVID-19 patients receiving dexamethasone showed significantly lower mortality and hospitalization duration than controls [34]. The antiviral drugs such as remdesivir, chloroquine, hydroxychloroquine, lopinavir/ritonavir, ribavirin, favipinavir and umifenovir, have been considered as attractive options for COVID-19 therapy [35]. Among them, remdesivir, the first treatment for COVID-19 approved by FDA, was able to shorten the time to recovery from mild to fatal COVID-19 infections (NCT04280705), improve clinical status with five-day injection in moderate COVID-19 patients (NCT04292730), but couldn't change recovery rates or mortality rates in severe COVID-19 patients (NCT04292899). Similarly, chloroquine was highly effective in the control of SARS-CoV-2 *in vitro* [36], yet administration of hydroxychloroquine showed higher adverse events and a non-significantly higher probability of negative conversion than in non-recipients [37, 38]. The combination use of antiviral drugs with traditional Chinese medicines has been found effective against the COVID-19 infection [39].

Unlike most conventional drugs, biotherapeutics present higher potency and fewer side effects because of their high specificity. Biotherapeutics targeting COVID-19 have been rapidly developed and show promising clinical outcomes. In this review, we will review COVID-19 biotherapeutics involved in blocking viral fusion and entry, degrading the viral genome, preventing viral replication, enhancing antiviral innate immunity, and ameliorating the inflammatory cytokine storm.

2. Convalescent plasma

Convalescent plasma collected from recovered patients have been employed for over a hundred years for the treatment of many viral infections with varying degrees of clinical efficacy. During the outbreaks of Ebola virus in 2014 and MERS-CoV in 2015, convalescent whole blood or plasma was recommended by WHO as an empirical treatment [40, 41]. Convalescent plasma treatment for SARS and severe influenza also appears safe and reduces mortality, especially if administered early in the illness [42]. For COVID-19, five patients at the Shenzhen Third People's Hospital in Shenzhen, China, were first treated with convalescent plasma, and all five patients were discharged or stable from respiratory failure following the transfusion. The second study in ten patients with severe disease reported that three had been discharged and the others were ready for discharge following transfusion. In contrast, among ten matched historical controls with similar baseline characteristics, three died, one improved and six stabilized. Liu et al. [43] performed a

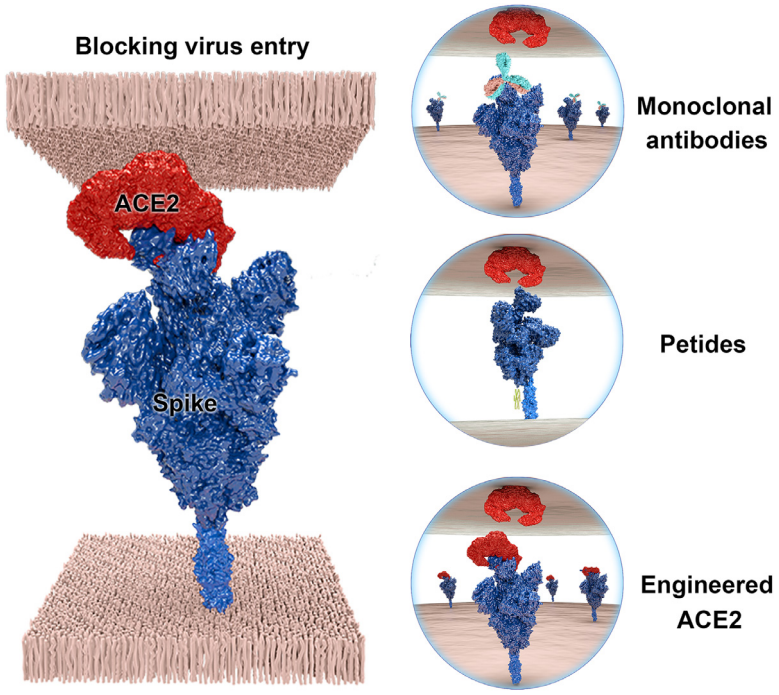

Fig. 4. Schematic diagram of blocking SARS-CoV-2 entry. The strategies to prevent the SARS-CoV-2 entry into host cells mainly contain therapeutic antibodies, peptide inhibitors, and engineered ACE2.

propensity score-matched case-control study to assess the effectiveness of convalescent plasma therapy in 39 patients, and results showed that supplemental oxygen requirements were reduced with increased survival in plasma recipients compared to the matched controls. The mass convalescent plasma clinical trials have since been initiated; however, many hospitals deployed convalescent plasma without clinical support data, mostly due to the urgency of the pandemic [44].

It is worth noting that the plasma component can differ significantly among convalescent patients. The viral neutralization titer of collected plasma against SARS-CoV-2 should be measured before treatment. Otherwise, transfusions of plasma without neutralizing antibodies will have no impact on treatment [45], and may even result in adverse immune responses caused by non-specific antibodies. Therefore, more large-scale clinical trials still need to be conducted for the evaluation of curative effects. Moreover, due to limited sources, convalescent plasma should only be used in emergency cases.

3. Therapeutic antibodies

The antiviral activity of antibodies is mediated by the inhibition of viral entry into host cells (neutralization) and by the effector functions of antibodies as they recruit other components of the immune response (Fig. 4) [46, 47]. Human monoclonal antibodies are the most common therapeutic strategy for human viral infections due to their high specificity, strong neutralizing activity and potentially low immunogenicity. Trimeric S protein exposed on the viral surface, which mediates receptor binding and viral entry into host cells, is a dominant target for SARS-CoV-2 neutralizing antibodies [11]. Currently, multiple SARS-CoV-2 specific monoclonal antibodies against the S protein have been developed, and three monoclonal antibodies have been evaluated in Phase III trials (Table 1). However, no therapeutic antibodies have been approved to treat COVID-19 to date.

3.1. Broadly neutralizing antibodies isolated from SARS-CoV infected subjects

The S protein shares high sequence similarity between SARS-CoV-2 and SARS-CoV, suggesting the possibility of conserved immunogenic surfaces on the RBD domain recognized by cross-neutralizing antibodies. One antibody (named S309), potently neutralizing SARS-CoV-2 and SARS-CoV pseudoviruses as well as authentic SARS-CoV-2 [48], was engineered to have a longer half-life and is currently in a phase III clinical trial, known as VIR-7831 and VIR-7832.

Besides, some of the broadly neutralizing antibodies were effective *in vitro*. A previously identified SARS-CoV-specific human monoclonal antibody from a convalescent SARS patient [49], CR3022, was confirmed to bind potently to the SARS-CoV-2 RBD [50]. The neutralizing activity of CR3022 against SARS-CoV-2 has not been conclusively defined, although one study reported neutralization through destruction of the prefusion S protein conformation [51]. In another study, H2L2 mice were immunized with the S protein of human coronavirus OC43 (HCoV-OC43), SARS-CoV, and MERS-CoV, which resulted in the identification of one monoclonal antibody, 47D11, with cross-neutralizing activity against SARS-CoV-2 and SARS-CoV [52]. Several monoclonal antibodies have also been identified that target the S glycoprotein of SARS-CoV-2 from memory B cells of an individual who was infected with SARS-CoV in 2003 [48]. Similarly, using single B-cell sorting, multiple human monoclonal antibodies against the viral S protein of SARS-CoV-2 were isolated from the memory B cells of a survivor infected with SARS-CoV [53]. Eight RBD-targeted antibodies showed potent and broad neutralization against SARS-CoV-2, SARS-CoV, and representative SARS-like virus WIV1 by blocking receptor attachment and inducing S1 shedding, as demonstrated by cryogenic electron microscopy (cryo-EM) structure [53].

3.2. Neutralizing antibodies isolated from SARS-CoV-2 infected individuals

SARS-CoV-2 infected patients produce SARS-CoV-2 specific antibodies, which can be rapidly isolated to develop therapeutic neutralizing antibodies. Several of them have been developed and tested in clinical trials. Human monoclonal antibody CB6 was collected from recovered COVID-19 patients using SARS-CoV-2 RBD as the antigen. It can strongly neutralized SARS-CoV-2 with an IC_{50} of 0.036 μg/mL. Moreover, CB6 greatly decreased the viral load in the respiratory tract of SARS-CoV-2-infected rhesus monkeys [54] and has entered a phase II clinical trial in China and USA with the name as JS016. A cocktail of

Table 1
Neutralizing antibodies for SARS-CoV-2.

mAb name	Screening method	Affinity (K_D)	Neutralizing activity)IC_{50}(SARS-CoV-2	Neutralizing activity)IC_{50}(SARS-CoV	Binding region of S protein	Competing epitope	Anti-viral activity in animal model	Clinical trials /Ref
47D11 chimeric human IgG	SARS-S hybridoma derived from immunized transgenic H2L2 mice	S1: 10.8 ± 2.46 nM $S1_B$: 9.56±2.68 nM	Pseudoviruses: 0.08 μg/mL Authentic viruses: 0.57 μg/mL	Pseudoviruses: 0.06 μg/mL Authentic viruses: 0.19 μg/mL	$S1_B$	Non-ACE2-competing	N/A	[52]
S309 human IgG	SARS-CoV-2-reactive memory B cell from convalescent SARS-CoV patients	S1: 0.0428 nM $S1_B$: 1 pM	Pseudoviruses: 0.24 μg/mL Authentic viruses: 0.079 μg/mL	Pseudoviruses: 0.12–0.18 μg/mL	$S1_B$	Non-ACE2-competing	N/A	[48]NCT04545060
P2B-2F6, P2C-1F11 human IgG	Single cell sorting of convalescent SARS-CoV-2 patients	$S1_B$: 5.14 nM	Pseudoviruses: 0.05,0.03 μg/mL Authentic viruses: 0.41,0.03 μg/mL	N/A	$S1_B$	ACE2-competing	N/A	[64]
CB6 human IgG	Single cell sorting of SARS-CoV-2 infected patients	$S1_B$: 2.49 nM	Authentic viruses: 0.036 μg/mL	N/A	RBS	ACE2-competing	Prophylactic and therapeutic in rhesus monkeys at 50 mg/kg	[54] NCT04292340, NCT04327349, NCT04321421
BD-368–2, BD-629 human IgG	High-throughput single-cell sequencing of convalescent Patients' B Cells	$S1_B$: 0.82 nM 0.78 nM	Pseudoviruses: 1.2 ng/mL 6 ng/mL Authentic viruses: 15 ng/mL	N/A	RBM	ACE2-competing	Prophylactic and therapeutic in hACE2 mice at 20 mg/kg	[61, 127]
CC12.1 human IgG	Single cell sorting of SARS-CoV-2 infected patients	N/A	Pseudoviruses: 0.019 μg/mL	N/A	$S1_B$	ACE2-competing	Prophylactic in hamster at 16.5 mg/kg	[63]
4A8 human IgG	Single cell sorting of SARS-CoV-2 infected patients	S1: 92.7 nM S-ECD 0.996 nM	Pseudoviruses: 49 μg/mL Authentic viruses: 0.61 μg/mL	N/A	NTD	Non-ACE2-competing	N/A	[67]
ADI-55,689, 56,046 human IgG	SARS-CoV-2-reactive memory B cell from convalescent SARS-CoV patients	N/A	Pseudoviruses: ~0.1 μg/mL Authentic viruses: ~0.1 μg/mL	Pseudoviruses& Authentic viruses: ADI-55,689: ~0.01 μg/mL ADI-56,046: ~0.05 μg/mL	$S1_B$	ACE2-competing ADI-56,046: ACE2 &CR3022-competing	N/A	[53]
ADI-55,690 human IgG	SARS-CoV-2-reactive memory B cell from convalescent SARS-CoV patients	N/A	Pseudoviruses: ~1 μg/mL Authentic viruses: ~10 μg/mL	Pseudoviruses: ~0.05 μg/mL Authentic viruses: ~0.05 μg/mL	$S1_B$	ACE2-competing& CR3022-competing	N/A	[53]
ADI-56,010 human IgG	SARS-CoV-2-reactive memory B cell from convalescent SARS-CoV patients	N/A	Pseudoviruses: ~0.5 μg/mL Authentic viruses: ~1 μg/mL	Pseudoviruses& Authentic viruses: ~0.05 μg/mL	$S1_B$	ACE2-competing& CR3022-competing	N/A	[53]
ADI-55,951 human IgG	SARS-CoV-2-reactive memory B cell from convalescent SARS-CoV patients	N/A	Pseudoviruses: ~1 μg/mL Authentic viruses: ~5 μg/mL	Pseudoviruses& Authentic viruses: ~0.01 μg/mL	$S1_B$	ACE2-competing& CR3022-competing	N/A	[53]
H014 chimeric human IgG	Biopanning of scFv phage-display library	$S1_B$: 0.096 nM	Pseudoviruses: 3 nM Authentic viruses: 38 nM	Pseudoviruses: 1 nM	$S1_B$	ACE2-competing	Prophylactic in hACE2 mice at 50 mg/kg	[68]

(*continued on next page*)

Table 1 (*continued*)

mAb name	Screening method	Affinity (K_D)	Neutralizing activity)IC_{50}(SARS-CoV-2	Neutralizing activity)IC_{50}(SARS-CoV	Binding region of S protein	Competing epitope	Anti-viral activity in animal model	Clinical trials /Ref
REGN10933 human IgG	Single cell sorting of both spike and RBD immunized humanized mice and convalescent patients	S1: 4.17 nM $S1_B$: 3.37 nM	Pseudoviruses: 0.0428 nM Authentic viruses: 0.0374 nM	N/A	$S1_B$	ACE2-competing	N/A	[55] NCT04426695 and NCT04425629
REGN10987 human IgG	Single cell sorting of both spike and RBD immunized humanized mice and convalescent SARS-CoV-2 patients	S1: 0.0428 nM $S1_B$: 45.2 nM	Pseudoviruses: 0.0406 nM Authentic viruses: 0.0421 nM	N/A	$S1_B$	Non-ACE2-competing	N/A	[55] NCT04426695 and NCT04425629
CV30 human IgG	Single cell sorting of SARS-CoV-2 infected patients	$S1_B$: 3.63 nM	Pseudoviruses: 0.03 μg/mL	N/A	$S1_B$	ACE2-competing	N/A	[128]
B38, H4 human IgG	Single cell sorting of SARS-CoV-2 infected patients	$S1_B$: 70.1 nM 4.48 nM	Authentic viruses: 0.177 μg/mL 0.896 μg/mL	N/A	$S1_B$	ACE2-competing	Therapeutic in hACE2 mice at 25 mg/kg	[65]
CV07–209 human IgG	Single cell sorting of SARS-CoV-2 infected patients	$S1_B$: 2.5 nM	Authentic viruses: 3.1 ng/mL	N/A	$S1_B$	ACE2-competing	Prophylactic and therapeutic in hamster at 18 mg/kg	[129]
W25 alpaca V_HH	*E. coli* surface-displayed V_HH library derived from immunized alpaca	$S1_B$: 0.295 nM	Authentic viruses: 9.82 nM D614G variant authentic viruses: 5.09 nM	N/A	$S1_B$	ACE2-competing	N/A	[69]
Sb23 humanized llama VH	Biopanning of synthetic nanobodies library	S1: 4.9 nM	Pseudoviruses: 0.6 μg/mL	N/A	RBS	ACE2-competing	N/A	[70]
Nb11–59 llama V_HH	Biopanning from a phage displayed libraries derived from immunized camels	$S1_B$: 21.6 nM	Authentic viruses: 0.55 μg/mL	N/A	$S1_B$	ACE2-competing	N/A	[71]
MR3 humanized V_HH	Biopanning from a ribosome and phage displayed synthetic nanobodies library	$S1_B$: 1 nM	Pseudoviruses: 0.4 μg/mL	N/A	$S1_B$	ACE2-competing	N/A	[72]
n3130 human VH	Biopanning from a fully human VH phage displayed library	S1: 55.39 nM	Pseudoviruses: 0.7 μg/mL Authentic viruses: 15 μg/mL	N/A	$S1_B$	Non-ACE2-competing & CR3022-competing	N/A	[73]
n3088 human VH	Biopanning from a phage-displayed fully human VH library	S1: 3.7 nM	Pseudoviruses: 0.51 μg/mL Authentic viruses: 15 μg/mL	N/A	$S1_B$	Non-ACE2-competing & CR3022-competing	N/A	[73]
V_H-Fc ab8 human VH fused to Fc	Biopanning from a phage-displayed fully human VH library	$S1_B$: 0.54 nM	Pseudoviruses: 0.03 μg/mL Authentic viruses: 0.04 μg/mL	N/A	$S1_B$	ACE2-competing	Prophylactic in mice at 8 mg/kg & prophylactic and therapeutic in hamster at 10 mg/kg	[74]

(*continued on next page*)

Table 1 (*continued*)

mAb name	Screening method	Affinity (K_D)	Neutralizing activity)IC_{50}(SARS-CoV-2	Neutralizing activity)IC_{50}(SARS-CoV	Binding region of S protein	Competing epitope	Anti-viral activity in animal model	Clinical trials /Ref
Trivalent Nb6 humanized V_HH	Biopanning from a yeast surface-displayed synthetic nanobody library	S1: < 1 pM	Pseudoviruses: 1.2 nM Authentic viruses: 0.16 nM	N/A	$S1_B$	ACE2-competing	N/A	[75]
Nbs 21 llama V_HH	Panning from an immunized camel through proteomics	$S1_B$: < 1 pM	Pseudoviruses: 0.7 ng/mL Authentic viruses: 0.3 ng/mL	N/A	$S1_B$	ACE2-competing	N/A	[76]
VHH-72-Fc llama V_HH fused to Fc	Panning from a phage-displayed library of immunized llama	N/A	Pseudoviruses: 0.2 μg/mL	Neutralize pseudoviruses	$S1_B$	ACE2-competing	N/A	[77]
Ty1 llama V_HH	Biopanning from a phage-displayed library of immunized llama	$S1_B$: 5–10 nM	Pseudoviruses: 0.77 μg/mL	N/A	$S1_B$	ACE2-competing	N/A	[78]
H11-H4-Fc llama V_HH fused to Fc	Biopanning from a phage-displayed library of llama	N/A	Authentic viruses: 4 nM	N/A	$S1_B$	ACE2-competing	N/A	[79]

N/A: not available.

two potent neutralizing antibodies, REGN10987 and REGN10933, targeting non-overlapping epitopes on the SARS-CoV-2 S protein, were derived from genetically humanized mice immunized by SARS-CoV-2 protein and convalescent humans, respectively [55]. These two antibodies can greatly reduce viral load in lower and upper airways and decrease virus induced pathological sequelae when administered prophylactically or therapeutically in rhesus macaques. Similarly, administration in hamsters decreases lung titers and evidence of pneumonia in the lungs [56]. This antibody cocktail is one of the most potent therapeutic antibodies against SARS-CoV-2 with low pM activity and is being evaluated in a phase III clinical trial. Baum et al. tested natural variants and possible emergence of escape mutants following antibody treatment, indicating that a combination of antibodies binding to distinct and non-overlapping regions of the viral target is a powerful way to minimize mutational escape [57]. To tackle the escaping SARS-CoV-2 variants that may emerge, various epitope-targeted antibodies should be developed and combined as therapeutics. Many natural mutations have already been identified in the spike protein of SARS-CoV-2 (https://bigd.big.ac.cn/ncov/variation/statistics?lang=en). Among them, a variant with the D614G mutation has rapidly become the dominant pandemic form probably due to its fitness advantage [58]. Indeed, the emergence of antibody or convalescent plasma-resistant SARS-CoV-2 variants has been confirmed [59, 60]. Therefore, antibody cocktails are a promising strategy to decrease the potential for the emergence of virus escape mutants.

There are also a number of antibodies that have shown protective efficacy in animal models. A group isolated 8558 antigen-binding $IgG1^+$ clonotypes from 60 convalescent patients, and 14 potent neutralizing antibodies were identified, with the most potent one, BD-368–2, targeting an ACE2 binding site and exhibiting an IC_{50} of 1.2 and 15 ng/mL against pseudotyped and authentic SARS-CoV-2, respectively. BD-368–2 also displayed strong therapeutic and prophylactic efficacy in SARS-CoV-2-infected hACE2-transgenic mice [61]. A combination of BD-368–2 and BD-629 represents a potent cocktail of two distinct epitope-binding antibodies and can rescue mutation-induced neutralization escapes of BD-368–2 [62]. Another study also reported the identification of over 1800 antibodies from a cohort of SARS-CoV-2 recovered participants using a novel high-throughput antibody discovery platform. One human monoclonal antibody (mAb) CC12.1 has an *in vitro* IC_{50} neutralization of 0.019 μg/mL and provides protection against SARS-CoV-2 infection in Syrian hamsters [63].

Moreover, numerous SARS-CoV-2 antibodies have been identified by neutralization assays *in vitro*. Ju et al. isolated 206 RBD-specific antibodies from eight individuals infected with SARS-CoV-2, and three monoclonal antibodies displayed neutralization against authentic SARS-CoV-2. The most potent antibody, P2C-1F11, neutralized authentic SARS-CoV-2 with an IC_{50} value of 0.03 μg/mL by blocking the interaction of RBD and ACE2 [64]. The antibody is not cross-reactive with SARS-CoV. RBD-specific mAbs H4 and B38 were isolated from a convalescent patient and found to inhibit viral infection by blocking the RBD from binding to ACE2. Since H4 and B38 bind to different epitopes, the two antibodies can bind simultaneously and exhibit additive viral inhibition effects [65]

In some coronaviruses, the N-terminal domain (NTD) may recognize specific sugar moieties upon initial attachment and might play an important role in the pre-fusion to post-fusion transition of the S protein. The NTD of the MERS-CoV S protein can serve as a critical epitope for neutralizing antibodies [66]. So far, several SARS-CoV-2 neutralizing antibodies against NTD also have been isolated from convalescent patients [53, 67]. For example, a fully human neutralizing mAb, 4A8, recognizes a vulnerable epitope of the NTD on the S protein of SARS-CoV-2 and acts through a mechanism that is independent of receptor binding inhibition but may restrain the conformational changes of the S protein. These NTD-targeting antibodies may be useful for combining with RBD-targeting antibodies in therapeutic cocktails.

3.3. Neutralizing antibodies isolated from phage-displayed library

Phage-display technology has also been applied in the biopanning of SARS-CoV-2 antibodies. H014, screened from a scFv phage-display library that was prepared from the mice immunized with recombinant

SARS-CoV RBD, prevents attachment of SARS-CoV-2 to ACE2, and protects against SARS-CoV-2 in the ACE2 humanized mouse model [68].

An attractive alternative for mAbs is single-domain antibodies from camelid immunoglobulins, termed VHH, or nanobody (Nb), which are the smallest naturally occurring antibody with a molecular weight of 12–15 kilodaltons (kDa). The small size and favorable biophysical characteristics make nanobodies particularly suitable for the treatment of the respiratory diseases COVID-19 by inhaled delivery. Fully human Nbs W25 [69], Sb23 [70], Nb11–59 [71], and MR3 [72] were found to potently bind to the SARS-CoV-2 RBD and neutralize SARS-CoV-2 infection by blocking the RBD-ACE2 interaction. Fully human Nbs n3088 and n3130, which were found to be synergistic with n3113, neutralize SARS-CoV-2 by targeting a cryptic epitope located in the spike trimeric interface, demonstrating the advantage of the small-size of Nbs [73]. By directly interfering with ACE2 binding, the fully human bivalent ab8 [74], trivalent Nb6 [75], Nb20 and Nb21 [76] exhibited higher avidity to the S protein, and correlated with a stronger neutralization of SARS-CoV-2 than the respective monomeric Nbs. VHH-72 [77], Ty1[78], H11-D4 and H11-H4 [79], isolated from dromedary llamas or alpaca, recognize epitopes on the RBD and have been demonstrated to neutralize pseudotyped and/or authentic SARS-CoV-2. In light of the discovery that Nb can be humanized to reduce the risk of immunogenicity [80], multimerize or cooperate with other mAbs by a variety of means to enhance half-life and avidity [81], and expressed in high quantities in bacteria or yeast, Nb is an excellent candidate for COVID-19 treatment from a biopharmaceutical manufacturing perspective.

With such a great number of SARS-CoV-2 antibodies developed, some characteristics of SARS-CoV-2 neutralizing antibodies have also been discovered. Some studies found that neutralizing mAbs targeting SARS-CoV-2 S protein are minimally mutated [82] and show little somatic mutation over time [83]. For instance, it was found that the immunoglobulin heavy-chain variable region 3–53 gene was the most frequently used among 294 RBD-targeted antibodies, which have few somatic mutations [84]. Besides, through analysis of humoral responses in SARS-CoV-2 infected patients, most antibodies in plasma target non-neutralizing epitopes that are outside the RBD [83]. However, the most potent neutralizing antibodies are SARS-CoV-2 RBD-specific that account for 90% of plasma neutralizing activity [85], indicating SARS-CoV-2 RBD is immunodominant. Collectively, the epitope of the ACE2-binding site on RBD, named receptor binding motif (RBM), dominates SARS-CoV-2 polyclonal neutralizing antibody responses [85] and induces strongly neutralizing antibodies [86]. These findings should facilitate the design of antigens that elicit specific neutralizing antibody responses.

4. Viral inhibitors targeting ACE2

As the critical receptor of SARS-CoV-2, additional exogenous ACE2 to block the interaction of virus and host cells is regarded as a potential therapeutic strategy for preventing the replication of SARS-CoV-2 (Fig. 4). Human recombinant soluble ACE2 (hrsACE2, amino acids 1–740) showed dose-dependent inhibition of viral growth in Vero-E6 cells, as well as significant blocking of SARS-CoV-2 infection in engineered human blood vessel organoids and kidney organoids, with no toxicity to the organoids. Additionally, it was well tolerated in 27 healthy subjects of a phase II clinical study [87]. However, hrsACE2 has a half-life of only 10 hours, which limits its clinical application. Therefore, additional approaches were taken to engineer ACE2 protein with a longer-lasting effect *in vivo*. Lei et al. [88] constructed a fusion protein ACE2-Ig consisting of the extracellular domain of human ACE2 and the Fc region of human IgG1, and reported that ACE2-Ig could inhibit the entry of pseudovirus SARS-CoV-2 into 293T cells and A549 cells with an IC_{50} of 0.1 μg/mL and exhibit desired pharmacological properties. Additionally, it potently inhibited the cell fusion mediated by the S protein of SARS-CoV-2 with IC_{50} values of 0.65 μg/mL. Although pharmacokinetic studies have not been conducted, ACE2-Ig is very likely to provide long-lasting effects *in vivo*, based on a previous study showing that ACE2-Ig fusion protein retained full peptidase activity and had a plasma half-life of over a week [89]. Since exogenous ACE2 has already been developed for treatment of SARS-CoV, it can be rapidly deployed for the treatment of COVID-19.

The structural-based computational design of small peptides provides an efficient way to quickly identify potential therapeutics for emerging diseases. A peptide inhibitor was designed to include α1-, α2-helices and the residues 349–357 of ACE2, which are the 15 critical residues involved in the ACE2-RBD interaction [90]. Cao et al. [91] designed peptides incorporating the α-helix of ACE2, which makes more interactions with the RBD. A variant, AHB1, by affinity maturation of the ACE2-scaffolded using PCR mutagenesis, potently bound RBD with an affinity of 1 nM and blocked the interaction of RBD with ACE2 on targeted cells. The smaller size and the stabilization traits of peptide inhibitors derived from ACE2 permit its potential application of intranasal administration or nebulization in clinics. These two examples illustrate the power of computational protein design for rapidly generating potential therapeutic candidates against SARS-CoV-2.

The autologous nature of ACE2-based drugs eliminates the risk of immunogenicity, and their small-molecular weight makes them optimal for inhalation administration for direct delivery to the lung. Nevertheless, it is worth noting that the effect on the ACE2/angiotensin axis with regards to blood pressure and kidney function has yet to be determined.

5. Peptide inhibitors

The trimeric hairpin structure formed by HR1 and HR2 regions in the S2 subunit of SARS-CoV-2 plays a key role during the viral membrane fusion process, which makes it an attractive target for drug design. A pan-coronavirus fusion inhibition peptide, EK1 [92], exhibits effective inhibitory activity against SARS-CoV-2 virus and pseudovirus with IC_{50} values of 0.19 μM and 2.38 μM, respectively [93]. However, crystallographic analysis revealed more potent stability of trimeric hairpin structure in SARS-CoV-2 than that of SARS-CoV, which might reduce the antiviral efficacy of EK1 [94]. By conjugating the cholesterol molecule to the EK1, Xia et al. [94] found that the lipopeptide, denoted as EK1C4, potently inhibited SARS-CoV-2 S-mediated membrane fusion and pseudovirus infection, about 240- and 150-times more than EK1, respectively. A novel HR2-derived peptide, designated 2019-nCoV-HR2P (aa1168–1203), could significantly inhibit SARS-CoV-2 pseudovirus infection with an IC_{50} value of 0.98 μM [93]. Given that the peptide-targeting sequences in HR1 and HR2 domains are highly conserved, SARS-CoV-2 fusion inhibition peptides possess a broad-spectrum anti-coronavirus activity and prevent drug-resistant mutations. In addition, they can be used by inhalation formulation, which would be beneficial for treating COVID-19 and other coronaviruses.

6. Interferon (IFN) family

The IFN response constitutes the major first line of defense against viral infections. Type I IFNs are secreted by plasmacytoid dendritic cells and contain five subtypes in humans, IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω. Type I IFNs bind to the ubiquitously expressed type I IFN receptor (IFNAR) and activate powerful antiviral defense. Type III IFNs (IFN-λ) bind to the type III IFN receptor (IFNLR), preferentially expressed on epithelial cells and certain myeloid cells. After viral infection, many viral proteins are dedicated to modulating the host IFN response and result in highly impaired IFN production in patients [95], which could contribute to disease progression and severity. These mechanisms have been extensively investigated for SARS-CoV, MERS-CoV and SARS-CoV-2 [96]. As critical antiviral agents, without approved antiviral therapeutics or vaccines to this ongoing global threat, IFN therapy could serve as a treatment option for COVID-19.

IFN-α and IFN-β have been demonstrated to have inhibitory activity against SARS-CoV-2 *in vitro* and *in vivo*, and are more sensitive than

many other human pathogenic viruses, including SARS-CoV [97]. In these studies, pre-treatment with IFN-α or IFN-β drastically reduced viral titers. These findings suggest that type I IFNs may be effective as a prophylactic agent or an early treatment option for SARS-CoV-2. In a retrospective study, early administration of IFNα2b reduced in-hospital mortality in COVID-19 patients [98]. In fact, nebulized IFN-α has been recommended as an antiviral agent in the national guidelines for the treatment of COVID-19 patients (published by Chinese Center for Disease Prevention and Control (CDC)), and in combination with Ribavirin or lopinavir/ritonavir to treat severe COVID-19 patients.

Studies have shown that IFN-β, particularly the β1 subtype (IFN-β1a or IFN-β1b), is a more potent inhibitor than IFN-α in coronavirus infections and thus INF-β1 is also a potential COVID-19 treatment. INF-β1 exerts anti-viral activity by maintaining the endothelial barrier function of the lungs via up-regulation of cluster of differentiation 73 (CD73) in lung endothelial cells and secretion of anti-inflammatory adenosine [99]. IFN-β1 and IFN-γ1 treatment has been shown to inhibit SARS-CoV-2 infection in primary human airway epithelial cells [100]. A randomized clinical trial carried out in severe COVID-19 patients concluded that early subcutaneous administration of IFN-β1a, in addition to hydroxychloroquine plus lopinavir-ritonavir or atazanavir-ritonavir, significantly increased discharge rate on day 14 and decreased 28-day mortality compared to the control group without IFN-β1a administration [101]. Additionally, treatment with inhaled IFN-β1a reduced the odds of developing dyspnea and severe disease by 79% in patients, compared to the placebo group [102]. An open-label, randomized, phase II trial of 127 participants showed that early triple antiviral therapy (IFN-β1b, Lopinavir-Ritonavir, and Ribavirin) was safe and superior to lopinavir-ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19 [103].

Unlike type I IFNs which are already widely used in clinics, type III IFNs are not yet approved for any indication. Nevertheless, the unique qualities of type III IFN including being response-focused, long-lasting, and non-inflammatory, render IFN-λ an attractive intervention strategy in COVID-19. In previous studies, IFN-λ administration has been shown to offer therapeutic and protective effects similar to IFN-α but more protective than IFN-β in mice challenged with influenza A virus [104, 105]. In particular, IFN-λ treated mice have no appreciable immunopathology, while IFN-α4 exacerbated the disease by promoting pro-inflammatory cytokine secretion and immune cell infiltration. A recent study showed that SARS-CoV-2 is sensitive to IFN-λ. In a newly developed mouse model of SARS-CoV-2 infection, both prophylactic and therapeutic administration of pegylated IFN-λ1a diminished SARS-CoV-2 replication [106]. Therefore, clinical use of IFN-λ in COVID-19 holds promise, and clinical trials are under way (NCT04343976, NCT04331899). Some studies indicated that the detrimental activities of IFN-λ only occur upon chronic exposure and in the presence of tissue damage [107]. Therefore, Type III IFNs may help to achieve a sustained antiviral state that limits viral spread in the lower airway as well as the lung.

Taken together, IFNs are promising as repurposed drugs for COVID-19 treatment. Early administration prior to viral peak or as a prophylactic treatment may offer maximal protection without appreciable pathology. Combination administration with other antiviral drugs could result in more potent therapeutic effects.

7. Anti-inflammation pharmaceuticals

SARS-CoV-2 infection is capable of triggering aggressive inflammatory responses with the release of a large amount of pro-inflammatory cytokines in an event known as “cytokine storm”, which leads to ARDS aggravation and widespread tissue damage resulting in multi-organ failure and death. Therapeutic strategies targeting cytokines, accompanied by other anti-inflammation methods, during the management of COVID-19 patients could improve survival rates and reduce mortality (Table 2).

7.1. IL-6 inhibitors

IL-6 is one of the major cytokines that amplifies the immune response and mediates lung damage and respiratory failure during cytokine storm. In COVID-19 patients, the IL-6 level was observed to be almost two-fold higher in severe patients compared with mildly symptomatic patients [108]. Inhibition of IL-6 was speculated to be effective in treating severe COVID-19 patients. As a humanized monoclonal antibody against IL-6 receptor (IL-6R), Tocilizumab (Actemra, Roche) has been approved for the treatment of severe COVID-19 patients with elevated levels of IL-6. In a retrospective study, 20 severe or critical patients received five days of Tocilizumab treatment, and it was found that the clinical symptoms are effectively improved, as demonstrated by significantly lower C-reactive protein levels and percentage of peripheral lymphocytes [109]. However, the study did not include a control group. In another study enrolling 450 severe COVID-19 patients in a double-blind, placebo controlled, randomized clinical trial, the tocilizumab group did not decrease 4-week mortality or make improvement in clinical symptoms over a 4-week period (NCT04320615). Sarilumab is another anti-IL-6R antibody approved by the FDA for the treatment of rheumatoid arthritis. However, in a phase III randomized clinical trial among hospitalized patients with COVID-19, no therapeutic benefit was observed in the Sarilumab treatment group compared with the control group both on a seven-point ordinal scale and mortality (NCT04315298). Even though IL-6 inhibitors have shown a corrective effect on cytokine over-release in some severe patients, the large-scale, randomized clinical trials failed to show promising results. More studies are needed to investigate the use of IL-6 inhibition as a therapy for COVID-19 patients.

7.2. IL-1β inhibitors

IL-1β is another pro-inflammatory interleukin produced following immune recognition of SARS-CoV-2. A cohort study enrolling 96 patients found that 10-day subcutaneous administration of Anakinra, an IL-1 receptor antagonist, reduced the mortality and need for invasive mechanical ventilation significantly in patients with COVID-19-related bilateral pneumonia, typical lung infiltrates, or signs of respiratory failure [110]. Another retrospective cohort study also reported that high-dose intravenous Anakinra benefited COVID-19 patients by decreasing mortality, serum C-reactive protein, and improving clinical status [111]. Anakinra has shown a survival benefit without increased adverse events in sepsis patients with hyperinflammation in a phase III randomized controlled trial [112], which may be helpful in controlling hyperinflammation status in COVID-19 patients.

7.3. GM-CSF antagonists

GM-CSF can induce macrophages and neutrophils to secret pro-inflammatory cytokines such as IL-1, IL-6 and IL-23, as well as stimulate multiple downstream signal pathways that have effects on activation and differentiation of myeloid cells after binding to its receptor [113]. Given the critical role of GM-CSF in inflammation, an antibody against GM-CSF receptor-α (GM-CSFRα) to block downstream signaling was considered an option for treating hyperinflammation in COVID-19 patients. Mavrilimumab is an antibody targeting GM-CSFRα that has undergone phase I and phase II efficacy and safety clinical trials in patients with rheumatoid arthritis [114]. In a COVID-19 cohort study, the Mavrilimumab treated group showed earlier improvement from pneumonia and systemic hyperinflammation, as well as lower mortality than the controlled patients receiving only standard care [115]. Compared with other potential anti-cytokine agents like IL-6 inhibitors, inhibition of GM-CSFRα exhibits effects on the upstream inflammatory cascades, which could yield robust results, though placebo-controlled randomized trials are needed to confirm these initial findings.

Table 2
Potential anti-inflammation biotherapeutics for COVID-19.

	Mechanism/Clinical status
IL-6 inhibitors	Blockade of IL-6 receptor and its downstream pro-inflammatory pathways
Tocilizumab	Phase III clinical trial didn't show expected clinical benefit (NCT04320615)
Sarilumab	Phase III clinical trial didn't show expected clinical benefit (NCT04315298)
IL-1β inhibitors	Blockade of IL-1β receptor and its downstream pro-inflammatory pathways
Anakinra	A case-control study of 19 COVID-19 patients with moderate to severe ARDS, and hyperinflammation indicated efficacy [110]
GM-CSF inhibitors	Blockade of GM-CSF receptor-α on an upstream of inflammatory cascades
Mavrilimumab	A case-control study of 13 COVID-19 patients with pneumonia, hypoxia, and systemic hyperinflammation indicated efficacy[115]
Complement inhibitors	Blockade of C3 or C5 and its cascades of membrane attack complex formation
AMY101	A case reported successful treatment of a COVID-19 patient with ARDS [130]
Zilucoplan	Under phase II clinical trial (EudraCT 2020–001736–95)
Eculizumab	Successful treatment of four COVID-19 patients with ARDS or severe pneumonia [118]
Ravulizumab	Under phase III clinical trial (NCT04369469)
CD6 inhibitors	Blockade of CD6 to attenuate T cell infiltration and cytokine expression
Itolizumab	Approved by CDSCO for 'restricted emergency use' for the treatment of CRS in moderate to severe ARDS patients with COVID-19.

Table: Potential anti-inflammation biotherapeutics for COVID-19.
Last search run on 29 October using https://clinicaltrials.gov and https://pubmed.ncbi.nlm.nih.gov.
ARDS = acute respiratory distress syndrome.
CDSCO = Indian Central Drug Standard Control Organisation.
CRS = cytokine release syndrome.

7.4. Complement-targeted therapeutics

Severe COVID-19 patients have been reported to possess significant complement activation in their lung and sera, and the complement cascade has also been speculated as a promoter of cytokine storm, lung inflammation, and thrombotic microangiopathy (TMA) in COVID-19 [116]. Several complement-targeted therapeutic candidates have been developed and undergone various stages of clinical trials. A complement C3 inhibitor, AMY-101, was reported to successfully restore the normal lung function in a COVID-19 patient with severe ARDS after 14 days of treatment [117]. Anti-complement C5 therapy with Eculizumab also downregulated inflammatory markers and promoted recovery of four ICU COVID-19 patients [118]. Several complement therapeutics targeting C3 or C5, such as APL-9, AMY-101, Zilucoplan, Eculizumab, and Ravulizumab are in phase II or III clinical trials [119] to evaluate their immune modulatory efficacy for COVID-19.

7.5. CD6 inhibitors

CD6 is a co-stimulatory molecule required for optimal T-cell stimulation by antigen-presenting cells, which is crucial in T-cell proliferation to form Th1 and Th17 cells. A humanized IgG1 monoclonal antibody, Itolizumab (Alzumab, Biocon Ltd.), specifically binds to domain 1 of CD6 and downregulates the transcription of pro-inflammatory cytokine genes, thus leading to decreased levels of IFN-γ, IL-6, and TNF-α, resulting in attenuation of cytokine storm and T cell infiltration. Itolizumab was initially developed for various cancers and was later approved in India in 2013 for treatment of moderate to severe chronic plaque psoriasis [120]. Considering its unique mechanism of action in ameliorating CRS, which is the leading cause of death in COVID-19, itolizumab has been repurposed for COVID-19. In a trial conducted in Cuba, 94.7% of the patients were discharged after two weeks. Similarly, a prospective, randomized, placebo-controlled phase II trial was conducted in 30 severe COVID-19 patients in India and showed therapeutic benefits, as evidenced by significant improvement in blood oxygen levels, reduced levels of proinflammatory cytokines, and reduced mortality rate (CTRI Number: CTRI/2020/05/024959). Due to these positive results, the Indian Central Drug Standard Control Organisation (CDSCO) approved Itolizumab for "restricted emergency use" for the treatment of CRS in moderate to severe ARDS patients with COVID-19.

Taken together, hyperinflammatory status with incapacitated defense against viral invasion was found in many COVID-19 patients and can be eased by anti-inflammation therapeutics. However, anti-inflammation drugs should be used only for a limited period of time, and patients should be carefully monitored to avoid severe infections [121]. The existing large-scale, randomized clinical trials may not support the beneficial outcome of some agents, but anti-inflammation therapy is probably needed for patients with life-threatening COVID-19 disease.

8. Nucleic acid-based therapy

A promising approach for a more specific anti-viral therapy could be based on endogenous RNA interference (RNAi) mechanisms whose physiological goal is to regulate protein synthesis events. RNAi has been adopted for anti-viral therapy using synthetic double-stranded small interfering RNAs (siRNAs) with 19–27 nucleotides, or *in situ* production of short hairpin RNAs (shRNAs) by silencing the post-transcriptional expression of homologous target genes to degrade the viral RNA and prevent viral replication. RNAi has been widely investigated for treating previously encountered coronaviruses, including SARS-CoV [122]. Therefore, a similar line of investigation would be a promising treatment against SARS-CoV-2. Vir Biotechnology and Alnylam Pharmaceuticals have reported a joint endeavor to explore a library of siRNAs targeting all available SARS-CoV-2 and SARS-CoV genomes, including targets in highly conserved regions of the coronavirus RNAs. A candidate compound, VIR-2703 (also referred to as ALN–COV), was shown to have an IC_{50} of less than 100 pM and an IC_{95} of less than 1 nM in the SARS-CoV-2 authentic virus model, and thus will be advanced as an inhalational formulation for the potential treatment and/or prevention of COVID-19. The siRNAs developed by OilX Pharmaceuticals (Suwan, South Korea) also target highly conserved regions of coronavirus RNA that play important roles in viral replication such as 3CL-protease, RdRp, and S-protein. To date, no therapeutic RNAi studies have been reported on SARS-CoV-2 silencing. Therefore, the validation and safety of siRNAs remain to be explored.

9. Conclusion and perspective

Strong transmission capacity coupled with no effective therapeutics has resulted in the continuing threat of COVID-19. Currently, several

vaccine candidates have entered phase III trials and might be available within months [123]. Despite this, viral evolution might hamper the protective effects of vaccines, and some elderly or immunocompromised individuals may not develop strong immune responses after vaccination [124]. Therefore, the situation demands an urgent need to explore all potential therapeutic strategies that can be made available to prevent the disease progression and improve patient outcomes.

Currently, a total of 212 drug sets and 1796 unique drugs, including biotherapeutics related to COVID-19 research, have been collected in the COVID-19 Gene and Drug Set Library (https://amp.pharm.mssm.edu/covid19/) [125]. The 849 interactions, 25 targets, and 247 clinical trials of 639 drugs are also shown in the CORDITE (CORona Drug InTEractions database, https://cordite.mathematik.uni-marburg.de) [126]. These databases accelerate drug design and allow the research community to work together towards a cure for COVID-19. However, formulating appropriate biotherapeutics for COVID-19 treatment in the clinic is still a considerable challenge for multiple reasons. The large-scale production of biotherapeutics is usually complicated and expensive, which may limit their application in developing countries. Biopharmaceutical repurposing processes also have many challenges, such as prioritizing drug candidates, overcoming limited intellectual property, and competing with off-label use. To overcome these issues, it is rational to consider rapid initiation of therapy in high-risk populations, ideally in the context of a prospective, randomized, placebo-controlled clinical trial.

Overall, development of biotherapeutics to treat COVID-19 has been flourishing. Improving international collaboration and expanding clinical trials with large numbers of patients should be the way forward to provide significant and definitive results. As the clinical manifestation of COVID-19 is a combination of multiple factors, the use of combination therapy with biotherapeutics or other drugs is strongly recommended.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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