

# ANTIVIRAL STRATEGIES

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FOR  
**EMERGING  
INFECTIOUS  
DISEASES**

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# Using Existing Therapeutics Against SARS-CoV-2

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*Editor's Note:* This article was updated from the original printing to reflect the FDA approval of remdesivir on October 22, 2020.

Existing FDA-approved drugs that have a known favorable safety profile are being examined for strategies to manage the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection that causes coronavirus disease 2019 (COVID-19) and fast-track a treatment plan. The influenza drug favilavir (favipiravir; sold for research use only under the name T-705) has been approved as an investigational therapy, and the Ebola virus drug remdesivir has been approved by the FDA for the treatment of COVID-19 requiring hospitalization, setting the standard for future COVID-19 antivirals. The rational selection of drugs already on the market is being made based on their ability to inhibit any proteins essential for virus-receptor interaction and/or viral life cycle.

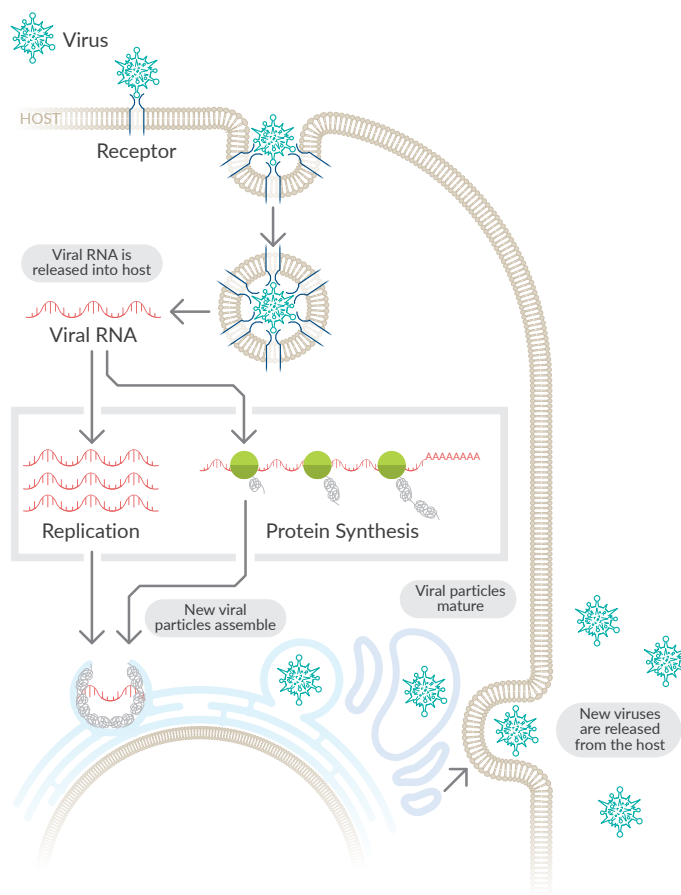
SARS-CoV-2 is a positive-sense, single-stranded RNA virus that shares 79.5% sequence identity with SARS-CoV. All coronaviruses consist of several key proteins, including a spike protein, a hemagglutinin-esterase dimer, a membrane glycoprotein, an envelope protein, and a nucleocapsid protein, to facilitate infection. The S protein mediates viral entry into host cells by binding to the host angiotensin-converting enzyme 2 (ACE2) receptor, which enables the fusion of viral and host membranes. ACE2 is highly concentrated in airway epithelial cells. Coronaviruses, including SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and infectious bronchitis virus (IBV), fuse at the plasma membrane or use receptor-mediated endocytosis and fuse with endosomes, depending on the cell or tissue type. This virus-receptor interaction facilitates both cross-species and human-to-human transmission of the virus, allowing the viral genome to be delivered to the host cell cytoplasm for replication.

## Virus-Host Fusion Inhibition

Broad-spectrum antivirals such as arbidol can block viral fusion with target membranes, prohibiting viral entry into cells. Because it targets a common critical step for viral replication, this strategy is effective against numerous viruses, including influenza A, B, and C, as well as hepatitis B and C. A study has shown that arbidol can effectively inhibit SARS-CoV-2 infection *in vitro*. Besides its antiviral action, arbidol can also induce interferon production and stimulate the phagocytic function of macrophages, both of which are important immunomodulatory responses to an infection.

Blocking virus-host fusion through inhibiting the Abl kinase pathway is also a promising target for the development of antiviral therapies, since this kinase activity is required for entry of coronaviruses. Abl kinases are composed of distinct domains that enable them to act as scaffolds for signaling complexes and to regulate protein function through phosphorylation of downstream targets. Pathogens have been shown to exploit Abl kinase signaling to rearrange F-actin cytoskeleton and trigger phosphorylation of viral effector proteins to facilitate viral-host fusion. A high-throughput screen identified imatinib as an inhibitor of SARS-CoV and MERS-CoV. It is likely that inhibition of Abl interferes with the actin dynamics required for virus-host fusion.

In addition to the coronavirus entering the host by binding to the host cell's ACE2 receptor, participation of ACE in the renin-angiotensin system has been implicated in the acute, accelerated lung fibrosis associated with coronavirus infection. ACE mediates the conversion of angiotensin I



Host infection and viral replication.

to angiotensin II, which interacts with angiotensin II type 1 (AT<sub>1</sub>) receptors. In some pathological conditions, overactivation of AT<sub>1</sub> receptors may lead to damaging events like fibrosis in the liver and lungs, possibly through increasing TGF-β expression. Presumably, a drug that would inhibit ACE, such as lisinopril, or block AT<sub>1</sub>, like losartan, would have a beneficial effect of mitigating the heavy fibrosis associated with acute cases of SARS infections by shutting down the ACE-angiotensin II-AT<sub>1</sub> pathway. ACE inhibitors may further play a role in barring viral fusion of the coronavirus to the host cell and entry into the cell, denying its pathway to replication.

Viral entry into a host requires spike protein priming by host cellular proteases. This involves spike protein cleavage at S1/S2 surface units and the S2' site and allows fusion of viral and cellular membranes. This activity is essential for viral spread and pathogenesis in the infected host. SARS-CoV-2 has been shown to use the endosomal cysteine proteases cathepsin B and L and the serine protease TMPRSS2 for spike protein priming. This is evidenced by the ability of the serine protease inhibitor camostat (mesylate), which is active against TMPRSS2 to partially block SARS-CoV-2-spike protein-driven entry into cells. Full inhibition of viral entry has been achieved by combining camostat (mesylate) with E-64d, an inhibitor of cathepsin B and L.

Viruses entering host cells by endocytosis require an acidic pH in endosomal vesicles for virus-host fusion and to carry out the replication process. The antimalarial agent chloroquine (phosphate) is a weak base that shows broad-spectrum antiviral activities by increasing the endosomal pH required for viral activity. It can impair the replication of viruses by interfering with endosome-mediated viral entry as well as the late stages of replication of enveloped viruses whose glycosylation step requires a low pH for enzyme processing. Chloroquine (phosphate) can also suppress the release of TNF-α and interleukin-6, which contribute to inflammatory complications of viral diseases. In multicenter clinical trials conducted in China, chloroquine (phosphate) demonstrated potent efficacy in treating pneumonia associated with COVID-19. However, more recent trials of the drug have shown mixed efficacy and produced safety concerns due to risk of heart rhythm problems. For this reason, the FDA revoked its emergency authorization.

## Viral Replication Inhibition

After infection, genomic RNA is released into the cytoplasm of the host cell and translated into two long, overlapping polyproteins, pp1a and pp1ab, which are processed by two proteases, the main protease (M<sup>pro</sup> or 3C-like protease) and the papain-like protease (PL<sup>pro</sup>). The hydrolytic activity

of these proteases produces multiple functional proteins that are essential to forming the replicase complex for viral replication. Protease inhibitors block the viral life cycle by selectively preventing such proteolytic cleavage. The protein sequences of SARS-CoV M<sup>pro</sup> and SARS-CoV-2 M<sup>pro</sup> are 96% identical, indicating that protease inhibitors that have shown success against SARS-CoV should have similar efficacy against SARS-CoV-2. Both mycophenolic acid and the hepatitis C virus (HCV) protease inhibitors telaprevir, boceprevir, and grazoprevir have all been shown to bind to the active site of SARS-CoV-2 PL<sup>pro</sup> and hence may be useful in preventing viral replication. A molecular docking study also revealed the HIV protease inhibitor indinavir nearly perfectly overlaps the region of the protein pocket of M<sup>pro</sup>. Some success has already been shown in treating SARS-CoV-2-infected patients with the HIV protease inhibitors lopinavir and ritonavir in combination with the influenza neuraminidase inhibitor oseltamivir.

Once inside the host cytoplasm, the single-stranded RNA virus serves as an RNA template that is replicated into complementary strands through the action of the RNA-dependent RNA polymerase (RdRp). The initiation step of RNA synthesis involves the addition of a nucleoside triphosphate to the 3' end. The strand is elongated by repeated nucleotidyl transfer reactions with subsequent nucleoside triphosphates added to generate the complementary RNA. A class of nucleotide analogs has been developed as antiviral drugs to confuse RdRp as they are incorporated into RNA strands and induce non-obligate RNA chain termination. During the 2003 SARS outbreak, the RdRp inhibitor ribavirin in combination with the HIV protease inhibitors lopinavir and ritonavir was shown to reduce the disease course of clinical trial patients. The RdRp inhibitor BCX4430 (galidesivir) is in an advanced development stage under the FDA Animal Efficacy Rule to counteract viral threats from coronaviruses, flaviviruses, filoviruses, paramyxoviruses, togaviruses, bunyaviruses, and arenaviruses.

Development of some nucleoside-based therapeutics for SARS-CoV infections has been hampered by their removal via a proofreading 3'-5' exoribonuclease (ExoN), but remdesivir, an adenosine nucleoside analog that demonstrates broad-spectrum anti-RdRp activities, has been shown to evade ExoN surveillance. Remdesivir was originally developed to treat Ebola virus, but also shows promising efficacy against SARS-CoV and MERS-CoV in pilot studies with an excellent safety profile in clinical trials so far. Remdesivir was used to treat the first US patient infected with SARS-CoV-2 who recovered. Results from a study sponsored by the National Institute of Allergy and Infectious Diseases (NCT04280705) found that

remdesivir significantly shortened the duration of clinical symptoms and accelerated resolution of the disease in some patients. Multiple additional trials (NCT04292730, NCT04292899, 2020-000936-23, NCT04315948, ISRCTN83971151) indicate clinical benefit in some patients with severe COVID-19, but no difference from standard of care in patients with moderate disease. The ribonucleoside analog EIDD-1931 has also recently shown potency against remdesivir-resistant CoV mutations, demonstrating broad-spectrum antiviral activity against SARS-CoV-2, MERS-CoV, SARS-CoV, and related zoonotic group 2b or 2c bat-CoVs.

During viral replication, oxysterol-binding protein (OSBP) plays a vital role in producing the membrane-bound viral replication organelles that form at the membrane contact sites between the endoplasmic reticulum (ER) and Golgi. The antifungal drug itraconazole and the natural compound OSW-1, which is being investigated as an anticancer drug, have been identified as functioning through targeting OSBP. While the binding modality of itraconazole is not known, OSW-1 has been shown to affect binding to one of the two established OSBP ligand binding sites. OSW-1 induces a prolonged reduction of cellular OSBP levels and has been shown to inhibit enterovirus replication. Coronaviruses may also be a suitable target for OSBP-targeted compounds.

Another step that is essential for viral replication is the nucleocytoplasmic shuttling of viral proteins through the action of host importin proteins. The antiparasitic compound ivermectin has been shown to inhibit the interaction between the HIV-1 integrase protein and the importin  $\alpha/\beta 1$  heterodimer. This action disrupts integrase protein nuclear import, which prevents HIV-1 replication. Ivermectin has also been shown to inhibit nuclear import of simian virus SV40 large tumor antigen and dengue virus non-structural protein 5 and to limit infection by RNA viruses such as dengue virus 1-4, West Nile virus, Venezuelan equine encephalitis virus, and influenza. Such broad-spectrum activity is likely due to the reliance by many different RNA viruses on importin  $\alpha/\beta 1$  during infection. Ivermectin also shows efficacy against the DNA virus pseudorabies virus. Nucleolar localization of the nucleocapsid protein is a common feature of the coronavirus family, but the SARS-CoV nucleocapsid protein does not appear to localize to the nucleus or the nucleolus of infected cells. Interestingly, reports have shown that ivermectin's nuclear transport inhibitory activity is effective against cultured Vero/hSLAM cells infected with SARS-CoV-2. The mechanism of action for how ivermectin interferes with

this particular coronavirus is unclear.

ER stress and subsequent activation of the unfolded protein response (UPR) are thought to contribute significantly to viral replication during a coronavirus infection. Indeed, cells overexpressing the SARS-CoV spike protein and other viral proteins exhibit high levels of UPR activation, and the expression of the ER protein folding chaperones GRP78, GRP94, and other ER stress-related genes is increased to maintain proper protein folding. The gold-thiol complex auranofin functions to inhibit redox enzymes, which leads to a dysregulation of redox homeostasis that induces oxidative stress and apoptosis. It has been shown to inhibit SARS-CoV-2 replication in cells at a low micromolar concentration with a 95% reduction in the viral RNA in just 48 hours after infection. Auranofin also has anti-inflammatory actions that reduce cytokine production and stimulate an immune response, so it may be helpful in mitigating any associated cytokine storm.

## Conclusion

Various potential targets for development of COVID-19 therapeutics exist along the stages from when a positive-sense, single-stranded RNA virus infects host cells to its replication and release from the host. With little time available for drug testing and development, the repurposing of approved pharmaceutical drugs provides the most immediate solution for addressing the COVID-19 outbreak. Indeed, knowledge gained from the previous SARS outbreak has placed researchers in an advantageous position of better understanding solutions for how to address long-term treatment of this newly identified coronavirus. With hundreds of antiviral compounds in our catalog and custom synthesis services at the ready, Cayman scientists are poised to support the development of an effective therapeutic strategy against SARS-CoV-2 infection.

**Flip through the pages of this Currents issue to explore all that Cayman has to offer to study the treatment and prevention of infectious diseases.**

### Learn More about Remdesivir

Read the article on Remdesivir: The First FDA-Approved Treatment for COVID-19 to learn about the metabolism of remdesivir and how it prevents viral replication.

[www.caymanchem.com/remdesivir](http://www.caymanchem.com/remdesivir)

# SPOTLIGHT ON COVID-19

## Tools to Study SARS-CoV-2-Host Interactions

Cayman provides SARS-CoV-2 viral proteins, host cell receptor antibodies, and screening assays that can help researchers identify agents that will minimize or block viral entry and replication. Serological ELISAs are available to screen for antibodies against SARS-CoV-2 as well as validating controls for the identification of neutralizing antibodies.

### ACE2 Antibodies

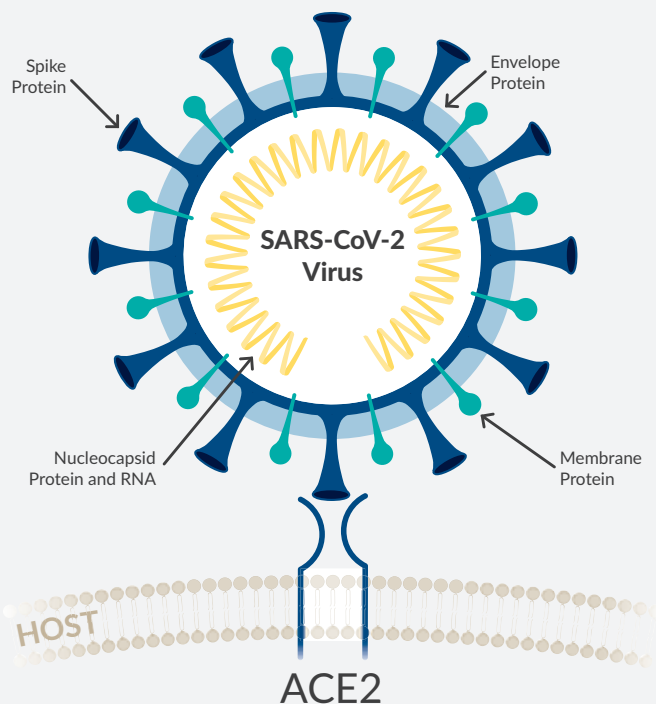
Item No.	Product Name
30582	ACE2 (human) Monoclonal Antibody (Clone AC18F)
30583	ACE2 (human) Monoclonal Antibody - Biotinylated (Clone AC18F)
30584	ACE2 (human) Monoclonal Antibody (Clone AC384)

### SARS-CoV-2 Spike Proteins

Item No.	Product Name
30430	SARS-CoV-2 Spike Glycoprotein (433-506)
30428	SARS-CoV-2 Spike Glycoprotein Receptor Binding Motif
30429	SARS-CoV-2 Spike Glycoprotein Receptor Binding Domain (human IgG1 Fc-tagged)

### SARS-CoV-2 Neutralizing Antibody & Controls

Item No.	Product Name
32526	SARS-CoV-2 (human) Neutralizing Recombinant Antibody
502080	SARS-CoV-2 Neutralizing Antibody Human Plasma Control Set
502090	SARS-CoV-2 Neutralizing Antibody Human Serum Control Set
31568	SARS-CoV-2 Neutralizing Antibody-Positive Human Serum
31567	SARS-CoV-2 Neutralizing Antibody-Negative Human Serum
31569	SARS-CoV-2 Neutralizing Antibody-Negative Pre-pandemic Human Serum



All coronaviruses consist of a spike (S) protein, an envelope protein, a membrane glycoprotein, and a nucleocapsid protein to facilitate infection. The S protein mediates viral entry into host cells by binding to the host ACE2 receptor, which enables the fusion of viral and host membranes.

### Serological SARS-CoV-2 ELISAs

Item No.	Product Name
502070	SARS-CoV-2 Neutralizing Antibody Detection ELISA Kit
31063	Q-Plex™ SARS-CoV-2 Human IgG (4-Plex)

## SCREEN FOR INHIBITORS OF SPIKE-ACE2 BINDING

### SARS-CoV-2 Spike-ACE2 Interaction Inhibitor Screening Assay Kit - Item No. 502050

- Plate-based assay
- Rapid results in <3 hours
- Colorimetric readout

### SARS-CoV-2 Spike S1 RBD-ACE2 Binding Cellular Imaging Assay Kit - Item No. 701970

- Cell-based imaging platform
- ACE2 expressed on cell surface using reverse transfection
- Semi-quantitative fluorescent readout

Learn more at [www.caymanchem.com/SARS-CoV-2Tools](http://www.caymanchem.com/SARS-CoV-2Tools)

# ANTIVIRAL COMPOUNDS

## Targeting Viral-Host Fusion

### Host Protease Inhibitors

TMPRSS2 as well as cathepsin B and L inhibitors prevent SARS-CoV and SARS-CoV-2 surface glycoprotein incorporation into cells.

Item No.	Product Name
16018	Camostat (mesylate)
10007963	E-64
10007964	E-64c
13533	E-64d

### Viral Entry/Fusion Inhibitors

Viral entry can be prevented by thwarting the hemagglutinin envelope glycoprotein fusion machinery or interfering with the binding domains of the spike protein.

Item No.	Product Name
10005167	Genistein
70675	<i>trans</i> -Resveratrol
16933	Umifenovir (hydrochloride)

### Abl Kinase Inhibitors

Abl kinases are composed of distinct domains that enable them to act as scaffolds for signaling complexes and to regulate protein function through phosphorylation of downstream targets. Blocking virus-host fusion with Abl kinase inhibitors is one antiviral strategy, since this kinase activity is required for viral entry.

Item No.	Product Name
16253	GNF-2
16254	GNF-5
13139	Imatinib (mesylate)
11497	Saracatinib

Note: The products listed in this newsletter are for biomedical research only. They are not for human or veterinary use.

### ACE Inhibitors

ACE inhibitors may play a role in barring viral fusion of SARS-CoV-2 to the host cell, but also have a role in mitigating the fibrosis associated with SARS infections.

Item No.	Product Name
15313	Captopril
22186	DX600
16833	Lisinopril

## STUDY THE ROLES OF ANGIOTENSIN II AND ACE2 IN COVID-19

Angiotensin II is hypothesized to prevent host cell entry of the virus from SARS-CoV-2 through competitive inhibition, downregulation, internalization, and then degradation of ACE2. Both ACE inhibitors and angiotensin II receptor blockers may promote ACE2 expression or activity, potentially by increasing plasma levels of angiotensin II.

The **ACE2 Inhibitor Screening Assay Kit (Item No. 502100)** can be used to test potential inhibitors of human ACE2 activity. This assay uses a fluorogenic ACE2 substrate, allowing users to measure ACE2 activity using a fluorescence plate reader.

The **Angiotensin II EIA Kit (Item No. 589301)**, manufactured by Bertin Bioreagent, enables the quantification of angiotensin II levels in plasma as well as culture supernatants in all mammalian species for further investigation.

### Endosomal pH Regulators

Viruses entering host cells by endocytosis require an acidic pH in endosomal vesicles for virus-host fusion and to carry out the replication process. Agents that interfere with endosome-mediated viral entry can impair virus replication.

#### Endosomal Acidification Inhibitors

Item No.	Product Name
14194	Chloroquine (phosphate)
17911	Hydroxychloroquine (sulfate)

# Targeting Viral Replication

## Protease Inhibitors

The main protease (M<sup>pro</sup> or 3C-like protease) and the papain-like protease (PL<sup>pro</sup>) process the genomic RNA released in the cytoplasm of the host cell after infection. Protease inhibitors block the viral life cycle by selectively preventing proteolytic cleavage that is essential to forming the replicase complex for viral replication.

### M<sup>pro</sup> and PL<sup>pro</sup> Inhibitors

Item No.	Product Name
33348	GRL-0617
33354	HY-17542
31344	M <sup>pro</sup> Inhibitor 11a
31345	M <sup>pro</sup> Inhibitor 11b

### HCV Protease Inhibitors

Item No.	Product Name
20835	Asunaprevir
18379	Boceprevir
22144	Simeprevir (sodium salt)

### HIV Protease Inhibitors

Item No.	Product Name
15866	Darunavir
13854	Lopinavir
15144	Nelfinavir (mesylate)
13872	Ritonavir
9001893	Saquinavir (mesylate)

See all protease inhibitors at [www.caymanchem.com](http://www.caymanchem.com)

## Oxysterol-Binding Protein Inhibitors

Oxysterol-binding protein (OSBP) plays a vital role in producing the membrane-bound viral replication organelles that form at the membrane contact sites between the ER and Golgi. OSBP-targeted compounds interfere with virus replication.

### Oxysterol-Binding Protein Inhibitors

Item No.	Product Name
13288	Itraconazole
30310	OSW-1

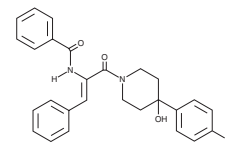
## Intracellular Membrane Remodeling

### FEATURED PRODUCT

#### K22

Item No. 31578

Impairs the remodeling of host cell membranes into double membrane vesicles that support viral RNA synthesis.



## DNA & RNA Polymerase Inhibitors

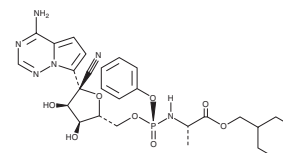
Viruses encode their own polymerases for transcription and replication. A class of nucleotide analogs has been developed as antivirals to confuse polymerase activity, thus counteracting viral replication.

### FEATURED PRODUCT

#### Remdesivir

Item No. 30354

An adenosine nucleoside analog originally developed to treat Ebola virus that demonstrates broad-spectrum anti-RdRp activities. It has been approved by the FDA to treat patients hospitalized with COVID-19.



### LEARN MORE

Read our News article to learn more about the metabolism of remdesivir and how it prevents viral replication.

[www.caymanchem.com/remdesivir](http://www.caymanchem.com/remdesivir)

### RdRp Inhibitors

Item No.	Product Name
9002958	EIDD-1931
29586	EIDD-2801
13831	Entecavir (hydrate)
30469	GS-441524
15402	PSI-7977
16757	Ribavirin
23384	T-705 (Favipiravir)

See all RdRp inhibitors at [www.caymanchem.com](http://www.caymanchem.com)

## Reverse Transcriptase Inhibitors

Retroviruses reverse transcribe viral RNA into DNA for insertion into the host DNA. Nucleoside analogs as well as non-nucleoside compounds have been developed to prevent viral replication by inhibiting reverse transcriptase activity.

### Reverse Transcriptase Inhibitors

Item No.	Product Name
14412	Efavirenz
18514	Lamivudine
21559	Rilpivirine
13874	Tenofovir
15492	Zidovudine

## Nuclear Transport Inhibitors

Many viruses rely on host importin proteins to shuttle viral proteins including integrases, oncoproteins, nucleocapsid proteins, and non-structural proteins from the cytoplasm to the nucleus. Disrupting this process can prevent viral replication. The antiparasitic ivermectin has been shown to inhibit nuclear transport.

### Ivermectin Analogs

Item No.	Product Name
18768	Ivermectin B <sub>1a</sub>
23824	Ivermectin B <sub>1b</sub>

## Integrase Inhibitors

Retroviral integrases integrate viral DNA into host cell DNA, forming a provirus that can be activated to produce viral proteins. Integrase inhibitors block incorporation of the virus into host DNA by preventing covalent bond formation with host DNA.

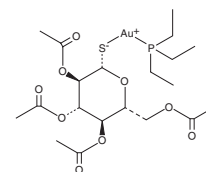
### Integrase Inhibitors

Item No.	Product Name
26532	Bictegravir
22191	Dolutegravir
16071	Raltegravir (potassium salt)
70740	U-73122

## Redox Homeostasis

### FEATURED PRODUCT

#### Auranofin Item No. 15316



A gold-thiol complex that inhibits redox enzymes related to ER stress and has anti-inflammatory actions that reduce cytokine production. It has been shown to reduce SARS-CoV-2 replication in cells.

## Potential Viral Active Site Targets

Using *in silico* modeling, Cayman scientists have identified several FDA-approved drugs that interact with the SARS-CoV-2 spike protein and/or M<sup>pro</sup> protein.

### Identified Spike Protein Interactions

Item No.	Product Name
23371	CCK Octapeptide (sulfated)
20383	DL-Folinic Acid (calcium salt)
23757	Octreotide (acetate)
14269	Pemetrexed (sodium salt hydrate)
14157	Polymyxin B (sulfate)
23696	TAK-599
15026	Tigecycline

### Identified M<sup>pro</sup> Interactions

Item No.	Product Name
20873	Azelastine (hydrochloride)
17348	Desmopressin
23950	Isavuconazonium (sulfate)
22275	Leuprorelin (acetate)
10008318	Montelukast (sodium salt)
14287	Neomycin (sulfate)

See our SARS-CoV-2 Screening Library on page 8 to learn more about obtaining the full data package or made-to-order library containing these compounds.

Access all that Cayman has to offer to support coronavirus research in one place by visiting our Coronavirus Resource Center.

[www.caymanchem.com/coronavirus](http://www.caymanchem.com/coronavirus)



# SIMPLIFY DRUG SCREENING & HIT-SEEKING

Many of the antiviral compounds featured in this issue of the Cayman Currents are conveniently packaged in our focused screening libraries. Discover our Anti-Inflammatory, Antiviral, FDA-Approved Drugs, and SARS-CoV-2 Screening Libraries, which have been designed to help speed up the process of identifying drugs that might be helpful to treat COVID-19 and other infectious diseases.

## Advantages of Cayman Compound Libraries

- **Careful Curation:** Rich compilation of biologically active molecules handpicked by Cayman scientists
- **Convenient Format:** 96-well Matrix™ tube rack format as 0.1-10 mM stock solutions in DMSO for HTS
- **Hit Compound Availability:** Compounds are available in bulk quantities when hits are identified
- **Library Customization:** Library compilations can be customized to your specifications

## Anti-Inflammatory Screening Library

Item No. 31530

## Antiviral Screening Library

Item No. 30390

## FDA-Approved Drugs Screening Library

Item No. 23538

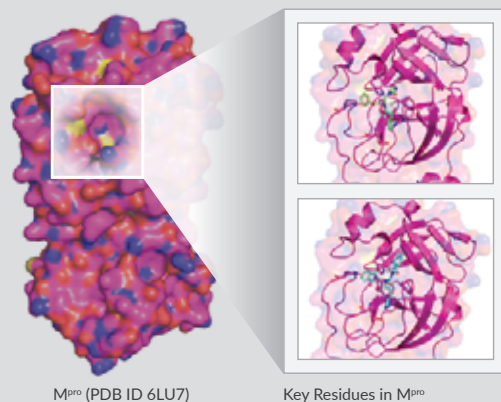


## SARS-CoV-2 Screening Library

Item No. 9003509

A made-to-order compound library curated through *in silico* modelling using Maestro (Schrödinger Suite) software by screening over 70,000 compounds targeting SARS-CoV-2 proteins. Options include:

- Full library of 2,000+ compounds
- Hand-curated libraries tailored to your project
- Access to the full data package comprised of compound characteristics and predicted physicochemical properties of nine SARS-CoV-2 targets



M<sup>pro</sup> (PDB ID 6LU7)

Key Residues in M<sup>pro</sup> SARS-CoV-2:  
His41 motif, His163-Glu166 motif, and catalytic Cys145

Learn more about Cayman Compound Libraries at [www.caymanchem.com/compoundlibraries](http://www.caymanchem.com/compoundlibraries)

# Vaccine Development for Emerging Infectious Disease

## STING Adjuvants in Viral and Bacterial Vaccines

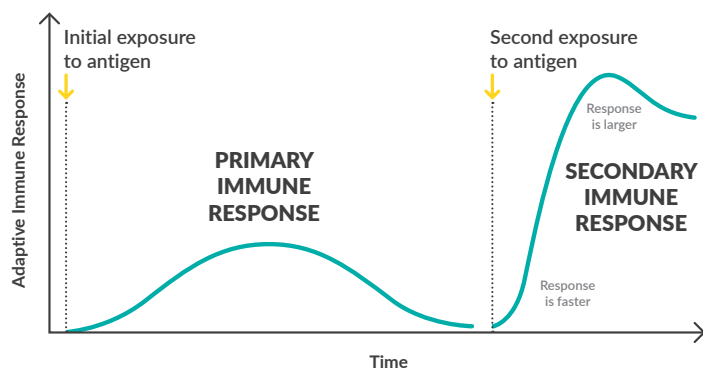
Melissa A. Bates, Ph.D., Cayman Chemical

### Vaccines Prevent Widespread Contagious Diseases

The pandemic caused by the unexpected emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, prompted an urgent need to develop a vaccine against this infectious disease. Vaccines provide protection against infectious diseases by inducing immunological memory to a pathogen.

### The Immunology of Vaccines

Immunological memory is a hallmark of the immune system that confers long-term protection against infectious agents. This property can be exploited through vaccines. Vaccines are formulated to initiate an innate immune response that directs the antigen-specific adaptive immune response. Pathogen-associated molecular patterns (PAMPs) are pathogen-specific signatures that are recognized by cells of the innate immune system, including macrophages, neutrophils, and dendritic cells (DCs), through a diverse repertoire of pattern recognition receptors (PRRs). PRRs that sense viral PAMPs include the endosomal toll-like receptors (TLRs), TLR3, TLR7, TLR8, and TLR9, as well as cytosolic nucleic acid sensors, including nucleotide-binding oligomerization domain-containing protein 1 (NOD1), NOD2, retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated protein 5 (MDA5), and cyclic GMP-AMP (cGAMP) synthase (cGAS). Adjuvants are substances included in a vaccine that boost the antigen-specific immune response by activating PRRs. They activate PRRs by either directly acting as PRR ligands themselves or by inducing the release of damage-associated molecular patterns (DAMPs), such as uric acid, that activate PRRs.



Vaccines provide defense against bacterial and viral pathogens by inducing immunological memory.

Activation of PRRs that have a signature immunostimulatory profile tailors the adaptive immune response towards one that is most effective against the target pathogen. It induces signal transduction pathways that result in a distinct profile of gene and co-stimulatory molecule expression, as well as the release of cytokines, chemokines, and other immunomodulators that direct the adaptive immune response. After antigen encounter at the site of vaccination, DCs migrate to the lymph nodes and present antigens in surface major histocompatibility complexes (MHCs) to antigen-specific T cells, which differentiate into T helper cells. Different subsets of T helper cells can influence the nature of the resulting immune responses to optimally eradicate the perceived threat. After the initial immune response, a small number of antigen-specific cells differentiate into long-lived, memory T and B cells. Upon re-exposure to the antigen, memory T and B cells rapidly expand into effector T cells and plasma cells, respectively, enabling a rapid response to the pathogen and preventing infectious diseases.

### Type I Interferons Are Critical for Antiviral Immunity

Type I interferons (IFN- $\alpha$  and IFN- $\beta$ ) are critical for host defense against viral pathogens. Type I IFNs induce the transcription of a variety of interferon-stimulated genes that act in an autocrine, paracrine, or systemic manner to induce a myriad of effects on the immune system that collectively facilitate defense against viral pathogens. They reduce viral replication in infected cells and induce an antiviral state in neighboring cells. Antigen-presenting cells (APCs) stimulated with type I IFNs increase surface expression of MHC and co-stimulatory molecules, increasing the ability of APCs to stimulate differentiation of naïve T cells into effector T cells. Type I IFNs also promote the induction and proliferation of memory T cells.

### STING Activation by Vaccine Adjuvants

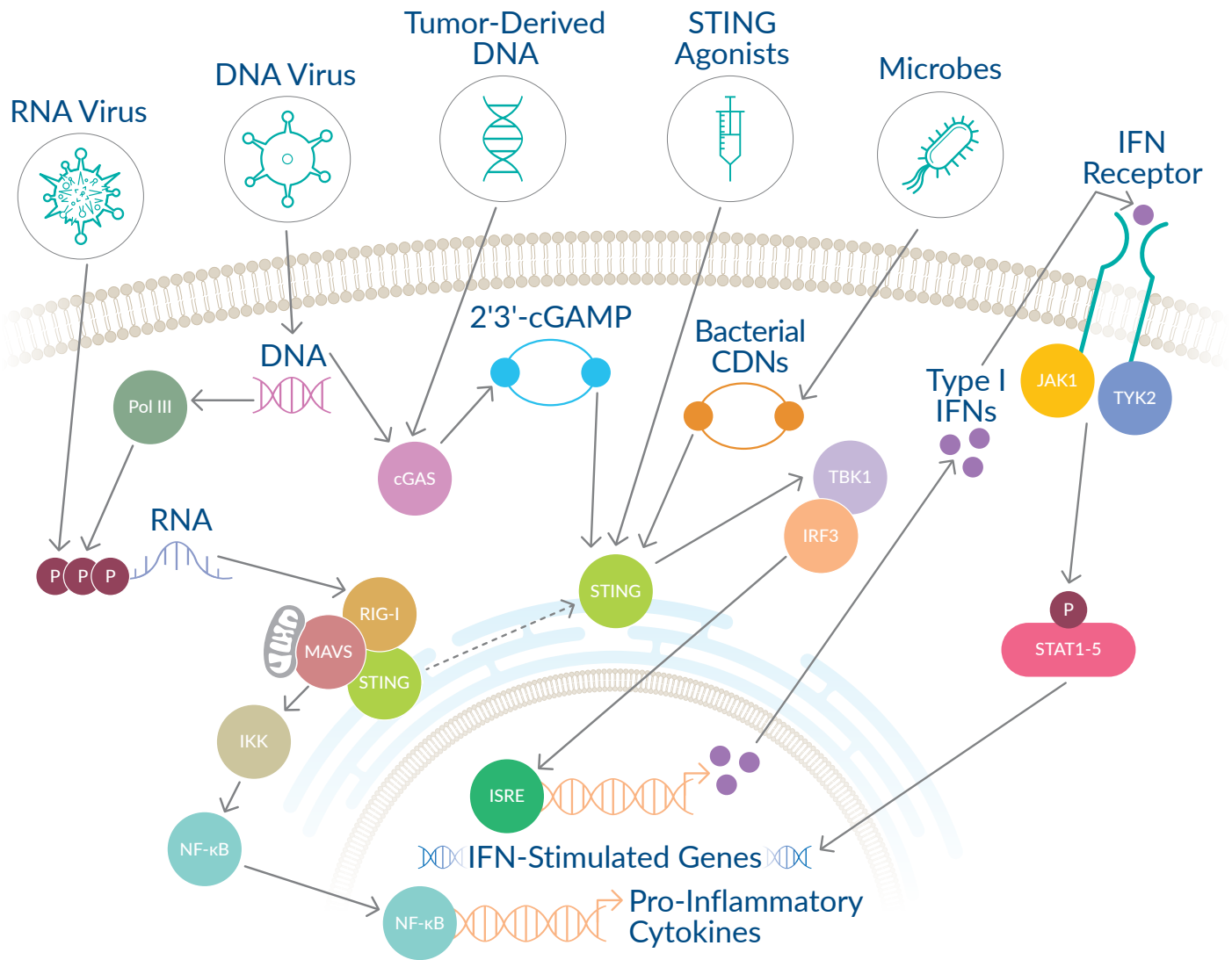
Ligands that activate STimulator of INTERferon Genes (STING) induce type I IFNs and have been used as vaccine adjuvants in preclinical models. STING is a signaling protein located on the endoplasmic reticulum and is widely expressed in immune cells. The cyclic dinucleotides (CDNs) cyclic di-GMP, cyclic di-AMP, and 3'3'-cGAMP are bacterial second messengers that bind to and activate

STING. STING can also be activated through the action of cGAS. cGAS is a cytosolic DNA sensor that catalyzes the formation of the STING activator 2'3'-cGAMP upon recognition of foreign DNA, including viral DNA.

STING activation recruits the adapter protein TANK-binding kinase 1 (TBK1), which phosphorylates and activates the transcription factor interferon regulatory factor 3 (IRF3), leading to the expression of type I IFNs. STING also activates NF-κB, resulting in the production of additional inflammatory cytokines. STING has also been shown to interact with RIG-I and mitochondrial antiviral-signaling protein (MAVS), which are key cytosolic sensors of viral RNA, though the precise molecular events leading to STING activation have yet to be elucidated.

Natural STING ligands have been used to boost vaccine efficacy against viral and bacterial pathogens. Wang *et al.* demonstrated that 2'3'-cGAMP preferentially induced

a Th1-mediated immune response that was associated with improved survival upon viral challenge when used as an adjuvant in the H1N1 swine influenza vaccine in mice. These authors also found that mice administered an H5N1 avian influenza vaccine containing 2'3'-cGAMP as an adjuvant developed antigen-specific antibodies within two weeks of immunization that remained in circulation for at least 40 weeks. Blauboer *et al.* showed that intranasal administration of cyclic di-GMP increases ovalbumin (OVA) uptake and processing by pulmonary DCs and decreases lung colony forming units in a mouse model of lung *S. pneumoniae* infection. STING ligands have also shown promise as cancer vaccine adjuvants. Gutjahr *et al.* demonstrated that immunization with OVA and 2'3'-cGAMP increased the percentage of OVA-specific IFN-γ<sup>+</sup> CD8<sup>+</sup> T cells and inhibited tumor growth in an OVA<sup>+</sup> EG7 tumor implant mouse model.



STING activators induce IFN and pro-inflammatory cytokines.

Nucleoside- and non-nucleoside-based STING activators have been successfully used as vaccine adjuvants in preclinical models. Inhibition of ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), a cGAMP hydrolase, is an additional approach that could be investigated for use in vaccines. Inhibitors of ENPP1 increase the concentration of 2'3'-cGAMP by reducing its degradation and thus could be further explored as a means to increase STING activation.

### Key Considerations for Vaccine Development

Successful implementation of a vaccine-based, population-wide, infectious disease control strategy requires that the vaccine is safe and effective in all individuals, including those most susceptible to infectious diseases, such as children, the elderly, and the immunocompromised. Antigens used in vaccines must be selectively and stably expressed by the pathogen. It should distinguish between commensal and pathogenic bacterial or viral strains and not subject to geographic or temporal variability. The combination of antigen and adjuvant used in a vaccine must be balanced to have sufficient immunogenicity without overt reactogenicity. Vaccines are a preventative approach to infectious diseases that requires vigilance for emerging pathogens. However, the utility of a vaccination program to control an ongoing pandemic caused by a novel pathogen is hindered by the time required for their design and is inevitably reliant on the availability of existing agents to inhibit pathogen replication and manage symptoms of the infectious disease.

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2. Blaauboer, S.M., Mansouri, S., Tucker, H.R. *et al.* The mucosal adjuvant cyclic di-GMP enhances antigen uptake and selectively activates pinocytosis-efficient cells in vivo. *Elife* **4**, e06670 (2015).
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10. Volckmar, J., Knop, L., Stegemann-Koniszewski, S. *et al.* The STING activator c-di-AMP exerts superior adjuvant properties than the formulation poly(I:C)/CpG after subcutaneous vaccination with soluble protein antigen or DEC-205-mediated antigen targeting to dendritic cells. *Vaccine* **37**(35), 4963-4974 (2019).
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## PRODUCTS MENTIONED IN THIS ARTICLE

### Viral Nucleic Acid Sensors

#### RIG-I helicase domain (human, recombinant)

Item No. 25620

- ≥80% pure recombinant human protein

#### RIG-I Monoclonal Antibody (Clone 1E3)

Item No. 25300

- For immunochemical detection of RIG-I
- **Applications:** ELISA, IHC, WB

#### cGAS (human, recombinant)

Item No. 22810

- ≥90% pure recombinant human enzyme
- cGAS activity demonstrated using Cayman's 2'3'-cGAMP ELISA Kit

#### cGAS Monoclonal Antibody (Clone 5G10)

Item No. 23853

- For immunochemical detection of cGAS
- **Applications:** IF, IP, WB

## IDENTIFY MODULATORS OF cGAS ACTIVITY

### cGAS Inhibitor Screening Assay Kit Item No. 701930

A robust and easy-to-use platform for identifying novel inhibitors of human cGAS. This assay directly measures 2'3'-cGAMP produced by cGAS in the presence of DNA, ATP, and GTP. The cyclic dinucleotide product of that reaction is quantified *via* ELISA using a 2'3'-cGAMP-specific antiserum. The cGAS inhibitor CU-76 is included as a positive control.

# Sensitive, Accurate Quantification of Cyclic Dinucleotides

Cayman has developed immunoassays for specific detection of 2'3'-cGAMP, cyclic di-GMP, and cyclic di-AMP in mammalian and bacterial cell lysates using a colorimetric 96-well microtiter plate format. With enough reagents to assay 24 samples in triplicate or 36 samples in duplicate, you can monitor the formation and hydrolysis of specific cyclic dinucleotides in a biological setting. By monitoring cyclic dinucleotides levels, these assays can be used to identify compounds that modulate their activation and degradation.

- **Specific:** Specific detection of 2'3'-cGAMP, cyclic di-GMP, or cyclic di-AMP
- **Highly Sensitive:** Sensitive immunoassay format down to low pg/ml range concentrations
- **Reliable:** Validated in THP-1 or *E. coli* cell lysates

## 2'3'-cGAMP ELISA Kit

Item No. 501700

Measure 2'3'-cGAMP in mammalian cell lysates

## Cyclic di-GMP ELISA Kit

Item No. 501780

Measure cyclic di-GMP in bacterial cell lysates

## Cyclic di-AMP ELISA Kit

Item No. 501960

Measure cyclic di-AMP in bacterial cell lysates

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## STING Activators

Item No.	Product Name
17753	Cyclic di-AMP (sodium salt)
17144	Cyclic di-GMP (sodium salt)
22485	Cyclic di-IMP (sodium salt)
17966	3'3'-cGAMP (sodium salt)
30022	CAY10748
22353	G10
30140	MSA-2
32520	STING Agonist 1a
27886	STING Agonist C11
32521	STING Agonist 12b
28054	diABZI STING Agonist-1 (hydrochloride)

## STING Antagonists

Item No.	Product Name
30159	C-171
25859	C-176
25860	C-178
25857	H-151

## ENPP1 Inhibitors

Item No.	Product Name
29864	3,3'-((2-Chlorophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one)
29865	CAY10761
31764	ENPP1-IN-1
29809	ENPP1 Inhibitor C

# Measure the Efficacy of OVA/Adjuvant Immunization

Measuring anti-ovalbumin (OVA) antibody levels in plasma or serum can be used to determine the effectiveness of an immunization by assessing the magnitude of the Th2 immune response.

- **Specific:** Selective detection of anti-OVA IgG1 and IgE in mouse plasma or serum
- **Highly Accurate:** Employs anti-OVA antibody from mice immunized with OVA/alum as the standard
- **Rapid:** Get results in under 4 hours; sample purification not required

## Anti-Ovalbumin IgE (mouse) ELISA Kit

Item No. 500840

## Anti-Ovalbumin IgG1 (mouse) ELISA Kit

Item No. 500830

# HOST IMMUNE RESPONSE & THE CYTOKINE STORM

When viral genetic material is detected, a cascade of signaling events such as activating the type I interferon (IFN) pathway is initiated. An excessive immune response with an abnormal release of circulating cytokines can have damaging effects throughout the body and has been called the cytokine storm. Many cytokines take part in this surge including IL-6, IL-1, IL-2, IL-10, CRP, MCP3, TNF- $\alpha$ , and IFN- $\gamma$ .

## Interferon Activation Proteins & Antibodies

Item No.	Product Name
22811	IRF3 (human recombinant)
23590	IRF3 (S386A, S396A mutant; human recombinant)
22817	TBK1 (human, recombinant)
24937	IRF3 Polyclonal Antibody
25924	TBK1 Monoclonal Antibody (Clone 4E6)

## NF- $\kappa$ B Transcription Factor Assays

Item No.	Product Name
10006912	NF- $\kappa$ B (human p50) Transcription Factor Assay Kit
10007889	NF- $\kappa$ B (p65) Transcription Factor Assay Kit
10009277	Nuclear Extraction Kit

## Single-Plex Cytokine Detection Assays

Item No.	Product Name
583301	Interleukin-1 $\alpha$ (human) ELISA Kit
583311	Interleukin-1 $\beta$ (human) ELISA Kit
501030	Interleukin-6 (human) ELISA Kit
583371	Interleukin-6 (mouse) ELISA Kit

## Immune Suppression

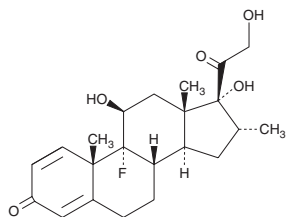
### FEATURED PRODUCT

#### Dexamethasone

Item No. 11015

Several established immunosuppressive agents, such as broadly acting anti-inflammatories, effectively overpower cytokine storms.

This synthetic glucocorticoid has been shown to reduce deaths by a third in patients hospitalized with COVID-19 in the RECOVERY trial. Its complex effects act primarily through inhibition of inflammatory cells and suppression of expression of inflammatory mediators. [Also available in our Anti-Inflammatory Screening Library \(page 8\).](#)



## Multi-Plex Cytokine Detection Assays

### HUMAN MULTIPLEX KITS

#### Cytokine Screen (16-plex)

Item No. 28327

Includes IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-15, IL-17, IL-23, IFN- $\gamma$ , TNF- $\alpha$ , TNF- $\beta$

#### High Sensitivity Cytokine Screen (15-plex)

Item No. 28328

Includes IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p70, IL-13, IL-15, IL-17, IL-23, IFN- $\gamma$ , TNF- $\alpha$ , TNF- $\beta$

#### Cytokine Release (16-plex)

Item No. 31810

Includes GM-CSF, IL-1 $\beta$ , IL-1RA, IL-2, IL-2R $\alpha$ , IL-6, IL-6R, IL-8, IL-10, IL-12p70, IL-13, MCP-1, MIP-1 $\alpha$ , IFN- $\alpha$ , IFN- $\gamma$ , TNF- $\alpha$

### MOUSE MULTIPLEX KITS

#### Cytokine Screen (16-plex)

Item No. 28329

Includes IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, IL-12p70, IL-17, MCP-1, IFN- $\gamma$ , TNF- $\alpha$ , MIP-1 $\alpha$ , GMCSF, RANTES

#### Inflammatory Cytokines (14-plex)

Item No. 28332

Includes IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, IL-3, IL-4, IL-6, IL-10, IL-12p70, IL-17, MCP-1, TNF- $\alpha$ , MIP-1 $\alpha$ , GMCSF, RANTES



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# NEUTROPHIL DEFENSE & CONTROLLING COLLATERAL DAMAGE

Neutrophils activated by platelets have an important role in the destruction of invasive pathogens through oxidative burst, the release of neutrophil extracellular traps (NETs), and phagocytosis. Excessive neutrophil infiltration and NETosis is linked to elevated pro-inflammatory cytokines, increased inflammation, and thrombosis. While targeting platelet activation could indirectly lead to reduced NET formation, targeting the enzymes essential to NET formation (*e.g.*, peptidylarginine deiminase 4 (PAD4) and neutrophil elastase) directly blocks their assembly. Cayman has developed several tools to identify NETs and inhibit their formation as well as compounds to control platelet activation.



Read the article on Casting NETs in COVID-19 to learn about how NETs are being examined as a complicating factor in the severity of the disease.

[www.caymanchem.com/SARS-CoV-2NETs](http://www.caymanchem.com/SARS-CoV-2NETs)

## Antiplatelet Compounds

Item No.	Product Name
21411	Anagrelide (hydrochloride)
18210	Carbaprostacyclin
16831	Cicaprost
14455	Cilostamide
15035	Cilostazol
18189	Dipyridamole
21690	Picotamide
18220	Prostaglandin I <sub>2</sub> (sodium salt)
15425	Ticagrelor

## Neutrophil Elastase Inhibitors

Item No.	Product Name
26083	AZD 9668
18615	BAY-678
27957	GW 311616A
14922	Neutrophil Elastase Inhibitor
17779	Sivelestat (sodium salt hydrate)
21477	SSR 69071

## PAD Inhibitors

Item No.	Product Name
17079	BB-Cl-Amidine
22653	CAY10723
26543	CAY10727
26546	CAY10729 (trifluoroacetate salt) (technical grade)
28320	CAY10740 (hydrochloride)
10599	Cl-Amidine (hydrochloride)
17489	GSK199 (hydrochloride)
17488	GSK484 (hydrochloride)
17731	YW3-56 (hydrochloride) (technical grade)

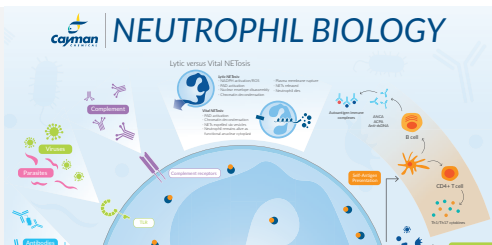
## NET Biomarker and Activity Kits

Item No.	Product Name
501620	Citrullinated Histone H3 (Clone 11D3) ELISA Kit
501410	Myeloperoxidase (human) ELISA Kit
601010	NETosis Assay Kit
600610	Neutrophil Elastase Activity Assay Kit
600620	Neutrophil Myeloperoxidase Activity Assay Kit
601130	Neutrophil/Monocyte Respiratory Burst Assay Kit

## Request the Neutrophil Biology Poster

Explore the events of NETosis and the relationship to the onset of disease as currently represented in peer-reviewed literature.

[www.caymanchem.com/neutrophilposter](http://www.caymanchem.com/neutrophilposter)



# SPOTLIGHT ON BIOACTIVE LIPIDS

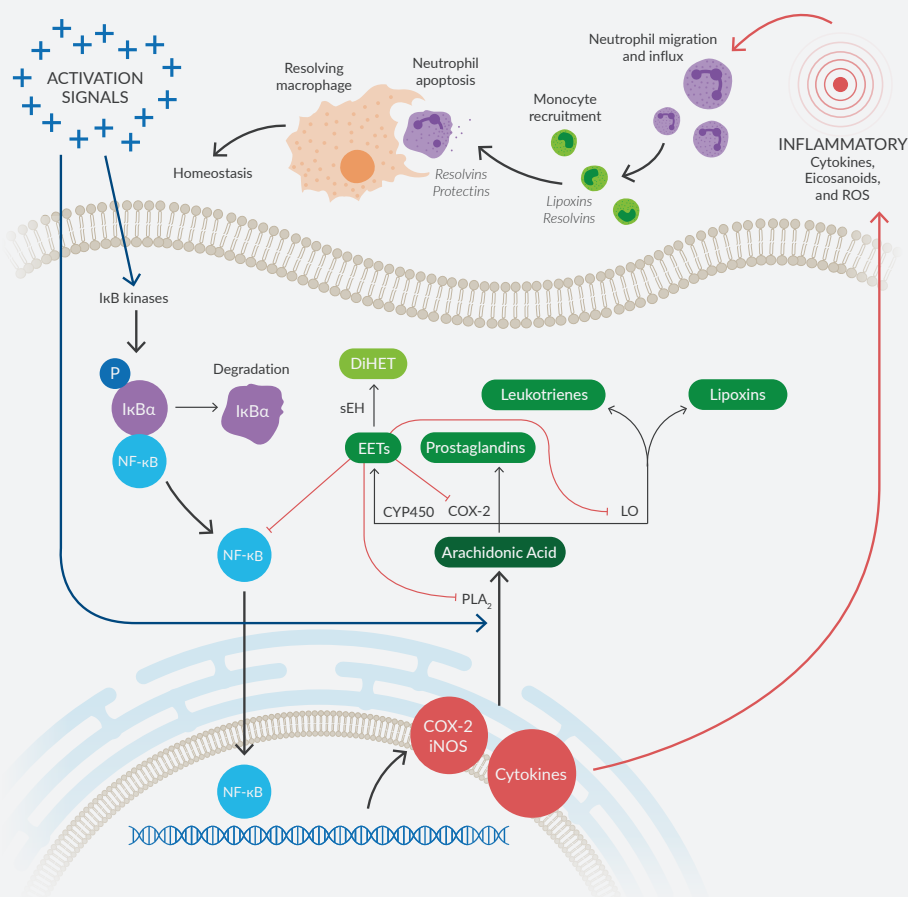
## Resolving Inflammation in COVID-19

Rather than just blocking individual cytokines, moving upstream to modulate them by stimulating their clearance and cellular repair is the body's natural way to turn off inflammation. Cayman has synthesized an array of key lipid mediators as standards for mass spectrometry and biochemical tools and developed ELISAs to aid in a better understanding of the role of specialized pro-resolving mediators (SPMs) in resolving the eicosanoid storm. Soluble epoxide hydrolase (sEH) inhibitors are also available to modulate the concentration of EETs and other fatty acid epoxides.



Read the article Resolving Inflammation in COVID-19 to learn how sEH inhibitors and resolvins may be as important as antiviral therapies to alleviate symptoms of this disease.

[www.caymanchem.com/resolvinginflammation](http://www.caymanchem.com/resolvinginflammation)



Inflammation leading to an eicosanoid storm can be prevented through EET and SPM signaling.

### Request the SPM Metabolic Pathways Wall Poster

Review the biosynthesis of SPMs from polyunsaturated fatty acids (AA, EPA, DPA, and DHA) that are liberated during the inflammatory process.

[www.caymanchem.com/SPMposter](http://www.caymanchem.com/SPMposter)

### Resolvins

Item No.	Product Name
10012554	Resolvin D1
13060	17(R)-Resolvin D1
10007279	Resolvin D2
11184	Resolvin D2-d <sub>5</sub>
13834	Resolvin D3
10007280	Resolvin D5
10007848	Resolvin E1
29590	Resolvin E4

### Lipoxins

Item No.	Product Name
90410	Lipoxin A <sub>4</sub>
90420	Lipoxin B <sub>4</sub>

### Maresins

Item No.	Product Name
10878	Maresin 1
16369	Maresin 2

### sEH Inhibitors

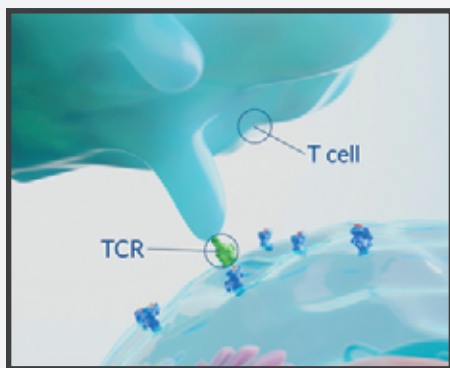
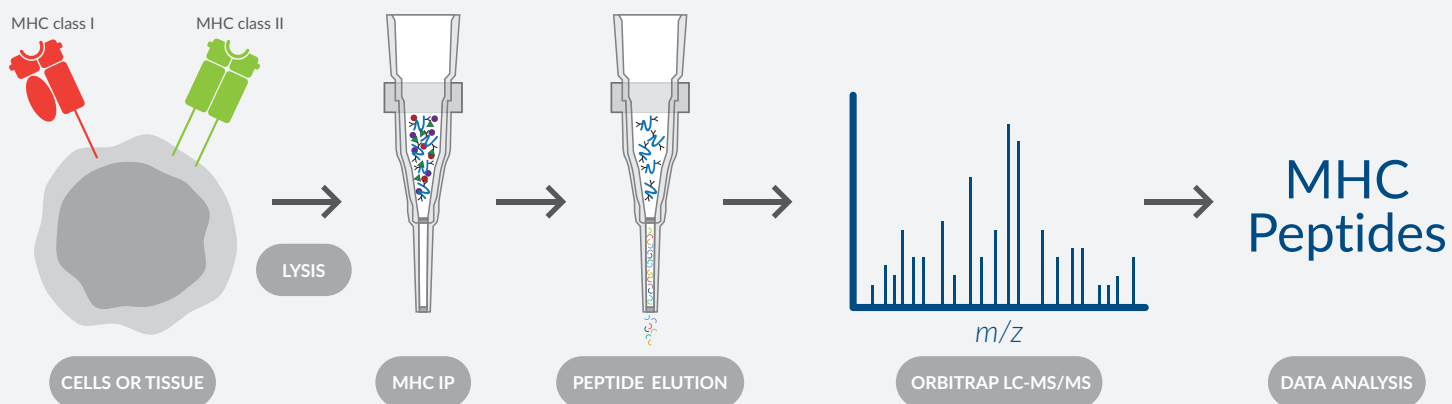
Item No.	Product Name
16568	<i>trans</i> -AUCB
10007927	AUDA
10642	CAY10640
10007923	CUDA
10004971	N,N'-Dicyclohexylurea
11120	TPPU



# IMMUNOPEPTIDOME PROFILING SERVICES

Cayman has optimized workflows for efficient, cost-effective deep sequence analysis of MHC-associated peptides to help clients identify neoantigens and potential immunogenic sequences.

- Customized antibody production
- Cell culture and transfection of MHC alleles
- Immunoprecipitation of MHC from multiple species
- MS-based sequence analysis of all MHC-associated peptides



## WATCH THE VIDEO

[www.caymanchem.com/MHCvideo](http://www.caymanchem.com/MHCvideo)

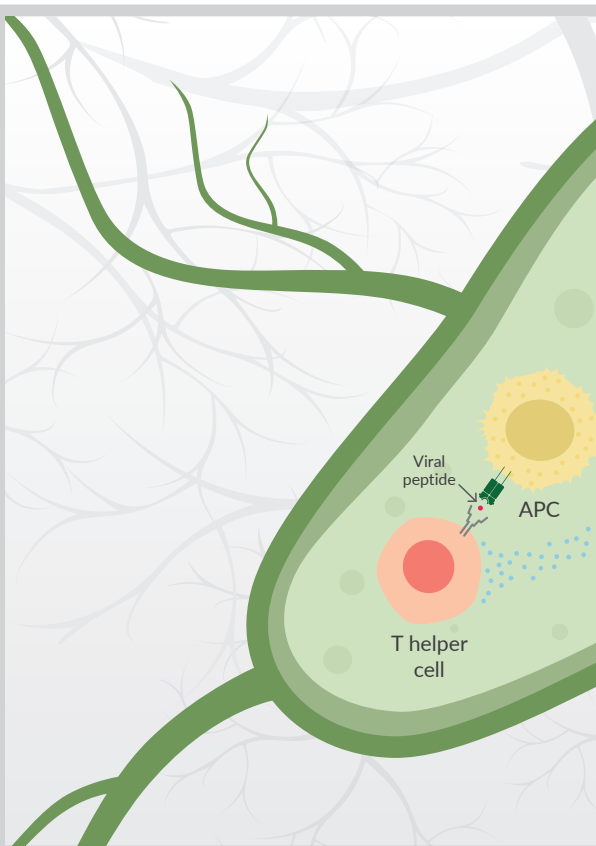
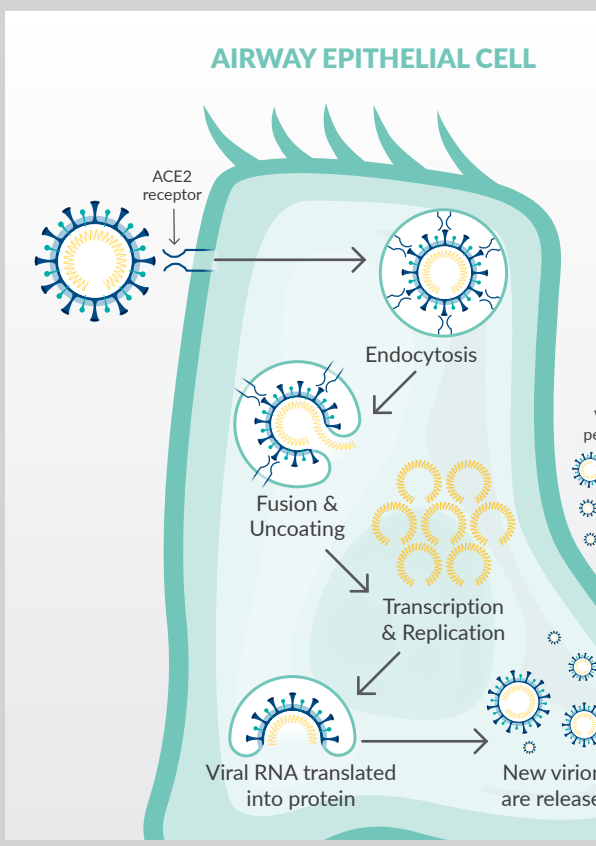
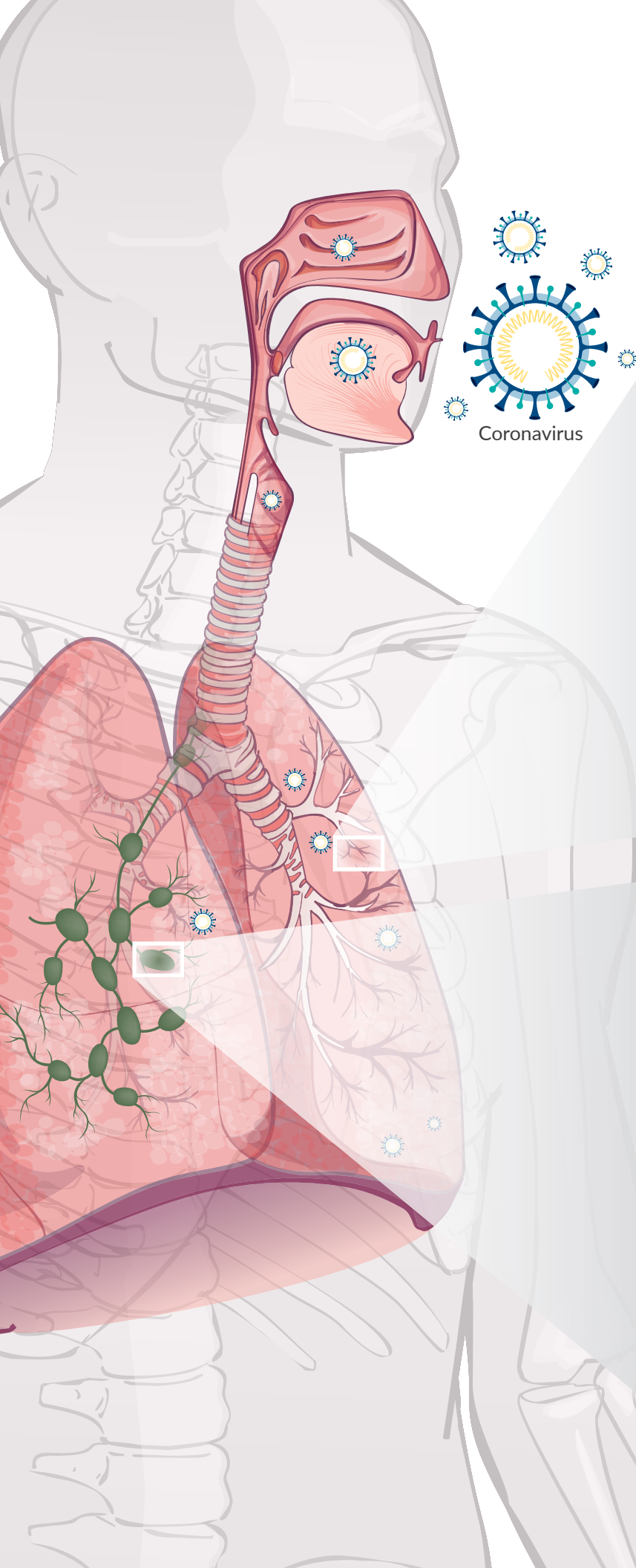
## Vaccine Antigen Identification

Peptide vaccines hold promise as a potential streamlined method for rapid vaccine development. The synthesis of effective peptide vaccines requires the identification of immunogenic sequences that stimulate not only antibody responses, but also cytotoxic and helper T cell responses. Profiling the immunopeptidome of cells that have been infected with the pathogen or have taken up immunogenic viral proteins can be a key step in determining the sequences of relevant peptides for building a vaccine.

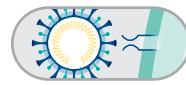
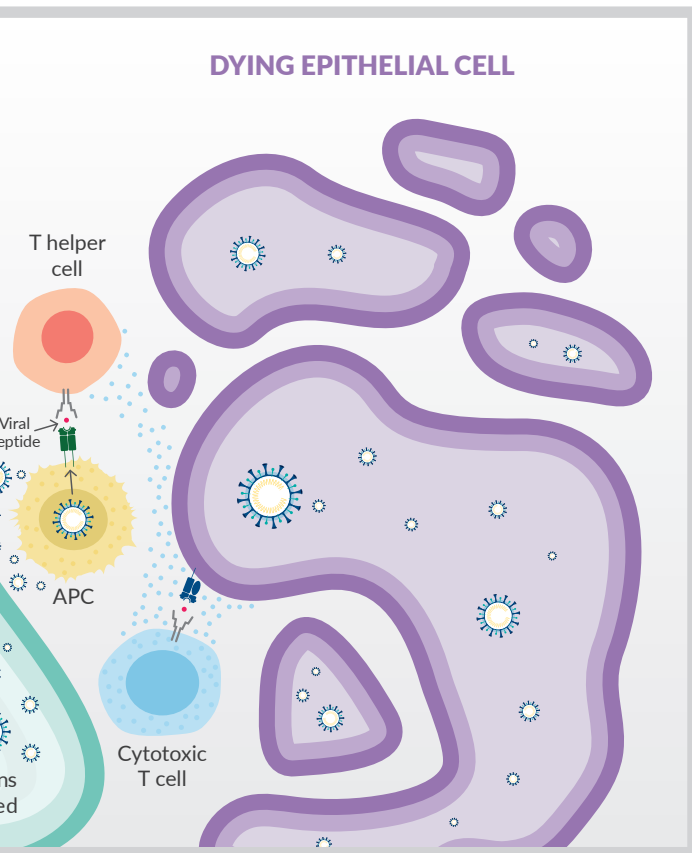
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# VIRAL INFECTION



# INFECTION LIFE CYCLE

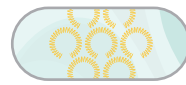


## VIRAL-HOST FUSION

Infection starts when the virus spike protein binds to the cell surface ACE2 receptors of the host and gains entry into cells through endocytosis or host-membrane fusion.

### THERAPEUTIC TARGETS

<b>Umifenovir</b>	Thwarts the hemagglutinin envelope glycoprotein fusion machinery.
<b>Imatinib</b>	Inhibits kinase activation of viral effector proteins that facilitate fusion.
<b>Camostat/E-64d</b>	Prevents spike protein priming by host proteases TMPRSS2 and cathepsin B/L.
<b>Chloroquine</b>	Increases endosomal pH since viruses prefer an acidic environment.

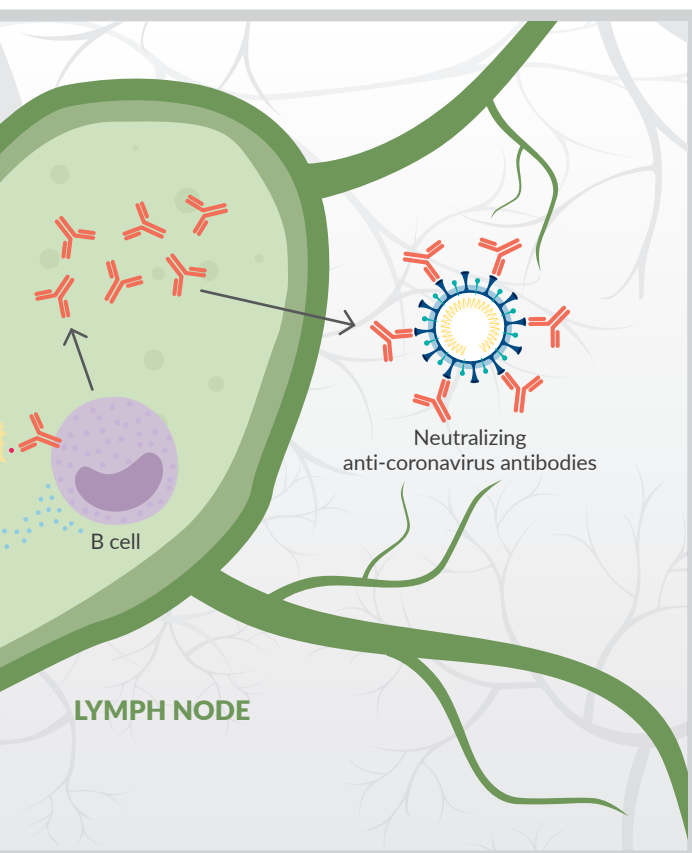


## VIRAL REPLICATION

Viral RNA is released, replicated by the viral RNA polymerase, and translated into proteins that are assembled into new virions.

### THERAPEUTIC TARGETS

<b>Lopinavir/Ritonavir</b>	Halts $M^{pro}$ and $PL^{pro}$ activity to prevent the production of replication proteins.
<b>Remdesivir/Favipiravir</b>	Inhibits RNA-dependent RNA polymerase replication of viral RNA.
<b>Itraconazole</b>	Disrupts the role of oxysterol-binding protein in producing replication organelles at the ER and Golgi.
<b>Ivermectin</b>	Inhibits nuclear transport of viral proteins such as integrases, nucleocapsid proteins, and non-structural proteins.
<b>Auranofin</b>	Controls ER stress and the unfolded protein response.



## IMMUNE ACTIVATION

Virus-infected cells release immunostimulatory proteins, recruiting innate immune cells to help clear virus and cytotoxic T cells to target infected cells. Local antigen-presenting cells (APCs) ingest the virions and display viral peptides to T helper cells, which coordinate an antibody response from the lymph node.

### THERAPEUTIC TARGETS

<b>STING Agonists</b>	Activate pattern recognition receptors.
<b>Immunosuppressive Agents</b>	Control the circulation of inflammatory cytokines.
<b>Immunopeptidome Profiling</b>	Identifies viral peptides to develop antibodies against.



## IMMUNE SURVEILLANCE

Memory B and T cells that recognize the virus will continue to patrol the body. A strong initial response bodes well for longer term immunity to the virus.



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