Journal of Experimental Biology and Agricultural Sciences

<http://www.jebas.org>

ISSN No. 2320 – 8694

TARGETING SPIKE PROTEIN OF SARS-COV-2 FOR DEVELOPMENT OF COVID-19 VACCINES AND THERAPEUTICS

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Received – September 25, 2020; Revision – October 15, 2020; Accepted – October 22, 2020

Available Online October 23, 2020

DOI: [http://dx.doi.org/10.18006/2020.8\(Spl-1-SARS-CoV-2\).S42.S56](http://dx.doi.org/10.18006/2020.8(Spl-1-SARS-CoV-2).S42.S56)

KEYWORDS

COVID-19

SARS-CoV-2

Spike protein

ACE2

Vaccines

Therapeutics

ABSTRACT

Coronavirus disease 2019 (COVID-19) was first reported in the sea-food market of Wuhan, China which and later declared as a pandemic. The novel coronavirus responsible for COVID-19 was later given the name severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to its close similarity with SARS-CoV. The entry of the virus is mediated through the interaction of spike glycoprotein with the host receptor angiotensin-converting enzyme 2 (ACE2). The Spike protein plays a pivotal role in SARS-CoV-2 infection as it is required for both receptor binding and viral fusion, hence the key target for neutralizing antibodies. Owing to its important role, Spike protein stands as the prime target for developing vaccines and therapeutics. The S glycoprotein carries the receptor-binding domain and the major B cell and T cell epitopes, which indicate that it is a potential target for vaccines and therapeutics. Several candidate vaccines have already entered into the clinical trials. The commonly employed vaccine platforms for COVID-19 include subunit, virus-like particles (VLPs), DNA, RNA, and viral vector-based platforms. The majority of these vaccine candidates target the Spike glycoprotein to elicit an efficient immune response. The safety profile and clinical efficacy of COVID-19 vaccines that are currently under trials are quite reassuring, but it is still way ahead from attaining commercial utility. In this review, we have highlighted the recent advances in S protein-based vaccine and anti-viral platforms along with their importance in prophylaxis and control of COVID-19.

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Peer review under responsibility of Journal of Experimental Biology and Agricultural Sciences.

Production and Hosting by Horizon Publisher India [HPI]
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1 Introduction

Coronavirus disease 2019 (COVID-19) was first reported in late December of 2019 that originated from the sea-food market in Wuhan, China, and later became a global pandemic affecting over 38 million people worldwide and resulting in nearly 1.1 million deaths as of 13th October, 2020 (Chan et al., 2020; <https://www.worldometers.info/coronavirus/>; WHO, 2020a; Zhu et al., 2020a). The novel coronavirus responsible for COVID-19 was later given the name severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (previously 2019-nCoV) due to its close similarity with SARS-CoV. Genomic characterization and phylogenetic analysis revealed that the novel coronavirus falls under the genus of Betacoronavirus lineage B (Lu et al., 2020; Dhama et al., 2020a). COVID-19 associated deaths are the highest in three major countries, USA, Brazil, and India as compared to other countries (Shah et al., 2020).

Genomic analyses suggest bat as the most probable source of SARS-CoV-2 although further investigations are needed to confirm the origin of this novel virus (Malik et al., 2020). The genome of SARS-CoV-2 showed 80.6-81.1% and 51% similarity with SARS-CoVs and MERS-CoV, respectively at the nucleotide level (Sharun et al., 2020a). Compared to the previous outbreaks caused by Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome CoV (MERS-CoV), SARS-CoV-2 has very high transmission potential (Dhama et al., 2020a). This is evident from the very high rate of disease transmission in the human population as well as the increased spill over to other species such as dogs, cats, tigers, lions, and minks (Dhama et al., 2020b; Rodriguez-Morales et al., 2020a; Sharun et al., 2020b; Tiwari et al., 2020). Therefore, the current situation warrants the need for biosafety and biosecurity measures at all levels to control and prevent the transmission of SARS-CoV-2 among human beings (Ahmad et al., 2020; Sivaprasad et al., 2020).

The immediate release of SARS-CoV-2 whole genome sequence following the outbreak has enabled the research community to analyze and develop diagnostic tests, vaccines, and therapeutic strategies against the novel pathogens (Bilal et al., 2020; Rodriguez-Morales et al., 2020b). Researchers around the world are on the run for identifying SARS-CoV-2-specific vaccines and therapeutics based on previous experience with zoonotic coronaviruses such as SARS-CoV and MERS-CoV (Dhama et al., 2020c; Frediansyah et al., 2020; Rubin et al., 2020). Although few of these candidate vaccines and therapeutics have shown promising results, it will take several months before we could confirm their benefits (Patel et al., 2020; Sharun et al., 2020c; Sharun et al., 2020d). In addition to the vaccines and small molecule therapeutics,

antibody-based immunotherapeutic such as convalescent plasma, monoclonal antibodies, and neutralizing antibodies can be used to reduce the mortality in COVID-19 patients (Sharun et al., 2020e). Preliminary studies conducted for the evaluation of the therapeutic potential of SARS-CoV-2-specific vaccines and therapeutics have to be performed in an efficient animal model before they are used for clinical trials. Vaccines against SARS-CoV-2 are mainly evaluated using non-human primates such as Rhesus macaque (*Macaca mulatta*) and Cynomolgus macaque (*Macaca fascicularis*) (Faslu Rahman et al., 2020; Sharun et al., 2020b).

In this review, we emphasize the importance of Spike (S) protein as a target for designing vaccines and therapeutics against COVID-19 and the recent advancements regarding the same.

2 Structural and genomic organization

SARS-CoV 2 is an enveloped virus with a positive-sense ssRNA genome of approximately 30kb in size (Khailany et al., 2020). The angiotensin-converting enzyme 2 (ACE2) mediates entry into the host cell and is followed by the translation of genomic RNA via two open reading frames (ORFs); ORF1a and ORF1b to produce non-structural proteins (Lu et al., 2019; Kim et al., 2020). ORF1a and ORF1b produce PP1a and PP1b respectively, which are then cleaved into NSP-1 to 16 through proteolytic cleavage mediated by viral proteases: papain-like protease and 3C like protease (Masters, 2006). The replication-transcription complex mediates synthesis of negative strand RNA template, genomic RNA (gRNA) amplification and production of sub-genomic RNA (sgRNA). Shorter sgRNA encode for conserved structural proteins Spike, Envelope, Membrane, Nucleocapsid and few other accessory proteins; whereas the genomic RNA is encapsulated and assembled (Khailany et al., 2020; Kim et al., 2020; Wu et al., 2020a; Hussain et al., 2020).

3 Prefusion S architecture

Spike protein is a Class I fusion glycoprotein and exists as a homotrimer on the surface of virus. The host cell recognition and entry is mediated by Receptor Binding Domain (RBD) of S glycoprotein through ACE2 receptors on the host cells (Shang et al., 2020b; Wrapp et al., 2020). The metastable prefusion state of S protein undergoes large scale conformational changes following its receptor binding and cleavage (Walls et al., 2017). The Spike glycoprotein (S protein) consists of two subunits: S1 subunit responsible for host cell receptor binding and S2 subunit equipped with fusion machinery. The S1 subunit consists of the N-terminal domain, RBD, Subdomains SD1 and SD2. The fusion machinery comprises a Fusion Peptide (FP), Heptad repeats HR1 and HR2, Transmembrane domain (TD) and Cytoplasmic tail (CT) (Wrapp et al., 2020; Bangaru et al., 2020).

4 Receptor binding and Post fusion S2 trimer

As mentioned earlier, the entry of SARS-CoV-2 is mediated by human ACE-2 receptor interaction with C-Terminal Domain (CTD) of S protein and occurs with a greater affinity than compared to the RBD of SARS-CoV (Wrapp et al., 2020; Wang et al., 2020b; Walls et al., 2020). Whereas, hACE2 binding affinity for SARS-CoV-2 spike is comparable or lower than the spike of SARS-CoV. This paradox is due to the fact that RBD of SARS-CoV is mostly in standing-up state but the SARS-CoV-2 RBD is mostly in its lying down state making it less accessible (Shang et al., 2020a). One more distinguishing feature of SARS-CoV-2 is the furin pre-activation of S protein, which compensates for the hidden RBD and also enhances its entry into some cell types (Shang et al., 2020a). Earlier investigations on different coronaviruses revealed that the spike protein activation is an irreversible and tightly regulated mechanism that occurs at various sites on S protein-mediated by host proteases (Hulswit et al., 2016). The spike protein shifts from its pre-fusion state to a hairpin-like post-fusion state following the receptor binding and this is mediated by proteolytic cleavage at both the S1/S2 boundary and S2' (Cai et al., 2020). Unlike the previous corona viruses, SARS-CoV-2 harbors a polybasic cleavage site (underlined, SPRRAR↓S) at the junction of S1 and S2 subunits and is believed to have contributed to the increased species to species transmission and cell-cell fusion (Coutard et al., 2020; Jaimes et al., 2020a). The presence of this polybasic cleavage site makes the S protein susceptible to a wide range of proteases along with furin. TTSPs (Type II transmembrane serine proteases) like TMPRSS2, matriptase, cathepsins, and various other host cell like proteases can act on the two important cleavage sites, unequivocally important for the virus entry, hence can be evaluated as the potential targets for the development of vaccine and therapeutic against SARS-CoV-2 (Belouzard et al., 2012; Jaimes et al., 2020b; Hoffmann et al., 2020a).

Receptor binding destabilizes the prefusion state of S protein and sheds off the S1 subunit. This releases the S2 subunit from its structural constraints exposing the FP which can then insert itself into the host cell membrane (Cai et al., 2020). A bridge is formed between virus and host cell membranes mediated by a pre-hairpin intermediate of S2 subunit. The membrane fusion is initiated by the formation of 6-Helical Bundle (6-HB) through interaction between three HR1 and HR2 segments each. The high fusogenic activity of SARS-CoV-2 than the other SARS-like coronaviruses may be due to the enhanced interaction between HR1 and HR2 segments (Zhu et al., 2020b; Liu et al., 2004; Tang et al., 2020).

5 SARS-CoV-2 Vaccine platforms based on S protein

Various methods are currently being employed for the development of COVID-19 vaccines that use either the whole virus as in traditional methods like live-attenuated vaccines and inactivated

vaccines or targets a specific portion of the virus. As in this case, the spike protein for the construction of modern vaccines using protein subunit, virus-like particles (VLPs), DNA, RNA and viral vector-based platforms. Various COVID-19 vaccines targeting Spike protein and details of their clinical evaluation are listed in Table 1.

Spike protein is critical for the virus infection and a major contributor in inducing host immune response and neutralizing antibodies. Characterization of spike glycoprotein revealed the presence of numerous B cell and T cell epitopes making it a prime target for vaccine design (Du et al., 2009; Walls et al., 2020; Tian et al., 2020; Zheng & Song, 2020; He et al., 2020). S based vaccines can be constructed using a full-length S protein, RBD, S1 and S2 subunits.

Candidate vaccines targeting full length S protein or S1 subunit may elicit a potent immune response but have safety concerns due to the competition between neutralizing and non-neutralizing epitopes, raising concerns about the efficacy and safety of vaccines that contain a full-length spike protein (Du et al., 2009; Wang et al., 2016). Studies have showed that recombinant full-length S-based vaccines produced an immune enhancement in vaccinated animals and a biased Th2 type response leading to the poor outcome of disease (Tseng et al., 2012; Zhu et al., 2013). This may lead to antibody-dependent enhancement (ADE) due to the heterogeneity of antigenic epitopes (Tetro, 2020). At present, there is no clinical proof supporting the occurrence of ADE with SARS-CoV-2. However, published data suggest that it bears great potential for ADE in SARS-CoV-2 (Ulrich et al., 2020).

One such strategy to overcome ADE is to limit the vaccine designs only the important antigenic epitopes. RBD happens to be one of the choices as it does not contain any such immunodominant regions that can produce non-neutralizing antibodies. But vaccine candidates targeting RBD may require the addition of specific adjuvants and repeated doses due to its comparatively low immunogenicity (Dai et al., 2020). Another choice is to target S1 as it contains a large set of neutralizing epitopes that are present outside the RBD and therefore more immunogenic (Wang et al., 2020d). The S2 subunit is a highly conserved region and can elicit a cellular immune response, but there are different speculations about its potency to develop neutralizing antibodies (Keng et al., 2005; Li et al., 2013; He et al., 2020). However, due to its high sequence homology, the S2 subunit can be considered as a potential target for developing universal vaccines against divergent CoV strains.

6 Considerations for vaccine development

Multiple vaccine platforms have been employed in the development of SARS-CoV-2 vaccines, advantages and disadvantages of each platform are discussed in Table 1. Vaccine development is a laborious and complicated process; and in such

Table 1 Spike protein-based COVID-19 vaccine candidates that are currently undergoing clinical trials (Ref: Foged et al., 2011; Choi & Chang., 2013; Pardi et al., 2018; Li & Petrovsky, 2016; WHO, 2020b; Pandey et al., 2020; Samrat et al., 2020; Bar-Zeev & Moss, 2020; Fuller & Berglund, 2020; Jeyanathan et al., 2020)

Type of technology	Vaccine/Manufacturer	Clinical trial/Stage	Type of Candidate
Protein subunit Advantages: Can target a defined region of immunogen, availability of various delivery systems, convenient large-scale production, safer and more stable so can be given even to immunosuppressed people Disadvantages: Low immunogenicity, requirement of adjuvant, typically require multiple doses, risk of denaturation of a protein antigen, relatively expensive	Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences	(Phase 1)/ NCT04445194 (Phase 2)/ NCT04466085	RBD-dimer based recombinant protein
	University of Queensland/CSL/Seqirus	(Phase 1)/ ACTRN12620000674932p	Molecular clamp stabilized Spike protein with MF59 adjuvant
	Vaxine Pty Ltd and Medytox	(Phase 1)/ NCT04453852	Recombinant spike protein with Advax adjuvant
	Kentucky Bioprocessing, Inc	(Phase 1/2)/ NCT04473690	Based on RBD
	Clover Biopharmaceuticals Inc./GSK/Dynavax	(Phase 1)/ NCT04405908	Native like Trimeric subunit Spike Protein
	NVXCoV2373; Novavax	(Phase 1/2) /NCT04368988	Full-length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M
	Medigen Vaccine Biologics Corporation/NIAID/Dynavax	(Phase 1)/NCT04487210	S-2P protein + CpG 1018
	Instituto Finlay de Vacunas, Cuba	(Phase 1)/ IFV/COR/04	RBD + Adjuvant
	West China Hospital, Sichuan University	(Phase 1)/ ChiCTR2000037518	RBD (baculovirus production expressed in Sf9 cells)
	FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo	(Phase 1)/NCT04527575	Peptide
DNA Advantages: Noninfectious; stable and easy to produce, cost-effective; induces effective innate immune response; effective induction of CTL; induces T cell and B cell-mediated immunity Disadvantages: Lower immunogenicity in humans than compared to animal models; require additional administration device; chances of integration into the human genome	INO-4800; Inovio Pharmaceuticals/International Vaccine Institute	(Phase 1/2)/ NCT04336410, NCT04447781	DNA plasmid vaccine with electroporation
	Osaka University/AnGes/Takara Bio	(Phase 1/2)/ NCT04463472	DNA plasmid vaccine + adjuvant
	Zydus Cadila	(Phase 1/2)/ CTRI/2020/07/026352	DNA plasmid vaccine
	Genexine Consortium	(Phase 1/2)/ NCT04445389	DNA Vaccine (GX-19)
	bacTRL-Spike; Symvivo Corporation	(Phase 1)/ NCT04334980	Bifidobacterium longum engineered to deliver plasmids containing synthetic DNA encoding spike protein
RNA Advantages: Non-infectious, non-integrating platform; rapid and stable production; induces effective innate immune response; induces T cell and B cell-mediated immunity; inherent immunogenicity can be regulated Disadvantages: Lower immunogenicity in humans than compared to animal models; concerns regarding instability, require efficient carrier methods	mRNA-1273; Moderna/NIAID	(Phase 1)/ NCT04283461 (Phase 2)/ NCT04405076 (Phase 3)/ NCT04470427	LNP-encapsulated mRNA
	BioNTech/Fosun Pharma/Pfizer	(Phase 1/2)/ ChiCTR2000034825 (Phase 3)/ NCT04368728	3 LNP-mRNAs
	Curevac	(Phase 1)/NCT04449276 (Phase 2)/NCT04515147	mRNA
	Arcturus/Duke-NUS	(Phase 1/2)/ NCT0448057	Self-replication of mRNA with nanoparticle delivery system
	Imperial College London	(Phase 1)/ ISRCTN17072692	LNP-nCoVsaRNA

Type of technology	Vaccine/Manufacturer	Clinical trial/Stage	Type of Candidate
Viral vector-based Advantages: Effective stimulation of both humoral and cellular immune response; better presentation of antigen; easily engineered; broad range of cellular tropism Disadvantages: Pre-existing immunity; need of co-infection with helper virus for some viral vectors; limited host range; limited carrying capacity; chance of persistent or latent infection; risk of recombination	University of Oxford/AstraZeneca	(Phase 1/2)/ NCT04324606 (Phase 2)/ 2020-001228-32 (Phase 3)/ ISRCTN89951424	Non-Replicating Viral Vector; ChAdOx1 platform
	CanSino Biological Inc./ Beijing Institute of Biotechnology	(Phase 1)/ ChiCTR2000030906 (Phase 2)/ ChiCTR2000031781 (Phase 3)/NCT04526990	Non-Replicating Viral Vector; Adenovirus Type 5 Vector encodes for a full-length S protein
	Gamaleya Research Institute	(Phase 1)/ NCT04436471, NCT04437875 (Phase 3)/NCT045303	Non-Replicating Viral Vector; Adeno-based (rAd26-S+rAd5-S)
	Janssen Pharmaceutical Companies	(Phase 1/2)/NCT04436276 (Phase 3)/NCT04505722	Non-Replicating Viral Vector; Ad26COVS1
	ReiThera/LEUKOCARE/Univercells	(Phase 1)/NCT04528641	Non-Replicating Viral Vector; Replication defective Simian Adenovirus (GRAd) encoding S
	Institute Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme	(Phase 1)/NCT04497298	Replicating Viral Vector; Measles-vector based

critical times a pandemic paradigm can be employed for better results. There are several considerations for an effective vaccine design like optimizing antigen design, host-related factors, duration of immunity, and selection of good animal models and choice of adjuvants (Lurie et al., 2020). Nanotechnology can significantly contribute in the development of modern vaccines. Nanomaterials are ideal materials for delivering antigens and can be used as adjuvants in the vaccines. The first vaccine candidate for COVID-19 that was launched into clinical trials was in fact an mRNA-based vaccine that was delivered via lipid nanoparticles (Shin et al., 2020). mRNA-1273 is the lipid nanoparticle-encapsulated vaccine candidate that encodes the SARS-CoV-2 S glycoprotein (Jackson et al., 2020). Preliminary in vivo study of mRNA-1273 vaccine were conducted in non-human primates (Rhesus macaque model) and the vaccine was found to induce robust SARS-CoV-2 neutralizing activity (Corbett et al., 2020). In the clinical trial involving older adults, immunization with mRNA-1273 vaccine was only associated with mild to moderate side effects. The side effects mostly included chills, headache, myalgia, fatigue, and pain at the injection site and were mostly observed following the second immunization (Anderson et al., 2020). NVX-CoV2373 is a recombinant SARS-CoV-2 nanoparticle vaccine that contains trimeric full-length SARS-CoV-2 spike glycoproteins (Keech et al., 2020). Findings from the clinical trial indicates that NVX-CoV2373 elicited good immune responses and appeared to be safe (ClinicalTrials.gov number, NCT04368988).

Safety profiles and clinical efficacy regarding COVID-19 vaccines under trials are quite reassuring, but still it is a long way ahead to form a clear point on safety and efficacy of each vaccine candidate. Although there has been a high demand for an effective COVID-19 vaccine, the standards for vaccine development have remained unaltered. Licensing a vaccine should be based on short term and long-term protection from disease, effect on rate of transmission,

safety and efficacy follow-ups (Bar-Zeev & Inglesby, 2020; Heaton, 2020). Host-related factors like target groups, duration of observation, clinical endpoints, ADE, seroprevalence, pre existing immunity and cross reactivity must be considered to establish a proper efficacy model for vaccine design (Lee & McGeer, 2020).

One of the major concerns with vaccine modality is the large-scale manufacture of billions of doses. Each vaccine platform has its own pros and cons with large scale manufacturing which may depend on various factors like durability, productivity, storage, distribution, dose requirement, vehicles or adjuvants, yield and cost of production. Manufacturing of large number of doses is a challenge for few modern platforms like nucleic acid and viral vector vaccines (DeFrancesco, 2020). During the early days of pandemic, we have seen conflicts regarding distribution of health care equipment and pharmaceuticals. This led to the case of medical protectionism and it is still continuing. Care must be taken to avoid such situations during vaccine development and distribution stages. A unified global governance, exchange of cross trail data and technology and a coordinated approach between government and manufacturing agencies are crucial for the development of a pandemic vaccine (The Lancet, 2020).

7 S-protein based therapeutics

Apart from the Spike protein-based vaccines, researchers are also focusing on therapeutics that target S protein and its interaction with the ACE2 receptor (Frediansyah et al., 2020; Dhama et al., 2020a). These include peptides and peptidomimetics against Spike-ACE2 interaction, host protease, and fusion inhibitors along with monoclonal antibodies targeting major epitopic determinants on the S protein. Few of which have already shown promising results in preclinical trials and the rest continue to be the potential targeting for developing COVID-19 therapeutics (Sharun et al., 2020a).

8 Therapeutics targeting Spike-ACE2 interaction

The main entry point of SARS-CoV-2 is via the interaction of RBD with host ACE2 and remains the major target for inhibiting the entry of the virus into host cells. Several therapeutics including recombinant RBD, recombinant ACE2, and peptides targeting several regions on ACE2 and RBD are currently being evaluated.

The peptidase domain (PD) $\alpha 1$ helix of ACE2 is essential for its interaction with RBD (Zhang et al., 2020). Zhang et al. chemically synthesized a 23-mer peptide fragment from this region called SBP1 which acts as a peptide binder that can effectively inhibit the RBD-ACE2 interaction. The peptides to be effective must bind to three regions on the RBD namely, Gly485/Phe486/Asn487, Gln493, and Gln498/Thr500/Asn501n (Barh et al., 2020). Computational studies led by several teams have revealed the presence of key amino acid stretches on RBD and ACE2 required for the interaction and can be considered as potential targets for the development of peptide-based therapeutics (Barh et al., 2020; Huang et al., 2020a; Han & Král, 2020; Vanpatten et al., 2020). AlphaLISA assay can be used to study protein-protein interactions for screening peptide-based ACE2-RBD therapeutics (Hanson et al., 2020). Inhibitors 1-4 (Han & Král, 2020) extracted from ACE2 yielded promising results in blocking RBD-ACE2 interaction. The binding affinity of such inhibitors can be improved by attaching the peptide inhibitors with clusters, dendrimers, or nanoparticles (Han & Král, 2020). Some of the important therapeutic peptides designed against SARS-CoV include P6, RBD-11b, S(471-503) and SP-10 that targets the interaction between RBD and ACE2, thereby preventing the entry of the virus into host cells (Hu et al., 2005; Ho et al., 2006; Han et al., 2006; Struck et al., 2012).

In silico screening approach used for repurposing drugs against SARS-CoV-2 and ACE2 receptor interface revealed numerous potential candidates that can be used as antiviral therapeutics (Choudhary et al., 2020). Alexpandi et al. proposed that rilapladib is the only quinolone that can target RBD interface between Spike and ACE2 (Alexpandi et al., 2020). Simeprevir and Lumacaftor interact with the side chains residues on RBD binding pocket thereby preventing RBD-ACE2 binding in silico (Trezza et al., 2020). Use of exogenous ACE2 in the form of recombinant-human angiotensin-converting enzyme 2 (rhACE2) can inhibit the entry of SARS-CoV-2 into host cells as well as decrease the incidence of its complications like ARDS, thereby rendering beneficial effects in organs like kidneys and lungs (Pang et al., 2020; Roshanravan et al., 2020; Alhenc-Gelas & Druke, 2020).

Various other drugs like angiotensin receptor blockers (ARB), Calmodulin antagonists that inhibit CALM-ACE2 interaction and selective estrogen receptor modulators can also be considered for modulating ACE2 mediated entry of SARS-CoV-2 (Ragia & Manolopoulos, 2020). Angiotensin-(1-7), a cardioprotective angiotensin peptide; ACE inhibitors, ARBs and anti-hyperlipidemic

like Simvastatin and Atorvastatin are in various phases of clinical trials as a part of therapeutics targeting the RASS-ACE2-AT1 receptor system thereby inhibiting ACE2 interaction with spike protein and also to reduce the risk of ARDS in COVID-19 patients (Peiró & Moncada, 2020; Talreja et al., 2020; Katsiki et al., 2020; Poduri et al., 2020).

9 Therapeutics targeting Cleavage S protein

As mentioned earlier, various host proteases like TMPRSS2, furin and cathepsins are required for the priming of S protein that is required for the fusion and entry processes (Bestle et al., 2020). One of the main proteases of SARS-CoV-2 is the TMPRSS2. Recent studies based on *in silico* screening revealed that topoisomerase I inhibitor, Rubitecan and Loprazolam, a benzodiazepine along with two other novel drug-like compounds displayed promising inhibitory effect on TMPRSS2 generated via homology modeling approach (Elmezayen et al., 2020). Owing to their known actions and already established safety profile, they can be used as candidate drugs against COVID-19 infection (Sternberg et al., 2020). Several therapeutic agents that target TMPRSS2 have successfully inhibited the priming process in *in vitro* analysis (Sanders et al., 2020; Yamamoto et al., 2020; Hoffmann et al., 2020b; Bittmann et al., 2020). Clinical trials are being conducted to evaluate the therapeutic effects of TMPRSS2 inhibitors like Camostat mesylate, Nafamostat mesylate and Bromhexine against TMPRSS2 mediated entry of SARS-CoV-2 (Cannalire et al., 2020).

Cathepsins, especially CatL are essential for the cleavage of S1 subunit in acidic lysosomal and endosomal compartments and thereby a potential target in modulating endosome mediated SARS-CoV-2 entry (Liu et al., 2020; Ou et al., 2020). Although there are no CatL/B inhibitors that are undergoing clinical trials, the preferential CatL inhibitors like CID 23631927 and CLIK-148, MDL28170, K11777, and E-64d have shown promising results in the inhibition of Cathepsin mediated viral entry (Cannalire et al., 2020).

Along with TMPRSS2, furin remains an important protease and is abundantly found in various organs. The presence of a furin cleavage site most likely increases the pathogenicity and cell tropism of SARS-CoV-2. Unfortunately, potent serine protease inhibitors are poor furin inhibitors, therefore we need to develop broad-spectrum protease inhibitors or cocktails containing both TMPRSS2 and furin inhibitors for effective modulation of S protein priming (Barile et al., 2020). Furin inhibitors like decanoyl-RVKKR-chloromethyl ketone (CMK) and naphthofluorescein inhibited both cleavage and cytopathic effect in SARS-CoV-2 infected cells (Cheng et al., 2020). Furin and furin-like several enzyme inhibitors have already been elucidated for their metabolic and antiviral effects, including Hexa-D-arginine (D6R), PI8, α -1-PDX (α 1-antitrypsin Portland), and MI-701 can be considered for prevention and control strategies against COVID-19 (Dahms et al., 2017; Braun & Sauter, 2019; Hasan et al., 2020; Huang et al., 2020b).

10 Therapeutics targeting Fusion-active core formation

Currently, available SARS-CoV and MERS-CoV based antifusogenics include HR2-8, CP-1, HR1-1, HR2-18, P6, P8, P10, SR9, HR2P, P1, HR2P-M2 and P21S10 (Bosch et al., 2003; Liu et al., 2004; Zheng et al., 2005; Ujike et al., 2008; Gao et al., 2013; Yuan et al., 2014; Lu et al., 2014; Wang et al., 2018; Xia et al., 2019). A novel peptide, 2019-nCoV-HR2P successfully inhibited SARS-CoV-2 pseudovirus infection (Xia et al., 2020). Apart from this, several pan-coronavirus fusion inhibitors like OC43-HR2P, EK1, and EK1C4 inhibit human coronavirus infection by targeting HR1 on the S2 subunit (Wang et al., 2020c). However, the effect of these fusion inhibitors needs to be elucidated based on *in vivo* studies. Recent research using drug repurposing studies revealed that four compounds namely phthalocyanine, hypericin, TMC-647055 and quarfloxin can be used as antiviral agents against SARS-CoV-2, as they inhibit the fusion of S protein with the host cells (Romeo et al., 2020). In addition to these, an HIV protease inhibitor called nelfinavir mesylate (Viracept) inhibits Spike mediated membrane fusion along with proteolytic cleavage of S within the cells (Musarrat et al., 2020).

Among coronaviruses, S2 subunit of the S protein is highly conserved and therefore a potential candidate for developing pan-coronavirus vaccines and therapeutics (Walls et al., 2020). Fusion inhibitors targeting mainly the HR2 region of the S2 subunit represent a promising therapeutic strategy against human coronaviruses. However, the effect of these fusion inhibitors needs to be elucidated based on *in vivo* studies.

11 Antibodies targeting Spike protein

Spike protein is the major antigenic determinant of coronaviruses and it is the key target for host immune response. Neutralizing antibodies generated against the spike protein can provide protective immunity by inhibiting receptor recognition and membrane fusion. After the outbreak of SARS-CoV, numerous antibodies were produced against various regions of S protein like RBD, whole S1 or S2 that showed promising results in the *in vitro* studies (Table 2). Unfortunately, none of these neutralizing

antibodies entered into the clinical evaluation.

Although the repository contains a number of neutralizing antibodies (nAbs) against SARS-CoV, very few turned out to be effective against SARS-CoV-2. One such example is CR3022, which was able to potentially neutralize SARS-CoV-2 despite being a SARS-CoV-specific Ab (Tian et al., 2020). In addition to these, nAbs generated against the spike protein of MERS-CoV successfully inhibited the MERS infection in both *in vitro* and *in vivo* systems (Du et al., 2017; Zhou et al., 2019). There is a need for developing broad-spectrum neutralizing antibodies with cross-reactivity/cross-neutralization capacity against various human coronaviruses. Despite the speculations around safety concerns and efficacy, rapid production at a reasonable cost make nAbs, a potential candidate for the prophylaxis and control of COVID-19.

Conclusion and Future Prospects

Spike protein plays a pivotal role in SARS-CoV-2 infection as it is required for both receptor binding and viral fusion. S protein determines the cell tropism and also acts as the key target for neutralizing antibodies, hence the prime candidate for designing vaccines and therapeutics. Over 33 vaccines entered into the clinical trial phase and more than 140 vaccine candidates are currently in their pre-clinical evaluation breaking all the records and setting a pace in this era of modern vaccinology. A major chunk of these candidates targets the S protein to elicit an efficient immune response. S protein carries the RBD and also major B cell and T cell epitopes, hence making it a potential candidate for the development of vaccines. Apart from the traditional platforms like live attenuated and inactivated vaccines, researchers have adopted recombinant genetic technology for designing COVID-19 vaccines. Various factors like immunogenicity, rate and cost of production, delivery systems, ADE have to be considered for developing an effective vaccine system.

To date, no vaccine has been approved for use against human coronaviruses. Meanwhile, various peptides and small-molecule inhibitors based on S protein can be adopted to modulate SARS-CoV-2 entry into host cells. Most of which are familiar to us with known safety profiles and metabolic effects. Most of the therapeutics strategies discussed here have shown promising results in controlling

Table 2 Potential Neutralizing Abs targeting spike protein of SARS-CoV and SARS-CoV-2

Corona virus	Neutralizing Antibody (nAb) name	References
SARS-CoV	S230.15, m396, S109.8, S227.14, S230.15, 80R, CR3022, CR3014, 33G4.35B5, 30F9, 68, 201, 4D4, F26G18, F26G19, 1A9, B1, 1F8, 5E9	Sui et al., 2004; Greenough et al., 2005; Duan et al., 2005; He et al., 2006; Lip et al., 2006; Coughlin et al., 2007; Zhu et al., 2007; Rockx et al., 2008; Berry et al., 2010; Elshabrawy et al., 2012; Ng et al., 2014; Tian et al., 2020
SARS-CoV-2	B38, H4, 47D11, CR3022, 311mab-31B5, 311mab-32D4, n3130, n3088, S309, P2C-1F11, P2B-2F6, 4A8	Wang et al., 2020a; Wu et al., 2020b; Tian et al., 2020; Chen et al., 2020; Wu et al., 2020c; Pinto et al., 2020; Ju et al., 2020; Chi et al., 2020

COVID-19 infection *in vitro* and continue to be the same in clinical evaluation too. Host protease inhibitors and antifusogenics seem to be potential candidates for diminishing viral entry yet varying results are seen with different classes of inhibitors. The successful strategy in such cases can be achieved by using a cocktail of agents to boost their individual properties. Neutralizing antibodies raised against different regions of spike protein remain an important focus in prophylaxis and control of COVID-19.

Further focus on structural and immunological aspects can aid in the designing of better vaccines and antiviral agents. The S2 subunit is highly conserved among coronaviruses and therefore can be targeted for designing vaccines or therapeutics against a broad range of coronaviruses. With the recent fruitful outcomes in different phases of clinical evaluation, S protein-based vaccine and therapeutic platform may help us to overcome the pandemic in the coming days.

Acknowledgments

All the authors acknowledge and thank their respective Institutes and Universities.

Funding

This compilation is a review article written by its authors and required no substantial funding to be stated.

Disclosure statement

All authors declare that there exist no commercial or financial relationships that could, in any way, lead to a potential conflict of interest.

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