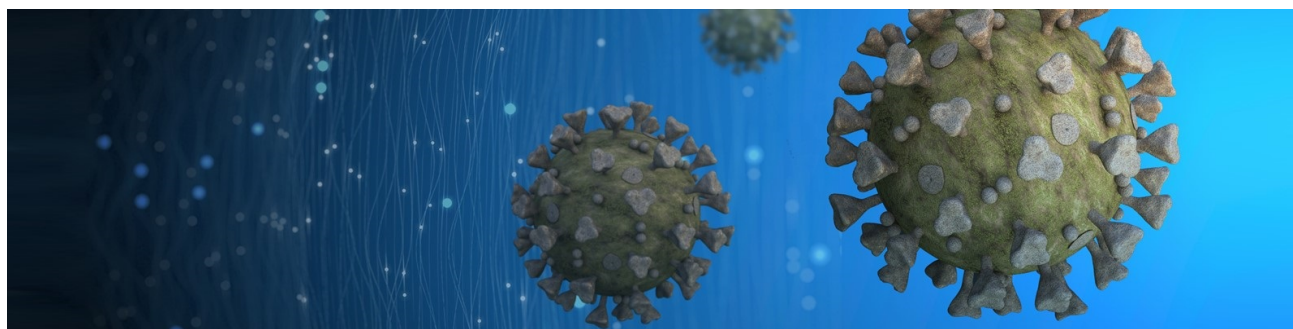




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The Molecular Targets of SARS-CoV-2



April 29, 2020 | [Donne Estipona](#)

The SARS-CoV-2 virus and its resulting disease COVID-19 have greatly impacted livelihoods across the world since its discovery in December of 2019. By late April 2020, the pandemic had infected over 3 million people and claimed over 200,000 lives¹. In an unprecedented display of effort and collaboration, the scientific community has made great strides in such a short amount of time. Over 1,000 SARS-CoV-2 genomes had been published by March². Several crystal structures of key SARS-CoV-2 proteins have now been solved, including the spike glycoprotein, RNA replication machinery proteins, and the two viral proteases³. The life cycle of SARS-CoV-2 is now reasonably well understood, owing to years of study on related [coronaviruses](#). Here we will discuss what researchers have now learned about the viral infection pathway of COVID-19 with an emphasis on the emerging targets for new drugs and vaccines.

The SARS-CoV-2 Virus

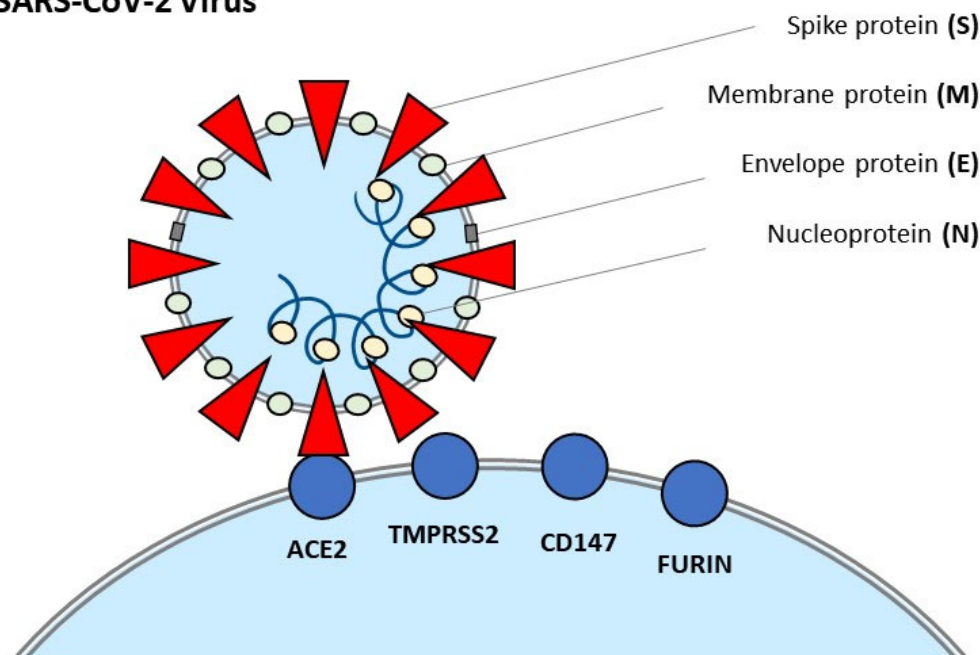


Image 1: This diagram summarizes components of the SARS-CoV-2 virion and the reported host cell receptors involved in viral binding.

Host cell recognition and binding

As a member of the SARS-related species of coronaviruses, SARS-CoV-2 shares many of its defining characteristics^{4,5}. The spike glycoprotein embedded in the viral lipid envelope recognizes the human host cell receptor, ACE2. An alternative receptor, CD147, has also been reported. After receptor binding, spike is cleaved by certain proteases in order to be primed for membrane fusion with the host cell. The proposed proteases for this task in SARS-CoV-2 are TMPRSS2 and furin^{6,7}.

Angiotensin-converting enzyme 2

(ACE2): ACE2 is a cell surface receptor and peptidase that cleaves angiotensin II and other peptide hormones. ACE2 is the

known binding partner of the SARS coronavirus spike protein. New functional studies now reveal ACE2 to be the recognized receptor for the entry of SARS-CoV-2 as well. Cell lines stably expressing ACE2 were highly transduced by SARS-CoV-2 pseudoviruses, while treatment with anti-ACE2 antibodies reduced viral entry^{6,7}. These findings make the ACE2-spike interaction an ideal target for antiviral therapeutics.

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Transmembrane serine protease 2 (TMPRSS2): TMPRSS2 is a cell surface protease known to cleave both ACE2 and the spike protein of coronaviruses. Its cleavage of ACE2 is believed to promote viral uptake, while cleavage of spike primes the viral particle for membrane fusion into the host cell. Recent studies have confirmed the TMPRSS2 enzyme activity to be a requirement of SARS-CoV-2 infection of lung cells. Reduced viral entry is observed when cells are treated with [camostat mesylate](#), an inhibitor with clinical applications in other pathways⁷.

Related products: [TMPRSS2 antibodies](#), [TMPRSS2 ELISA kits](#), [TMPRSS2 proteins](#), [TMPRSS2 vectors](#)

Furin: Furin is a protease known for cleaving inactive precursor proteins into their biologically active product. Notably, it functions in cleaving viral envelope proteins including those of HIV, influenza, dengue virus, ebolavirus, and some coronaviruses. While a furin-specific cleavage site has not been found in the SARS coronavirus, a site has been discovered in the protein sequence of the SARS-CoV-2 spike protein. Furin inhibitors have since been proposed in the search for new SARS-CoV-2 therapeutics⁸.

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CD147: Cluster of differentiation 147, also known as Basigin and EMMPRIN, has been implicated as a possible alternative receptor for the SARS-CoV-2 spike protein. An anti-CD147 antibody called meplazumab was shown to inhibit viral infection⁹. SARS-CoV-2 has been reported to infect T lymphocyte cell lines that express low levels of ACE2, supporting the possibility of CD147 as an alternate entry receptor¹⁶.

Related products: [CD147 antibodies](#), [CD147 ELISA kits](#), [CD147 proteins](#), [CD147 vectors](#)

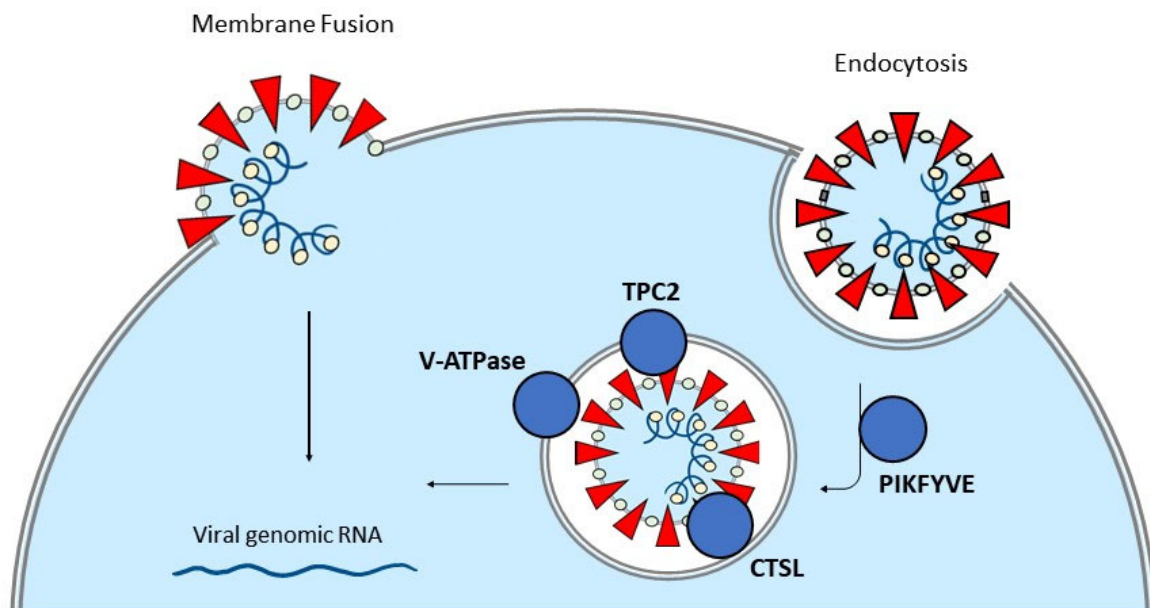


Image 2: The diagram depicts two proposed methods of viral entry (membrane fusion and endocytosis), with a focus on proteins involved in the endocytosis pathway.

Viral entry

In addition to direct fusion with the host cell membrane, SARS-CoV-2 has also been proposed to enter via endocytosis⁶. This route involves key proteins involved in endosome formation.

Phosphatidylinositol 3-phosphate 5-kinase (PIKFYVE): Endocytosis is an alternate mode of viral entry into host cells and is regulated in part by phosphoinositide lipids. The PIKFYVE kinase synthesizes a class of phosphoinositides that are required in early endosome formation. Activity of PIKFYVE has been discovered to be a requirement in the SARS-CoV-2 infection of human cells via endocytosis. PIKFYVE inhibitors [apilimod](#) and [YM201636](#) were found to significantly reduce SARS-CoV-2 entry⁶.

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Two pore segment channel 2 (TPC2): TPC2, encoded in humans as TPCN2, is a calcium channel expressed in lysosomal membranes and activated by phosphoinositides. TPC2 has been reported to be essential in the endocytosis of SARS-CoV-2, as its inhibition by [tetrandrine](#) led to a decrease in viral entry⁶.

Related products: [TPCN2 antibodies](#), [TPCN2 ELISA kits](#), [TPCN2 proteins](#), [TPCN2 vectors](#)

Cathepsin L (CTSL): Cathepsin L is a lysosomal pH-dependent protease known to mediate the cellular entry of SARS virus via endosomes by priming the virus for membrane fusion¹⁰. Studies with broad and specific inhibitors of cathepsin L—[E64D](#) and [SID 26681509](#)—have shown reduced entry of SARS-CoV-2 pseudovirions⁶. This suggests a similarly essential function for CTSL in the entry of SARS-CoV-2 and of its potential role as a drug target.

Related products: [Cathepsin L antibodies](#), [Cathepsin L ELISA kits](#), [Cathepsin L proteins](#), [Cathepsin L vectors](#), [Cathepsin L inhibitors](#)

Vacuolar-type H⁺ ATPase (V-ATPase): V-ATPases act as proton pumps that drive protons into endosomes and lysosomes, lowering the pH. An acidic environment is required by pH-dependent proteases such as cathepsins in order to complete the endocytosis of SARS-CoV-2. [Bafilomycin A](#), which specifically inhibits V-ATPase, is a known lysosomotropic agent. Other agents that inhibit endosome acidification include [ammonium chloride](#) and [chloroquine](#)⁶.

Related products: [V-ATPase antibodies](#), [V-ATPase ELISA kits](#), [V-ATPase proteins](#), [V-ATPase vectors](#)

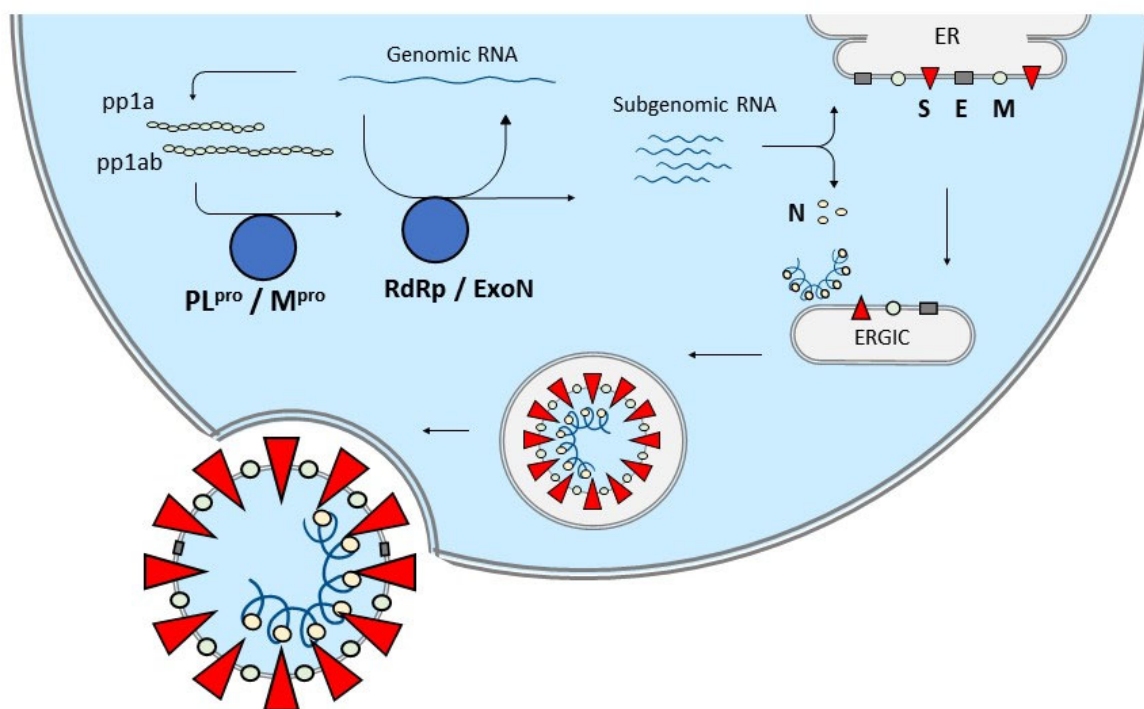


Image 3: This diagram summarizes the replication pathway of new SARS-CoV-2 virions for secretion outside of the host cell.

Viral replication and secretion

Upon uptake of viral genomic RNA, polyproteins and mature non-structural proteins are translated and processed. Assembly of the multi-subunit replicase-transcriptase complex (RTC) leads to both transcription and synthesis of new genomic RNA. Host translation machinery leads to the production of all proteins, with the envelope proteins (M, E, S) being inserted into the endoplasmic reticulum. An endoplasmic reticulum–Golgi intermediate compartment (ERGIC) mediates the assembly and maturation of new viral particles until their final release by exocytosis⁵.

Papain-like protease (PL^{Pro}): The SARS family of coronaviruses express a papain-like protease that functions in the proteolytic processing of three nonstructural proteins—Nsp1, Nsp2, and Nsp3. The SARS-CoV PL^{Pro} crystal structure has been solved. Screening chemical libraries for non-peptidic, reversible inhibitors for PL^{Pro} has led to the identification of one lead compound, [GRL0617](#)¹¹.

Related products: [PLpro antibodies](#), [PLpro proteins](#), [PLpro vectors](#)

Main protease (M^{Pro}): M^{Pro} (also known as 3C-like proteinase or 3CL^{Pro}) is responsible for processing the remaining nonstructural proteins of SARS coronaviruses, including RdRp and other subunits of the replicase–transcriptase complex (RTC). Several peptidomimetic inhibitor candidates have been reported for SARS-CoV M^{Pro}, including HCV protease inhibitors [telaprevir](#) and [boceprevir](#), and human rhinovirus protease inhibitor [rupintrivir](#)¹¹. The crystal structure of SARS-CoV-2 M^{Pro} has recently been reported, along with candidate α -ketoamide inhibitors for blocking its activity¹². HIV-1 protease inhibitors [lopinavir](#) and [ritonavir](#) have been reported to interact with the active site of M^{Pro}¹³.

Related products: [3CLpro vectors](#)

RNA-dependent RNA polymerase (RdRp): The RTC of coronaviruses functions in both the replication of the genomic viral RNA and transcription of subgenomic RNA. The complex is formed from multiple nonstructural protein subunits, including RNA-dependent RNA polymerase (nsp12), RNA helicase and 5'-triphosphatase (nsp13), exoribonuclease ExoN (nsp14), and processivity clamps (nsp7 and nsp8)⁶. The crystal structure of the SARS-CoV-2 RdRp (complexed as nsp12-nsp7-nsp8) has been solved, providing a possible binding and inhibition mechanism for the candidate drug, remdesivir¹⁴. [Remdesivir](#) is a selective nucleotide analog of ATP that causes the termination of RNA synthesis¹⁵.

Related products: [RdRP antibodies](#)

Exoribonuclease ExoN: ExoN, or CoV nsp14, is a proofreading 3'-5' ribonuclease that helps protect against errors in RNA replication, such as those caused by antiviral nucleoside inhibitors. Loss of ExoN proofreading has been found to enhance the antiviral effect of remdesivir¹⁷.

Viral immune response

Clinical reports and emerging research now tie SARS-CoV-2 infection to the life-threatening complication known as cytokine storm syndrome¹⁸. This extreme form of immune response has been associated with other viruses, including H5N1 and H1N1 influenza virus, variola virus, and SARS-CoV¹⁹. Cytokine storms are marked by the uncontrolled elevation of pro-inflammatory cytokines, over-recruitment of immune cells, and systemic inflammation that leads to tissue and organ damage. To account for cytokine storms, a combination therapy approach has been proposed that targets not only the pathogen but also key components of the immune response pathway²⁰.

Cytokines, including chemokines, interleukins, interferons and tumor necrosis factors (TNF), are small secreted proteins that mediate inflammation. Patients with severe COVID-19 requiring intensive care were found to have higher plasma levels of the proinflammatory cytokines GCSF, IP10, MCP1, MIP1A, and TNF α ²¹. Therapeutic targeting of certain cytokines, such as with anti-TNF antibodies, has been proposed as a means of limiting COVID-19 severity²².

Related products: [Cytokine ELISA kits](#), [Cytokine antibodies](#), [Cytokine multiplex assays](#)

Table 1: This chart summarizes the various reagents for SARS-CoV-2 research that are listed on Biocompare. Click on an X to view the products.

Target	Antibodies	ELISA Kits	Proteins	Vectors	Inhibitors
SARS-CoV-2	X	X	X		
ACE2	X	X	X	X	X
TMPRSS2	X	X	X	X	
CD147	X	X	X	X	
Furin	X	X	X	X	X
PIKFYVE	X	X	X	X	X
TPC2	X	X	X	X	
Cathepsin L	X	X	X	X	X
V-ATPase	X	X	X	X	
PL^{pro}	X		X	X	
			X		

M ^{pro}	
RdRp	X

This article has been updated on May 5, 2020.

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