Severe acute respiratory syndrome-coronavirus-2: Current advances in therapeutic targets and drug development

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Summary

The current pandemic of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has quickly emerged as a global health concern with government bodies worldwide taking drastic control measures. Understanding the virology of SARS-CoV-2, its molecular mechanisms, and its pathogenesis are required for a targeted therapeutic approach. In this review, we highlight the current molecular and drug advances that target SARS-CoV-2 at the genome level. We also summarize studies that therapeutically target the host angiotensin-converting enzyme 2 and proteases. Finally, we summarize antibody-mediated therapeutic approaches, as well as recent trends in vaccine development. Hence, the purpose of this study is to investigate different molecular targets in SARS-CoV-2 pathogenesis and their usefulness in developing strategies for drug development.

KEYWORDS
ACE2, antibodies, SARS-CoV-2, TMPRSS2, vaccine development, virus

1 | INTRODUCTION

The current outbreak of coronavirus disease 2019 (Covid-19) due to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was initially reported in December 2019 in Wuhan, China. SARS-CoV-2 originated from zoonotic transmission, similar to that of severe acute respiratory syndrome-coronavirus (SARS-CoV) and Middle East respiratory syndrome-coronavirus (MERS-CoV), but with a severe pandemic potential.[1,2] Sustained human–human transmission of SARS-CoV-2 is an important characteristic, which facilitates rapid universal spread of Covid-19. By March 11, 2020, the disease outbreak had spread across 114 countries, infecting more than 118,000 and causing 4292 deaths, so that the World Health Organization (WHO) pronounced it a pandemic disease.[3] The WHO strategized to break human–human transmission by quarantining patients at an earlier stage, recognizing and reducing transmission from animal sources, and promoting research and vaccine development.[4] Severe social and economic impacts were felt amidst the struggle against the deadly virus. Despite the precautionary measures across different countries, SARS-CoV-2 had infected more than 13.8 million individuals by July 2020, causing 597,000 deaths worldwide.[5]

SARS-CoV-2, a 29.8 Kb positive-sense single-stranded RNA virus, shares more than 70% sequence homology with SARS-CoV.[6] Despite its similarity with SARS-CoV, its transmission competency and complexity are different. Investigations suggest that the contagious SARS-CoV-2 virus spread from human to human via respiratory droplet transmission from coughing or sneezing.[7] Recently, the WHO

has also announced airborne and aerosol as one possible mode of transmission of SARS-CoV-2.[8,9] The average incubation period, which is the duration between viral exposure and symptom onset, is estimated to range from 5 to 6 days, however; it can go up to 14 days in some cases.[10–12] Mostly, affected individuals experience mild symptoms, comprised of high body temperature in conjunction with symptoms such as fatigue, cough, diarrhoea, sore throat and headache.[13] Some patients experience pneumonia and acute respiratory distress syndrome (ARDS). Individuals with underlying health complications such as heart disease, chronic pulmonary disease and diabetes develop more severe symptoms.[14]

Numerous investigations on SARS-CoV-2 focus on delineating potential therapeutic targets, identifying viral inhibitors and re-purposing antiviral drugs to combat infection. The US Food and Drug Administration (FDA) and other regulatory agencies have granted permission to use drugs like remdesivir, dexamethasone and interferon-beta to treat severely ill Covid-19 patients[15–17] Vaccine research for Covid-19 is also progressing, with several significant studies in the clinical trial phase. With the urgent demand for a vaccine or specific antiviral drugs to combat Covid-19 pandemic and with the rapid growth of research on novel SAR-CoV-2 drug targets and approaches, it is of utmost importance to summarize the newest key findings. Updating findings related to SARS-CoV-2 may help understand which contemporary research approaches might provide the best protection until a vaccine can be made available. This review summarizes the recent drug approaches that target SARS-CoV-2 at the genome level. We have highlighted the recent therapeutic findings on host molecular targets, ACE2 (angiotensin-converting enzyme 2), and cell surface and lysosomal proteases, which are essential for the entry and pathogenesis of SARS-CoV-2 virus. Lastly, we have summarized antibody-mediated drug approaches, encompassing the recent trends in SARS-CoV-2 vaccine development. Hence, this review investigates the different molecular targets in SARS-CoV-2 pathogenesis, and their respective drug approaches, in an attempt to explain the present status of Covid-19 research.

2 | THERAPEUTIC TARGETS IN SARS-CoV-2

The genome of SARS-CoV-2 codes for non-structural proteins (nsps), structural proteins and accessory proteins, all of which mediate viral maintenance, replication and life cycle. The ORF 1a and ORF 1b coding for the polyproteins pp1a and pp1ab make up about two-thirds of the whole genome[18] (Figure 1A). These polyproteins are processed into 16 nsps (nsp1–16) by the main protease (M^{pro}) and the Papain-like protease (PL^{Pro}).[19] ORFs occupying one-third of the genome encode structural proteins such as spike (S), membrane (M), envelope (E) and nucleocapsid (N) proteins. The ORF3, ORF6, ORF7 and ORF8 genes encode 6–9 accessory proteins.[20] Recent studies employed different strategies to inhibit viral pathogenesis by targeting nsps and structural proteins, combating the progression of viral replication and life cycle progression inside host cells.

2.1 | | Targeting the nsps

Since viral proteases mediate the generation of mature nsps, inhibiting the proteolytic functions of M^{pro} and PL^{Pro} might halt the production of mature nsps. Drugs that target M^{pro} may decrease the risk of drug resistance, which results from mutations and might exhibit wide spectrum antiviral activity.[21] The SARS-CoV-2 M^{pro} inhibitor 11a showed a high inhibition rate and good pharmacokinetic properties.[19] Recently Jin et al. showed that an FDA approved antineoplastic drug, carmofur, inhibited SARS-CoV-2 M^{pro}-mediated viral replication in cell cultures.[22] Because HIV protease inhibitors lopinavir and ritonavir were tested on Covid-19 patients in non-randomized studies,[23] interim clinical guidelines for treating Covid-19 patients in Belgium, China, France, India, Italy, South Korea, Spain and Switzerland included lopinavir and ritonavir, either alone or in combination with interferon beta-1b, along with the standard of care recommended for moderate to severe infections.[24] Preliminary uncontrolled evidence from Chen et al. reported combined benefits of HCV inhibitor danoprevir and ritonavir in the recovery of Covid-19 patients following 4–12 days of treatment.[25] Most of the nsps (1–16) are critical to the replication of SARS-CoV-2 virus. Nsp12, a highly conserved RNA-dependent RNA polymerase (RdRp), is a potential drug target to alleviate viral replication inside the host. Recently, several molecular docking studies that highlighted the inhibition of RdRp via phytochemicals, antiviral terpenes and phenylpropanoids were published.[26,27] Additionally, re-purposed antiviral RdRp inhibitors remdesivir and favipiravir were clinically assessed for their effectiveness in Covid-19 patients in many countries.[28–30]

2.2 | Targeting the structural proteins

The major structural proteins responsible for viral assembly and SARS-CoV-2 pathogenesis are spike (S), membrane (M), envelope (E) and nucleocapsid (N) proteins. SARS-CoV-2 utilizes S protein to bind to the human ACE2 receptor and enables membrane-mediated fusion and viral entry, thus making this protein a leading target antigen in vaccine development.[31] Xia et al. have identified lipopeptide EK1C4 as a potential inhibitor of the S protein that reduces S protein-dependent membrane fusion of SARS-CoV-2.[32] While studies have seldom focused on the M protein of SARS-CoV-2 as a drug target, the E and N proteins have been understood to have critical functions. The E proteins form ion channels, rendering a crucial role in the assembly of viral particles and pathogenesis inside the host.[33] Molecular docking studies report that the antivirals glecaprevir, saquinavir, simeprevir might inhibit SARS-CoV-2 and reduce pathogenicity.[34,35] Recent studies have targeted the N proteins with pre-existing FDA approved drugs and re-purposed anti-human coronavirus (HCoV) drug combinations such as sirolimus with dactinomycin, mercaptopurine with melatonin, and toremifene with emodin to shorten the viral life cycle inside the host.[36] Due to the evolutionarily conserved nature
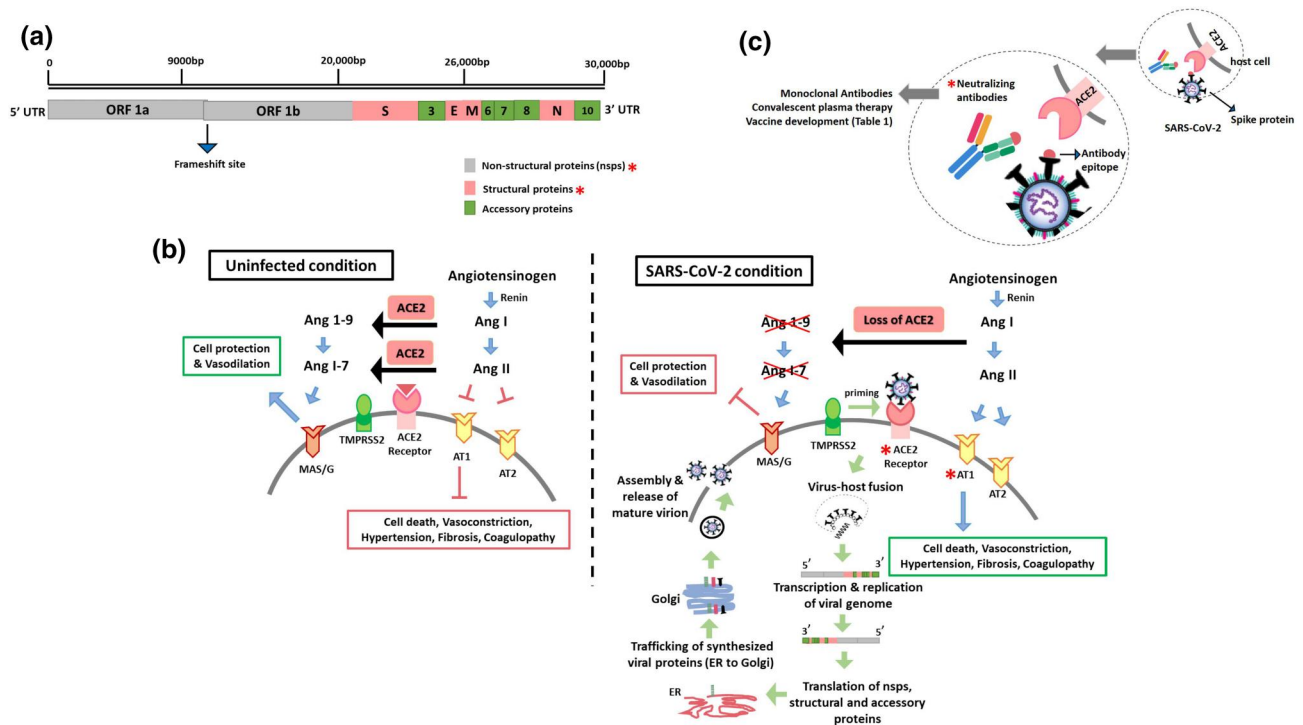
FIGURE 1 Diverse therapeutic targets to alleviate SARS-CoV-2 infection in humans. (A) SARS-CoV-2 viral genome. Molecular targets deployed for SARS-CoV-2 drug approach studies are marked by red asterisks. (B) Comparison between physiological condition and SARS-CoV-2 mediated host receptor invasion. (C) Neutralizing-antibody-dependent approach to combat SARS-CoV-2 infection

of the N protein sequence (~90% with SARS-CoV) and its contribution to high immunogenicity and abundant expression in infected people, it is one of the vaccine candidates that is highly studied.[37]

3 | SARS-CoV-2 AND ACE2 SIGNALLING

The primary dependency of SARS-CoV-2 on the ACE2 receptor has necessitated a detailed understanding of ACE2 downstream functions. Because its discovery over 20 years ago, ACE2 has been recognized as a crucial determinant of the renin-angiotensin system (RAS).[38,39] The harmful effects of the ACE/RAS pathway are counterbalanced via the ACE2/Ang1–7/MAS axis.[40] The ACE/RAS pathway is initiated upon the formation of active renin from an inactive precursor prorenin (Mr 46,000 protein). The renin released in blood cleaves angiotensinogen into Ang I (angiotensin I) (Figure 1B). Physiologically dormant Ang I acts as a precursor of active Ang II (angiotensin II). Binding of Ang II to AT1 and AT2 (Angiotensin Type 1 and Type 2) receptors results in vasoconstriction, endothelial injury, endovascular thrombosis and an elevated blood volume. Additionally, Ang II also promotes hypertension and thrombosis in arterioles. To alleviate the harmful effects of Ang II, ACE2, a monocarboxypeptidase, cleaves Ang I and Ang II into Ang 1–9 (angiotensin 1–9) and Ang 1–7 (angiotensin 1–7), respectively.[41] Activation of the ACE2 receptor impedes the harmful actions of Ang II on the cells, such as fibrosis, thrombosis

formation, angiogenesis and cell death. The Ang 1–9 and Ang 1–7 peptides exert beneficial outcomes like vasodilatory and anti-proliferative and defensive functions by activating the MAS/G receptor.[42] Taken together, these processes demonstrate the objective role of ACE2 receptor in the endogenous counter-regulatory system (ACE2/Ang1–7/MAS1 axis) that stabilizes the adverse effects of ACE/AngII/AT1 receptor signalling. The overall physiological outcomes of RAS activation elevate vascular tone, body sodium content and total body water.

Together, the affinity of ACE2 receptor to SARS-CoV-2 and the impaired endogenous downstream functions of ACE2 contribute to the observed clinical features of ARDS, pulmonary inflammation, myocardial injury, renal failure and increased mortality in the ageing population and people with heart and metabolic diseases.[43] Studies highlight the increased expression of membrane ACE2 receptors and its reduced expression in circulation (soluble form) in uninfected people.[44] Unfortunately, entry of SARS-CoV-2 through the ACE2 receptor-dependent paradigm leads to endocytosis of membrane ACE2 receptors together with SARS-CoV-2, and subsequently ACE2 receptor downregulation.[45] This results in the deprivation of the catalytic effect of ACE2 receptors at the membrane surface, explaining unopposed Ang II effects through the ACE/Ang II/AT1 axis.[46] Hence, the combined impact of ACE2 receptor downregulation and AT1 receptor upregulation suggest the use of AT1 receptor blockers, recombinant ACE2, and angiotensin 1–7 as beneficial targets against SARS-CoV-2 infection.

3.1 | Targeting ACE2 and its receptors

The AT1 receptor antagonist drugs losartan, telmisartan and olmesartan have been widely used in hypertensive patients since the 1990s since their adverse effects are rare.[47] The AT1 receptor antagonists elevate ACE2 expression in rats and humans. Currently, losartan and telmisartan are under phase II clinical trial for SARS-CoV2 infection.[48–50] While recombinant ACE2 can be an additional target, studies claim that a recombinant ACE2 (rhACE2) lacks the membrane-anchored domain, thus becoming soluble inside the cell.[51–53] Recently, the Centre for Drug Evaluation (CDE), China, ended a clinical trial for rhACE2 due to its lack of statistically significant effect as a drug treatment approach against SARS-CoV2.[54,55] However, scientists have identified a genetically altered human recombinant soluble ACE2 (hrsACE2), which showed a dose-dependent effect on SARS-CoV-2 viral replication in cell culture studies, and a reduced viral entry by a factor of 1000 to 5000.[56] Despite these benefits, hrsACE2 is not a favoured drug for clinical use because it is a glycosylated protein, and its production will require additional effort, time, and cost, which is not advantageous in drug development.[57]

Apart from ATI receptor blockers and recombinant ACE2, molecular docking studies revealed that two selected phytochemicals, 6-α-acetoxygedunin and echitamine, showed optimum binding to the human ACE2 receptor, which efficiently blocked the receptor and inhibited receptor-mediated SAR-CoV2 entry.[58] This preliminary evidence highlights the need for a comprehensive analysis of phytochemicals in an in vivo setting. Interestingly, a recent study by Minato et al.[59] showed that B38-CAP, a protein from *Paenibacillus*, had ACE2-like enzyme activity and decreased the Ang II levels in mice. Most importantly, recombinant B38-CAP protein converted Ang II to Ang 1–7 and contributed to the other ACE2 targeted functions. This study highlighted the functional similarity between bacterial B38-CAP and human ACE2 and B38-CAP is expected to undergo phase I clinical trial shortly.[57] Taken together, the studies mentioned above offer evidence that the ACE2 receptor is one of the leading potential targets against SARS-CoV-2.

Understanding the downsides of ACE2 might minimize the unexpected complications that may arise from ACE2 targeted drugs when used against SARS-CoV-2 infection. Stawiski et al.[60] identified variants in ACE2 receptors that modify virus-host interaction and significantly alter the host's vulnerability to SARS-CoV-2. They have deciphered 298 unique variants among 256 codons distributed through 805 amino acid residues of the human ACE2 receptor.[61] The understanding that the natural variations of the ACE2 receptor in human populations may alter ACE2 receptor binding affinity to SARS-CoV-2 S-protein produces divergent evidence regarding virus susceptibility. Additionally, ACE2 expression had a decreasing effect in aged individuals, to a greater extent in males than in females.[62] Diseases like diabetes mellitus reduce ACE2 expression, causing ACE2 deficiency. Though Ang 1–7 has a shielding effect against ARDS, enhanced Ang 1–7 formation from ACE2 in different organs

(heart, kidney and vessels) might not render a protective outcome. Patients with diabetes who were treated with pioglitazone, glucagon-like peptide-1 agonists and mineralocorticoid inhibitors showed increased endogenous ACE2 levels.[63] Hence, the combined use of these diabetic drugs and ATI receptor blocker/recombinant ACE2/B38-CAP might cause a decrease in cytosolic pH and an increase in viral load, resulting in exacerbation of SARS-CoV-2 infection and mortality.[64] Collective considerations provide essential insights into the ACE2 receptor as potential therapeutic targets; however, the downsides of ACE2 highlights the requirement for additional targets to attenuate SARS-CoV-2 infection significantly.

4 | TARGETING HOST PROTEASES

Following the recognition of the ACE2 receptor by the S1 receptor binding domain (RBD) of SARS-CoV-2, the spike protein undergoes proteolytic activation by host proteases, causing cleavage of S1/S2 and S2, and fusion of viral particles with cellular membranes.[65] Upon entry of SARS-CoV-2, activation of host cell surface proteases [e.g., transmembrane protease serine 2 (TMPRSS2)] and lysosomal proteases (e.g., cathepsins L/B) contribute to severe symptoms and fatality in some infected patients.[66,67] While these two kinds of proteases were actively investigated recently, furin and other proteases were also shown to contribute to the cumulative action of SARS-CoV-2.[65] The findings on TMPRSS2 stem from the earlier studies on influenza H1N1 and SARS-CoV outbreak, wherein this protease exhibited a similar mechanism to advance disease pathogenesis.[68] Therefore, researchers recommend the existing clinically proven TMPRSS2 inhibitors such as camostat, bromhexine, aprotinin, nafamostat to potentially combat SARS-CoV-2 infection.[69] Importantly, camostat has advanced to phase I clinical trial in March 2020, as one of the SARS-CoV-2 targets.[70,71] Similarly, many pre-existing cathepsin inhibitors like K11777, oxocarbazate, MDL28170, and E-64d were studied for their effectiveness against SARS-CoV-2.[72–76] Dexamethasone, a corticosteroid approved by FDA in 1958 as a broad-spectrum immunosuppressor, is one of the cathepsin L/B inhibitors that has been approved by WHO to treat critically ill Covid-19 patients.[77,78] One concern about using such inhibitors of host proteases may be the loss of function of innate TMPRSS2 and cathepsin L/B responses, which might result in side effects. Targeting TMPRSS2 and cathepsin L/B host protease at the same time using inhibitors might reduce the entry of the SARS-CoV-2 virus into host cells, thereby decreasing the viral load.

5 | ANTIBODY-MEDIATED DRUG THERAPEUTICS

5.1 | Neutralizing antibodies

Neutralizing antibodies (NAbs) produced as a humoral response from the adaptive immune system bind to the viral epitope, preventing viral epitope-human receptor attachment and initiating viral lysis by

TABLE 1 List of vaccines under phase trials for severe acute respiratory syndrome-coronavirus-2 infection[102–105]

Vaccine name	Technology	Industries/Institutes	Clinical trials
mRNA-1273	RNA vaccine	Moderna, NIAID, Lonza	Phase III
CoronaVac	Inactivated virus	Sinovac, Instituto Butantan	Phase III
Bacillus Calmette-Guerin (BCG)	Live-attenuated vaccine	University of Melbourne and Murdoch Children's Research Institute, Radboud University Medical Center, Faustman Lab at Massachusetts General Hospital	Phase II/III
AZD1222	Replication-deficient simian viral vector	The University of Oxford, Astrazeneca	Phase II/III
Ad5-nCoV	Replication-defecient adenovirus type 5	Cansino biological Inc.,	Phase II
RBD-Dimer	Adjuvant recombinant vaccine	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	Phase II
Inactivated vaccine	Inactivated virus	Institute of Medical Biology, Chinese Academy of Medical Sciences	Phase I/II
BNT162	RNA vaccine	BioNTech, Fosun Pharma, Pfizer	Phase I/II
T-COVIDTM	Replication-deficient adenovirus 5	Altimmune	Phase I/II
GX-19	DNA vaccine	Genexine	Phase I/II
BBIBP-CorV	Inactivated virus	Beijing Institute of Biological Products, Sinopharm	Phase I/II
Inactivated vaccine	Inactivated virus	Wuhan Institute of Biological Products, Sinopharm	Phase I/II
INO-4800	DNA vaccine	Inovio Pharmaceuticals, Inc.	Phase I/II
NVX-CoV2373	Protein subunit	Novavax, Emergent BioSolutions, Praha Vaccines, Serum Institute of India, AGC Biologics	Phase I/II
BBV152 (Covaxin)	Inactivated virus	ICMR-National institute of Virology, Pune, Bharat Biotech	Phase I/II
ZyCoV-D	DNA Vaccine	Zydus Cadila Healthcare	Phase I/II
CVnCoV	mRNA vaccine	CureVac	Phase I
LNP-CoVsaRNA	RNA vaccine	Imperial College London, VacEquity Global Health	Phase I
SCB-2019	Protein subunit	Clover Biopharmaceuticals Inc., GSK, Dynavax	Phase I
bacTRL-S	DNA Vaccine	Symvivo	Phase I
aAPC	Modified Lentiviral vector	Shenzhen Geno-Immune Medical Institute	Phase I
LV-SMENP-DC	Modified Lentiviral vector	Shenzhen Geno-Immune Medical Institute	Phase I
V-SARS	Inactivated virus	Immunitor Inc.	Phase I
AV-COVID-19	Patient-specific dendritic cell vaccine	Aivita Biomedical Inc.	Phase I
COVAX-19	Protein subunit	Vaccine Pty, Flinders University, Oracle	Phase I
Molecular Clamp Vaccine	Protein subunit	University of Queensland CSL	Phase I
AG0301-COVID19	DNA Vaccine	Osaka University, AnGes; Takara Bio	Phase I
ARCoV	mRNA Vaccine	PLA Academy of Military Sciences; Walvax Biotechnology	Phase I
Gam-COVID-Vac	Non-replicating viral vector	Gamaleya Research Institute	Phase I
Plant-derived VLP vaccine	Adjuvant recombinant vaccine	Medicago Inc., Universite Laval, GSK, Dynavax	Phase I

antibody-mediated opsonisation or complement activation[79,80] (Figure 1C). Interestingly, 95%–100% of SARS-CoV-2 infected patients show neutralizing activity 14 days after symptom onset, consisting of IgM, IgG and antibodies that target RBD of SARS-CoV-2.[81,82] Reports claim a high natural recovery rate of ~92% from SARS-CoV-2 infection; however, the remaining patients experience immunological anomalies like lymphopenia, neutrophilia, elevated inflammatory markers chemokines and cytokines.[83]

Especially, the lung injury observed in a few Covid-19 patients indicates a cytokine storm reaction that progressed to ARDS aggravation, causing multi-organ failure and death.[84,85] Therapeutic deployment of NAbs against SARS-CoV-2 is an important area of research that will likely contribute to controlling the pandemic and the potential re-emergence of viruses in the future.

Among SARS-CoV-2 targeted therapies, monoclonal antibodies (mAbs) may be efficient in providing immediate protection. Human monoclonal antibodies were studied against SARS-CoV during the epidemic in 2002–2004.[86,87] Genetic similarity between SARS-CoV and SARS-CoV-2 led the researchers to check for the cross-reactivity of SARS-CoV mAbs in SARS-CoV-2 infected samples.[88] Notably, the RBD-specific mAbs, CR3022 and S309, cross-reacted efficiently with the SARS-CoV-2 $S1_B$ RBD residues 318–510 and 337–444, respectively, without overlapping with ACE2 receptor binding sites.[89] However, mAbs, which can cross-react with the crucial SARS-CoV-2 $S1_B$ RBD residues 460–492, may be considered critical for achieving a therapeutically beneficial outcome. The above-mentioned critical residues are only 50% conserved between both viruses, entailing the need to develop mAbs that are specific to SARS-CoV-2 RBD.[90,91] Most importantly, a recent study reported the first human mAbs, 47D11, that neutralizes SARS-CoV-2 by binding to $S1_B$ RBD, similar to CR3022 and S309, establishing its capacity to cross-neutralize SARS-CoV as well.[92] The beneficial effect of mAb 47D11 was demonstrated in HEK-293T cells, which was independent of receptor-binding inhibition.[93] AbbVie, an American biotech company, has collaborated with this research team to support further preclinical activities and human trials on mAb 47D11.[94] The major limitation of mAbs is the cost; antibody-based drug treatment is more expensive than vaccines.

5.2 | Convalescent plasma therapy

Convalescent plasma (CP) therapy, an approach of passive immunization by infusion of blood plasma from recovered patients into infected individuals, is also being explored in several countries. CP therapy acquired its popularity because of its use against SARS-CoV, MERS, H1NI and Ebola viruses in the past.[95] Currently, based on non-randomized studies, the FDA has given emergency approval to CP therapy as a treatment option, which is mainly deployed in critically ill SARS-CoV-2 patients to reduce the viral load and mortality rate.[96] The challenges of CP therapy include the age and state of health of the donor, variations from unit to unit, informed consent from patients, and shortage of plasma.[97] Post-CP-therapy complications such as the transmission of other viruses, fever, chills, allergic reactions, acute lung injury, fluid overload and haemolytic events also need to be considered before opting for this treatment option.[98]

5.3 | Vaccines

Vaccination is defined as an active immunization technique whereby immunity against SARS-CoV-2 virus is induced in subjects artificially through exposure to antigens of the virus.[99] On 11 February 2020, the WHO announced that it would take approximately 18 months for a vaccine to become available to the public.[100] Currently, SARS-CoV-2 vaccines are under development using approaches like an inactivated virus, antigen presentation through viral vectors, recombinant vaccines, and DNA/mRNA vaccines.[101] As of July 2020, around 219 vaccines are under development worldwide, with 30 vaccines in human trials, including two in phase III clinical trial, two in phase II/III efficacy and dose-testing trials, two in phase II trials, 10 in phases I–II safety and efficacy trials, and fourteen in phase I trials (Table 1).[102–105]

6 | CONCLUSION

Taken together, specific drugs targeted to the viral genome, human ACE2 receptor, protease inhibitors, and antivirals can potentially aid in alleviating SARS-CoV-2 viral infection; however, only antibody-mediated immune response through vaccine development can hope to bring under control the SARS-CoV-2 pandemic.[106]

CONFLICT OF INTEREST

The authors have no competing interest.

AUTHORS CONTRIBUTION

Sakthivel Suganya, Suresh Divya and Madasamy Parani wrote the manuscript. Sakthivel Suganya and Suresh Divya contributed equally to the manuscript.

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