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Taking aim at a fast-moving target: targets to watch for SARS-CoV-2 and COVID-19

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Summary

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is characterized as a betacoronavirus and recognized as the seventh discrete coronavirus species capable of causing human disease. This new coronavirus causes febrile respiratory illness and on March 11, 2020, was characterized as a global pandemic. Investigators have accelerated the search for a vaccine to prevent infection and for agents to treat it. This article presents those drug targets that (as of March 20, 2020) are currently under active investigation for the treatment of COVID-19, the disease caused by SARS-CoV-2 infection.

Key words: SARS-CoV-2 – COVID-19 – Coronavirus – Therapeutic targets

Introduction

Coronaviruses are a group of large, enveloped, positive-sense, single-stranded RNA viruses belonging to the order *Nidovirales*, family *Coronaviridae*, subfamily *Coronavirinae*. More than two dozen different species are known and have been divided into four genera (alpha, beta, gamma and delta) characterized by different antigenic cross-reactivity and genetic makeup. Only the alpha- and betacoronavirus genera include strains pathogenic to humans and other mammals (1-3).

Coronaviruses have long been recognized as important veterinary pathogens, causing respiratory and enteric diseases in mammals as well as in birds. Before 2019, only six coronaviruses had been known to cause disease in humans: HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory virus coronavirus (MERS-CoV). The first four are endemic locally; they have been associated mainly with mild, self-limiting disease, whereas the latter two—both betacoronaviruses—can cause severe illness (1-3).

Given the high prevalence and wide distribution of coronaviruses, their large genetic diversity as well as the frequent recombination of their genomes, and increasing activity at the human–animal interface, these viruses represent an ongoing threat to human health (4). This fact recently became starkly evident, with the emergence and rapid spread of a novel coronavirus, first in mainland China and now globally. The virus—provisionally designated 2019-nCoV and later given the official name SARS-CoV-2, due to its similarity to SARS-CoV—was quickly isolated and the viral genome sequenced. SARS-CoV-2 was characterized as a betacoronavirus and recognized as the seventh discrete coronavirus species capable of causing human disease (5).

SARS-CoV-2 and COVID-19

In late 2019, the new coronavirus began causing febrile respiratory illness in mainland China; 2 months later, the rapidly spreading disease was officially named Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO). Earliest reports of the illness were issued by doctors in the densely populated city of Wuhan, Hubei province. Index cases were linked to the Huanan wholesale seafood market, which was immediately closed. Although the initial cases were traced to zoonotic transmission, human-to-human transmission was soon documented, both in healthcare settings and in familial clusters (6, 7). In fact, following the initial leap across the species barrier, human-to-human transmission quickly became responsible for widespread and rapid dissemination of the virus across populations with no pre-existing immunity; the disease spread from a single focal point across the entire country of China in just 30 days, and within 3 months had established

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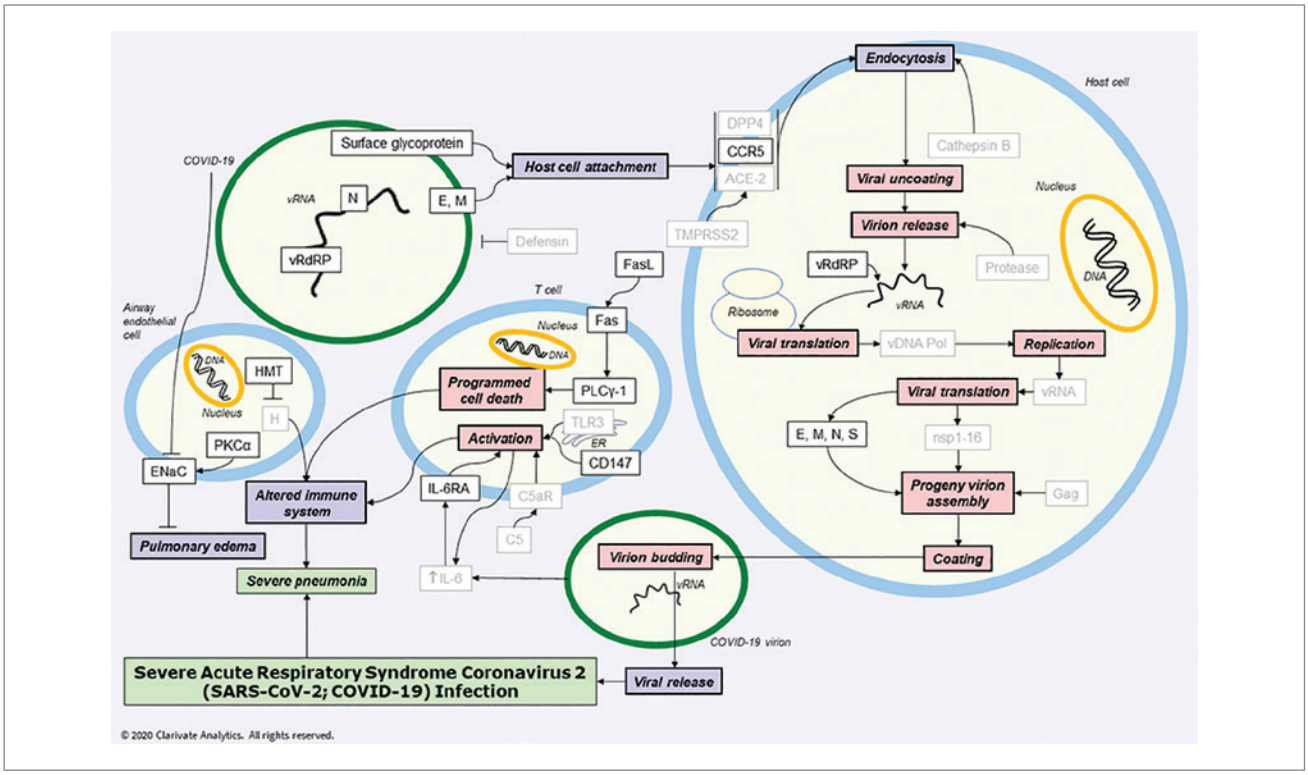

Figure 1. SARS-CoV-2 (COVID-19) infection targetscape. A diagram showing an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of SARS-CoV-2 infection and their biological actions. Gray or lighter symbols are targets that are not validated (i.e., targets not associated with a product that is currently under active development for SARS-CoV-2). ACE-2, angiotensin-converting enzyme 2; C5, complement C5; C5aR, C5a anaphylatoxin chemotactic receptor 1 (CD88); CCR5, C-C chemokine receptor type 5; CD147, basigin; DDP4, dipeptidyl peptidase 4; E, envelope protein (SARS-CoV-2; COVID-19); ENaC, epithelial sodium channel; Fas, tumor necrosis factor receptor type 6 (FASL receptor); FasL, tumor necrosis factor ligand superfamily member 6 (FASLG; FAS ligand); H, histamine; HMT, histamine *N*-methyltransferase; IL-6, interleukin-6; IL-6RA, interleukin-6 receptor subunit α; M, membrane glycoprotein (SARS-CoV-2; COVID-19); N, nucleocapsid (SARS-CoV-2; COVID-19); nsp1-16, nonstructural proteins 1-16 (SARS-CoV-2; COVID-19); PLCγ-1, 1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase γ-1; PKCα, protein kinase C α type; GDP, RNA-directed RNA polymerase (viral); S, surface glycoprotein (SARS-CoV-2; COVID-19); TMPRSS2, transmembrane protease serine 2; TLR3, Toll-like receptor 3; vDNA pol, viral DNA polymerase; vRNA, viral RNA.

footholds in more than 100 countries. On January 30, 2020, under recommendation from the International Health Regulations (2005) Emergency Committee, the Director-General of the WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern (PHEIC). On March 11, it was characterized as a global pandemic.

Enabled by open access to prepublication articles and collaboration across borders, the pace of drug and vaccine development during the COVID-19 outbreak has been unprecedented. This article provides a snapshot in time (as of March 20, 2020) of validated therapeutic targets, as reflected by the R&D pipeline on that same date. Those targets which are currently under active investigation for the treatment of COVID-19 are discussed (see also Fig. 1). Table I provides a selection of products under active development for each target.

Targets

Basigin (CD147)

CD147 is a member of the immunoglobulin superfamily of receptors involved in cell growth. It activates matrix metalloproteinase-9 (MMP-9) and membrane type 1-matrix metalloproteinase (MT1-MMP) synthesis. Its expression is detected on the surface of tumor cells. CD147 also mediates viral entry into host cells. Interaction of measles virus bound to cyclophilin B (a ligand of CD147) mediates entry of the virus into host cells. Studies have shown that nucleocapsid protein (N; COVID-19) binds to cyclophilin A (also a ligand for CD147). Interaction of CD147 with virion-associated cyclophilin A plays a functional role in facilitating invasion of host cells by SARS-CoV. CD147 may also, therefore, be implicated in host cell invasion by the closely related virus SARS-CoV-2 and represents a therapeutic target for the treatment of COVID-19 (8).

Table I. *Selected targets and products being actively investigated for SARS-Cov-2.*

Target name	Product/description	Source	Phase
1-Phosphatidylinositol 4,5-bisphosphate phosphodiesterase γ-1 (PLCγ-1)	Lopinavir/ritonavir	AbbVie	Clinical
Basigin (CD147)	Meplazumab	Fourth Military Medical University	I/II
Chemokine receptor CCR5	Leronlimab	CytoDyn	IND filed
Complement C5	IFX-1	Staidson Biopharmaceuticals	IND filed
Defensin (nonspecified subtype)	Brilacidin	Innovation Pharmaceuticals	Preclinical
Elongation factor 1-α2	Plitidepsin	Pharmamar	Preclinical
Envelope protein (SARS-CoV-2; COVID-19)	LV-SMENP-DC	Shenzhen Genoimmune Medical Institute	I/II
Epithelial sodium channel (ENaC)	Solnatide	APEPTICO	Clinical
Histamine *N*-methyltransferase	Chloroquine phosphate	Guangdong Zhongsheng Pharmaceutical	Clinical
Human coronavirus (SARS-CoV-2; COVID-19) proteins	Human COVID-19 coronavirus (SARS-CoV-2) mRNA vaccine	CureVac	Preclinical
	LUNAR-COV19	Arcturus Therapeuticus	Preclinical
	mRNA-1273	Moderna	Preclinical
	TNX-1800	Tonix Pharmaceuticals	Preclinical
Membrane glycoprotein (SARS-CoV-2; COVID-19)	LV-SMENP-DC	Shenzhen Genoimmune Medical Institute	I/II
Nucleocapsid (SARS-CoV-2; COVID-19 virus)	Lopinavir/ritonavir	AbbVie	Clinical
	Darunavir/cobicistat	Shanghai Public Health Clinical Center	Clinical
Protein kinase C α type	Solnatide	APEPTICO	Clinical
RNA-directed RNA polymerase	Remdesivir	Gilead	III
	Favipiravir	Sihuan Pharmaceutical	Clinical
Surface glycoprotein (spike glycoprotein) (SARS-CoV-2; COVID-19)	Human COVID-19 coronavirus (SARS-CoV-2) vaccine comprising replication-deficient simian adenovirus vector ChAdOx1 encoding spike glycoprotein of COVID-19 virus	Jenner Vaccine Foundation	Preclinical
	Human COVID-19 coronavirus (SARS-CoV-2) vaccine comprising recombinant COVID-19 spike glycoprotein; encapsulated in nanoparticles	Novavax	Preclinical
	LV-SMENP-DC	Shenzhen Genoimmune Medical Institute	I/II
Toll-like receptor 3	Rintatolimod	AIM ImmunoTech	Preclinical
Tumor necrosis factor ligand superfamily member 6	Lopinavir/ritonavir	AbbVie	Clinical
Tumor necrosis factor receptor type 6 (FASL receptor; Fas)	ASC-09/ritonavir	Ascletis	Clinical
	Lopinavir/ritonavir	AbbVie	Clinical
Unknown[a]	APN01	Apeiron Biologics	Clinical
Unknown[a]	Danoprevir	Ascletis	Clinical
Unknown[a]	INO-4800	Inovio Pharmaceuticals	Preclinical
Unknown[a]	Oseltamivir phosphate	Wuhan Tongji Hospital	Clinical
Unknown[a]	Umifenovir hydrochloride	Wuhan Tongji Hospital	Clinical

[a]Target unknown for SARS-CoV-2 virus.
Source: *Cortellis Drug Discovery Intelligence* as of March 20, 2020.

C-C chemokine receptor type 5 (CCR5)

CCR5 is a G protein-coupled, 7-transmembrane receptor expressed on monocytes, macrophages, T cells and B cells that binds the CC chemokines MIP-1α (macrophage inflammatory protein 1α), MIP-1β and RANTES with high affinity. It also binds viral MIP-2 with high affinity and has been shown to bind cyclophilin-18 and histidyl-tRNA synthetase. CCR5 acts as a coreceptor with CD4 for HIV type 1 infection and it functions as a fusion cofactor for macrophage-tropic and T-cell line-tropic isolates of HIV-1. Moreover, studies have shown that CCR5 is involved in host defense playing a role in T-cell recruitment. Targeting of CCR5 may be effective in the treatment of SARS-2-CoV-2 (9-11).

Envelope protein (E) (SARS-CoV-2; COVID-19 virus)

Envelope protein is a component of the viral envelope of COVID-19 that plays a central role in virus morphogenesis and assembly via its interactions with other viral proteins. Agents that are envelope protein-directed immunity inducers may be effective in developing a vaccine against SARS-CoV-2 (12-14).

Epithelial sodium channel (ENaC)

ENaC is a non-voltage-gated, amiloride-sensitive, membrane-bound ion channel (SCNN1) that is involved together with the Na^+/K^+-ATPase in transepithelial Na^+ transport and is considered rate-limiting for Na^+ reabsorption in many tissues. It is also permeable for lithium (Li^+) and protons. These channels are found on apical membrane of polarized epithelial cells of many tissues. ENaC channels are heteromultimeric proteins composed of three homologous subunits (α-, β- and γ ENaC or SCNN1A, SCNN1B and SCNN1G) that have been proposed to be arranged in either an α2βγ or a higher ordered configuration; a δ subunit (SCNN1D) can replace the α subunit. In the lung, these channels regulate airway surface liquid volume and the efficiency of mucociliary clearance. Mutations of ENaC can result in pulmonary disease. Studies have shown that following host cell infection, SARS-CoV proteins (S and E) are involved in the regulation of alveolar fluid clearance through reducing cell surface expression and activity of ENaC. Thus, agents activating ENaC could also be effective in attenuating pulmonary edema associated with SARS-CoV-2 infection, given the similarity of the viruses (15).

Histamine *N*-methyltransferase (HMT)

HMT (EC:2.1.1.8) is a transferase that inactivates histamine by N-methylation. It plays an important role in degrading histamine and in regulating the airway response to histamine. Histamine causes narrowing of the bronchial tubes and difficulty breathing. Inhibitors of HMT would therefore be effective in the treatment of respiratory distress secondary to SARS-CoV-2 infection (16, 17).

Interleukin-6 receptor subunit α (IL-6RA)

IL-6RA is the α chain of the IL-6 receptor complex (IL-6R). IL-6R is a class I cytokine receptor for IL-6. Association with the IL6ST subunit is required for a full functional receptor. The complex is involved in immune response regulation, acute-phase reaction and hematopoiesis. When SARS-CoV-2 infects the upper and lower respiratory tract, the results can be mild or highly acute respiratory syndrome with consequent release of proinflammatory cytokines, including IL-6. Suppression of inflammation in inflammatory diseases can be achieved by inhibiting IL-6 activity. Anti-IL-6RA agents would render IL-6R inactive and attenuate pulmonary inflammation in patients with COVID-19 (18-20).

Membrane glycoprotein (M) (SARS-CoV-2; COVID-19)

Membrane glycoprotein M is a component of the viral envelope of SARS-CoV-2 that plays a central role in virus morphogenesis and assembly via its interactions with other viral proteins. Agents which are membrane glycoprotein-directed immunity inducers may be effective in the prevention of COVID-19 (12-14).

Nucleocapsid (N) (SARS-CoV-2; COVID-19)

Nucleocapsid packages the positive strand viral genome RNA into a helical ribonucleocapsid (RNP) and plays a fundamental role during virion assembly through its interactions with the viral genome and membrane protein M. It plays an important role in enhancing the efficiency of subgenomic viral RNA transcription as well as viral replication. The N protein of SARS-CoV has been shown to induce apoptosis and actin reorganization. Targeting of this molecule by nucleocapsid-directed immunity inducers may be effective in the prevention of SARS-CoV-2 infection (12-14, 21).

1-Phosphatidylinositol 4,5-bisphosphate phosphodiesterase γ-1 (PLCγ-1)

PLCγ-1 is an enzyme (EC 3.1.4.11) that mediates the production of the second messenger molecules diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). Upregulation can occur with viral infections, resulting in increased proinflammatory cytokine release. Inhibition of this enzyme and its interaction with tumor necrosis factor receptor superfamily member 6 (CD95; FAS ligand) may be be effective in relieving respiratory distress in patients with COVID-19 (20, 22, 23).

Protein kinase C α type (PKCα)

PKCα is a membrane-associated protein and member of AGC Ser/Thr protein kinase family. It is involved in mitogen-activated protein kinase pathway, cell polarization and motility. PKCα has been shown to mediate lung endothelial

injury; thus, inhibition of PKCα may be effective in attenuating lung injury in patients with COVID-19 (20, 23-25).

RNA-directed RNA polymerase (RdRP) (viral)

RdRP is an unusual viral coded enzyme involved in the synthesis of negative-sense RNA strand during viral RNA replication within the nucleus of a host cell. The negative-sense strand of viral RNA acts as a template for synthesis of the positive-sense RNA strand, which in turn acts as a template for synthesis of the negative-sense stand of viral RNA. Inhibition of this enzyme would block viral replication and therefore be effective in the treatment of viral infections such as influenza, hepatitis C, Ebola and coronavirus (26-28).

Surface glycoprotein (S) (SARS-CoV-2; COVID-19)

Surface glycoprotein attaches the virion to the cell membrane by interacting with human ACE-2 (angiotensin-converting enzyme 2) and CLEC4M/DC-SIGNR (C-type lectin domain family 4 member M) and initiates the infection. Binding to the receptor and internalization of the virus into the endosomes of the host cell probably induces conformational changes in the S glycoprotein. Targeting of this molecule by nucleocapsid-directed immunity inducers may be effective in the prevention and treatment of SARS-CoV-2 (12-14, 21, 29, 30).

Tumor necrosis factor ligand superfamily member 6 (FASLG; FAS ligand; FasL) and tumor necrosis factor receptor type 6 (FASL receptor; Fas)

FAS ligand (FasL) is a type-II transmembrane, homotrimeric protein that belongs to the tumor necrosis factor (TNF) family. It is a ligand of Fas, a member of the TNF receptor family that is involved in the induction of cell death through caspase-mediated signaling. FasL/Fas interactions play an important role in the regulation of the immune system and the progression of cancer. Fas signaling also appears to regulate endothelial function and neutrophil lifespan. Studies have shown that caspase-dependent FasL-mediated apoptotic pathways play a central role in SARS-CoV-induced apoptosis which facilitates viral replication. Thus, inhibition FasL/Fas interaction may be effective in the treatment of SARS-CoV-2 (22, 31-34).

Disclosures

The authors are employees of Clarivate Analytics.

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