CAYMANCURRENTS
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LONG COVID:
BIOMARKER AND THERAPEUTIC DISCOVERY

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In It for the Long Haul: Research Tools for Long COVID Syndrome

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Novel coronavirus (COVID-19) symptoms can persist in an estimated 10% of patients long past recovering from the worst impacts of acute infection and testing negative for SARS-CoV-2. Inconsistencies in symptoms, patient phenotypes, and risk factors make it difficult to pinpoint the exact cause of Long COVID, otherwise known as post-COVID syndrome (PCS) or post-acute sequelae of SARS-CoV-2 infection (PASC). Large-scale research projects and population studies are now looking at the reported symptoms to define Long COVID and to understand its long-term effects and how it can be treated. The U.S. National Institutes of Health is investing $1.15 billion towards Long COVID research to generate basic understanding of the underlying causes of these prolonged symptoms that could lead to effective prevention and treatment of the syndrome.

Multi-System Disease

The constellation of symptoms associated with Long COVID range from serious sequelae to nonspecific clinical manifestations that require a whole-patient perspective. The most common symptoms involve the pulmonary, cardiovascular, and nervous systems and can be grouped into three types of complaints: exercise intolerance, autonomic dysfunction, and cognitive impairment. But many additional symptoms and disease associations have been cataloged in nearly every organ and regulatory system.

Mental Health
- Anxiety
- Depression
- Sleep problems
- Substance abuse

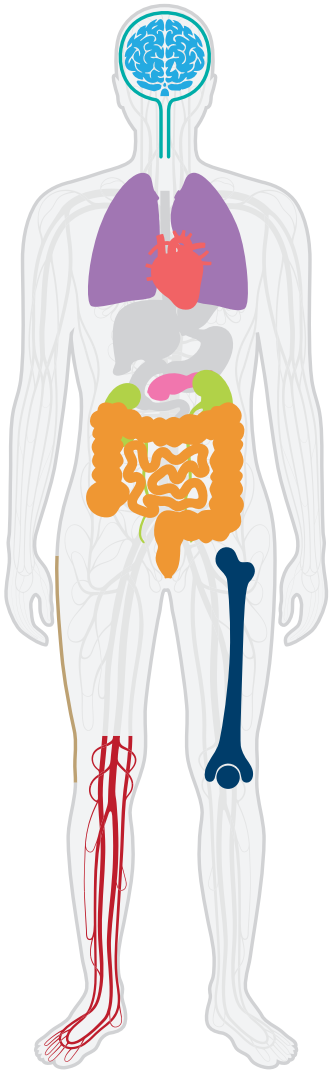
Respiratory System
- Cough
- Low blood oxygen
- Shortness of breath

Kidney
- Acute kidney injury
- Chronic kidney disease

Gastrointestinal
- Diarrhea
- Acid reflux
- Constipation

Skin Disorders
- Rash
- Hair loss

Blood Disorders
- Anemia
- Blood clots



Nervous System
- Stroke
- Headaches
- Memory problems
- Loss of smell and taste

Cardiovascular
- Arrhythmia
- Palpitations
- Heart failure
- Acute coronary disease

Metabolic/Endocrine
- Obesity
- Diabetes
- High cholesterol

Musculoskeletal
- Joint pain
- Muscle weakness

General
- Fatigue
- Malaise
- Mitochondrial dysfunction

An umbrella of symptoms and comorbidities have been documented in relation to Long COVID. Cayman carries thousands of products to support scientists examining this disease. Browse them all by viewing the full PDF at www.caymanchem.com/LongCOVIDimpact.

Cues from POTS and ME/CFS

Because this disease is so new, specific tests for lasting coronavirus symptoms are lacking, but a road map for treatment options has begun to be drawn from the current understanding of other disabling and complex health conditions with overlapping symptoms that can arise suddenly post viral infection. In fact, the new-found prevalence of Long COVID has brought fresh awareness to these other conditions along with new diagnosed cases.

One such example is postural orthostatic tachycardia syndrome (POTS), a blood circulation disorder that presents as a type of dysautonomia with profound fatigue, brain fog, headaches, chest tightness, and rapid heartbeat, especially when standing up from a prone position.[1] Patients with POTS tend to have a lower-than-normal level of plasma and red blood cells. Medications that have proven to be effective at treating POTS include nervous system depressants, cholinesterase inhibitors, hyperpolarization-activated cyclic nucleotide-gated channel blockers and beta-blockers to reduce heart rate, α_1-adrenergic agonists and somatostatin mimics to stimulate vasoconstriction and increase venous return, α_2-adrenergic receptor agonists to reduce hypertension, antidiuretics and corticosteroids to increase blood volume, hormones to stimulate the production of red blood cells, and selective serotonin uptake inhibitors to control blood pressure and heart rate through central serotonin availability. Each of these must be tailored to an individual's needs since some may exacerbate a certain set of symptoms while relieving others.

Another example often triggered by viral infection is myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).[2] ME/CFS is characterized by generalized fatigue that can lead to post-exertional malaise. Other symptoms include neuropathic pain, sleep abnormalities, cognitive dysfunction, orthostatic intolerance, and gastrointestinal problems. Current therapeutic options are largely limited to palliative care and cognitive management because the mechanistic basis of the disease is poorly understood. However, some symptoms can be treated or managed with antidepressants, psychostimulants, analgesics, sleep medications, and the drugs used to treat orthostatic intolerance mentioned above.[3]

Underlying Pathophysiology

For effective treatments to be developed for Long COVID, the molecular basis of the syndrome will first need to be understood. There are several leading theories for why COVID long haulers develop the syndrome.

Four Theories for Underlying Pathophysiology

Theory 1: A persistent latent SARS-CoV-2 infection

Theory 2: An autoimmune disorder evolved from the initial SARS-CoV-2 infection

Theory 3: An excessive immune response to SARS-CoV-2 infection with extreme inflammation

Theory 4: Impaired mitochondrial dynamics and energy production

Latent Infection

One theory is that the disease is a consequence of a persistent latent SARS-CoV-2 infection with failure to completely clear the pathogen. In cases of ME/CFS triggered by *Chlamydophila pneumoniae*, antibiotics helped improve symptoms.[4] However, ME/CFS observed after Epstein-Barr virus, dengue virus, Ebola virus, West Nile virus, or Chikungunya virus has not been successfully treated with existing antivirals for the most part.[5] One notable exception is the RNA polymerase inhibitor valganciclovir, which has been used to address elevated serum IgG levels for human herpesvirus 6 and Epstein-Barr virus in ME/CFS patients to improve fatigue and cognitive symptoms.[6]

As part of developing suitable antivirals designed to clear a latent virus to provide therapeutic relief in the case of Long COVID, researchers will also need to identify lingering, non-replicating SARS-CoV-2 products in biological samples and track neutralizing antibody levels over time in response to infection. More work will also be needed to establish the expression and localization of the angiotensin-converting enzyme 2 (ACE2) receptor throughout the body, as this is where SARS-CoV-2 enters host cells. Strategies to clear the latent viral infection could also potentially be controlled through scheduled vaccination or the delivery of monoclonal antibodies.

Flip to pages 4-5 to find Cayman's targeted compound screening libraries to explore potential antiviral therapies, tools to identify SARS-CoV-2 viral products and neutralizing antibodies, and tools to explore the interaction of SARS-CoV-2 with the human ACE2 receptor.

Learn more about the tools Cayman offers for research on the delivery of vaccines or therapeutic drugs using lipid nanoparticles on page 6.

Autoimmune Response

An alternative hypothesis is that Long COVID is an autoimmune disorder evolved from a misdirected or aberrant immune reaction to the initial SARS-CoV-2 infection. Immunological changes could come in the form of errant macrophages, impaired natural killer (NK) cell function, abnormal B cell activation (*e.g.*, antiphospholipid autoantibodies), diminished T cell counts, a reduced type 1 interferon (IFN) response (*e.g.*, developing neutralizing autoantibodies against IFNs), altered cytokine levels, or a gut microbiome imbalance. Identifying biomarkers associated with Long COVID will be important for understanding how to develop therapeutics to address those key effectors (*e.g.*, immunosuppressants, stimulants of NK cell function, immune adsorption/IgG depletion to remove autoantibodies). In cases involving dysautonomia, the antibodies produced after a SARS-CoV-2 infection may attack the autonomic nervous system causing nerve damage and disrupting its ability to regulate blood flow to the brain and muscles.

Activation of IFN signaling, which is mediated by the STING pathway and signaling through certain toll-like receptors (TLRs), is crucial for innate defense against viral infections. In ME/CFS patients, the TLR3 agonist rintatolimod is specifically being developed to increase NK cell function and is in an expanded access clinical trial program to treat fatigue-like symptoms of COVID long-haulers.[7,8] Other immune modulating compounds that have been investigated for the treatment of ME/CSF and may have benefit for Long COVID include γ-globulin, the anti-IL-6 antibody anakinra, the anti-CD20 B cell-depleting antibody rituximab, and the T regulatory cell-eliminating/IFN-inducing agent cyclophosphamide.[3]

Cayman offers a suite of innate immunity research tools to study the STING pathway and other pattern recognition receptor signaling pathways such as TLRs that can be viewed on pages 7-8.

Excessive Inflammation

Part of an excessive immune response to SARS-CoV-2 infection involves a disproportionate release of cytokines and extreme inflammation. The cytokine storm, characterized by increased levels of IL-2, IL-7, GM-CSF, CXCL10, CXCL20, CCL2/MCP-1, and TNF-α experienced by many COVID-19 patients, could be mediating a pattern of hyperinflammation that is associated with tissue damage or loss of cell function (*e.g.*, vasculitis, coagulopathy, endothelial dysfunction, neurological abnormalities) that could cause Long COVID symptoms.[2, 9-10] Inflammation and coagulation are two processes with considerable cross-talk, each driving the other towards detrimental pro-thrombotic and/or pro-inflammatory activation. Cytokine-mediated neuroinflammation could also be playing a role in causing fatigue and other neurological symptoms.

Inflammation is thought to be cleared by an active biochemical process that stimulates macrophage phagocytosis and efferocytosis and counters pro-inflammatory cytokine production through specialized pro-resolving lipid mediators (SPMs), such as resolvins.[11] Epoxyeicosatrienoic acids (EETs) can also stimulate the resolution of inflammation by promoting the production of pro-resolution mediators, such as lipoxins, and activating anti-inflammatory processes. EETs are rapidly metabolized by soluble epoxide hydrolase (sEH), but their levels can be stabilized with the use of sEH inhibitors. Both resolvins and EETs are known to diminish thrombosis and stimulate cytokine clearance and cellular repair. Thus, sEH inhibitors and resolvins may have a therapeutic role in alleviating symptoms of Long COVID.

Extensive infiltration of neutrophils, which extrude neutrophil extracellular traps (NETs) into the pulmonary capillaries of COVID-19 patients, is associated with fibrin deposition and vascular lesions and can serve as a scaffold for thrombogenesis that could lead to multiple system dysfunctions that are related to Long COVID symptoms.[12] The use of recombinant human DNase-I to degrade extracellular DNA associated with NETs is under investigation for improved blood flow and outcomes after experimental stroke, traumatic brain injury, and COVID-19-induced acute respiratory distress syndrome and may help address some of the deficits associated with Long COVID.[13,14]

The research tools Cayman offers to aid researchers in exploring the role of inflammation and thrombosis in Long COVID can be found on pages 9-13.

Mitochondrial Dysfunction

Increasing evidence suggests that SARS-CoV-2 takes over immune cell mitochondria, replicates within mitochondrial structures, and impairs mitochondrial dynamics leading to problems with energy production and normal cell death.[15] Mitochondria participate in an immune response to viral infection by engaging IFN signaling *via* retinoic acid-inducible gene I-like receptors (RLRs) and the mitochondrial antiviral-signaling protein (MAVS). Viruses can alter mitochondrial structure through fission and fusion to manipulate the IFN response or to prevent apoptosis, both of which benefit viral survival. These alterations can lead to poorer mitochondrial energy

production and oxidative stress. Metabolic disruption, increased mitochondrial damage, reductions in ATP production, and impaired oxidative phosphorylation are all associated with ME/CFS and are likely the case for Long COVID-19 patients as well.[3]

The mitochondrial modulating combination of NADH and coenzyme-Q_{10} (ubiquinol) can improve fatigue in ME/CSF patients.[16] Supplementing methylphenidate with various mitochondrial metabolites and antioxidants including acetyl-L-carnitine, α-lipoic acid, and N-acetyl-L-cysteine has been used to treat fatigue in severe cases of ME/CFS and may show benefit for similar symptoms associated with Long COVID.[17] Because a dysregulated pyruvate dehydrogenase complex may lead to mitochondrial deficits in these patients, investigators are exploring the use of pyruvate dehydrogenase kinase (PDHK) inhibitors to decrease expression of PDHKs that negatively regulate the complex and promote the conversion of pyruvate to lactate.[18] AMP-activated protein kinase (AMPK), which plays a key role in controlling metabolism, may also be impaired in these patients. Small molecule activators of AMPK, including the thiazolidinedione peroxisome proliferator-activated receptor (PPAR) agonists, stimulate mitochondrial biogenesis and have been explored as treatments for a variety of neurological diseases.[19] The oxidative stress created by dysfunctional mitochondria could be reversed through the use of antioxidants, which have also been shown to lessen fatigue.[20]

A wealth of tools that Cayman offers to study mitochondrial biology can be found on page 14.

Conclusion

While there is still a lot to learn about COVID-19 and its long-term effects, researchers' understanding is evolving by the day. Cayman aims to support the basic and drug discovery research needed to provide avenues for therapies and hope for people living with long-term COVID-19 effects.

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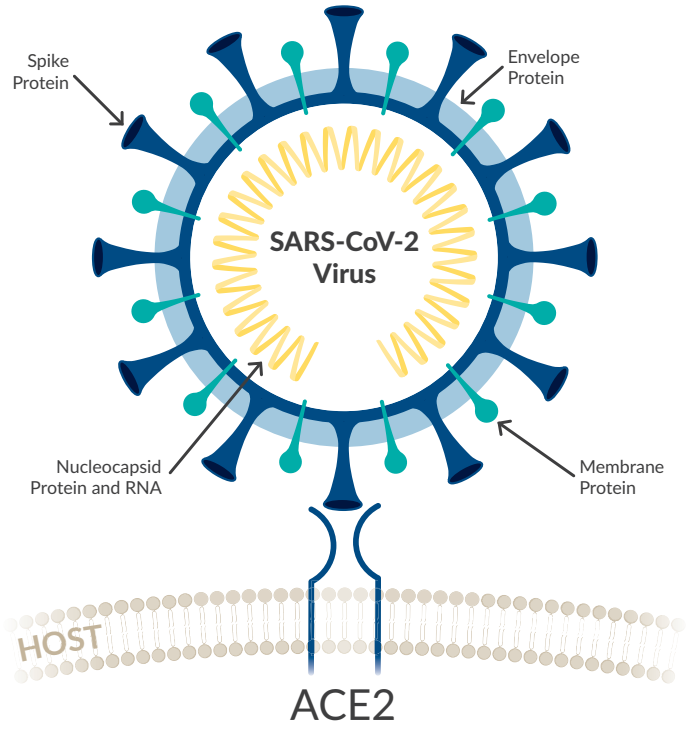
TOOLS TO STUDY LATENT SARS-CoV-2 INFECTION

Development of antiviral agents designed to clear a latent virus may provide therapeutic relief from Long COVID. Researchers will also need to identify lingering SARS-CoV-2 products in biological samples and track neutralizing antibody levels over time in response to infection. More work will also be needed to establish the expression and localization of the ACE2 receptor throughout the body.



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.

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

SARS-CoV-2 Proteins

Item No.	Product Name
30588	SARS-CoV-2 M^{pro} Protein
31817	SARS-CoV-2 Papain-like Protease
30429	SARS-CoV-2 Spike Glycoprotein Receptor Binding Domain (human IgG1 Fc-tagged)
33868	SARS-CoV-2 Spike Glycoprotein Receptor Binding Domain K417N, E484K, N501Y variant (rabbit IgG1 Fc-tagged)
33867	SARS-CoV-2 Spike Glycoprotein Receptor Binding Domain N501Y variant (rabbit IgG1 Fc-tagged)

See all SARS-CoV-2 proteins at www.caymanchem.com

SARS-CoV-2 Antibodies

Item No.	Product Name
33629	SARS-CoV/SARS-CoV-2 Nucleocapsid Protein Rabbit Monoclonal Antibody (Clone 0006-1)
30832	SARS-CoV/SARS-CoV-2 Spike Glycoprotein Chimeric Monoclonal Antibody

See all SARS-CoV-2 antibodies at www.caymanchem.com

SARS-CoV-2 Neutralizing Antibody and Detection Assays

Item No.	Product Name
32526	SARS-CoV-2 (human) Neutralizing Recombinant Antibody
502070	SARS-CoV-2 Neutralizing Antibody Detection ELISA Kit
31063	Q-Plex™ SARS-CoV-2 Human IgG (4-Plex)

ACE2 Protein and Antibodies

Item No.	Product Name
30587	ACE2 (human, recombinant)
30582	ACE2 (human) Monoclonal Antibody (Clone AC18F)
30583	ACE2 (human) Monoclonal Antibody - Biotinylated (Clone AC18F)

See all ACE2 proteins and antibodies at www.caymanchem.com

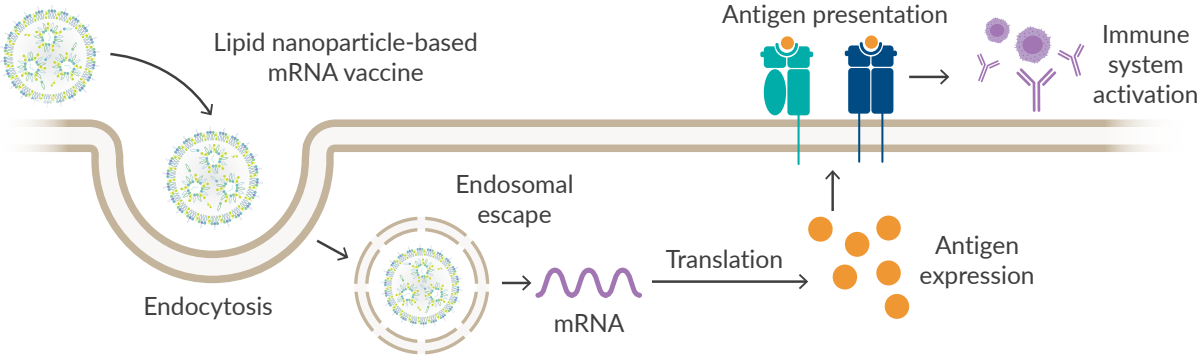
Inhibitor Screening Assays

Item No.	Product Name
502100	ACE2 Inhibitor Screening Assay Kit
701960	SARS-CoV-2 Main Protease Inhibitor Screening Assay Kit
502050	SARS-CoV-2 Spike-ACE2 Interaction Inhibitor Screening Assay Kit
701970	SARS-CoV-2 Spike S1 RBD-ACE2 Binding Cellular Imaging Assay Kit

SPOTLIGHT ON VACCINE DEVELOPMENT

Vaccine Antigen Identification

The synthesis of effective vaccines requires the identification of immunogenic sequences that stimulate not only antibody responses, but also cytotoxic and helper T cell responses. Following pathogen infection or uptake, pathogen-derived peptides are presented to immune cells by cell surface major histocompatibility complexes (MHCs). Profiling of these MHC-associated peptides, collectively known as the immunopeptidome, can provide valuable information about potentially immunogenic sequences or neoantigens that can be used towards the development of improved peptide or mRNA vaccines.



Following uptake, mRNA is translated into antigenic protein that is presented at the cell surface by MHC molecules to activate the immune system.

Learn more about Cayman's Immunopeptidome Profiling Services at **www.caymanchem.com/immunopeptidome**

Lipid-Based Nano Drug Delivery

Lipid-based drug delivery systems can prolong the stability of their cargo, enable cell- and even organelle-specific targeting, and help overcome bioavailability limitations associated with certain conventional drug delivery methods. Two well-known examples are the Pfizer and Moderna COVID-19 vaccines, which use lipid nanoparticles for mRNA delivery. Lipid composition can influence the size, charge, permeability, thermal transition, and lamellarity of the particle and can be customized to tailor the properties of lipid-based nanoparticles to suit their specific purposes.

Lipids for COVID-19 mRNA Vaccine Research

Item No.	Product Name
34336	ALC-0159
34337	ALC-0315
9003100	Cholesterol
15100	1,2-Distearoyl-*sn*-glycero-3-PC
33945	DMG-PEG(2000)
33474	SM-102

See all lipids for lipid-based drug delivery at www.caymanchem.com

CUSTOM LIPID SYNTHESIS SERVICES

Cayman offers custom lipid synthesis by skilled synthetic organic chemists and formulation and QC of lipid nanoparticles through our partnerships with T&T Scientific and NanoImaging Services.

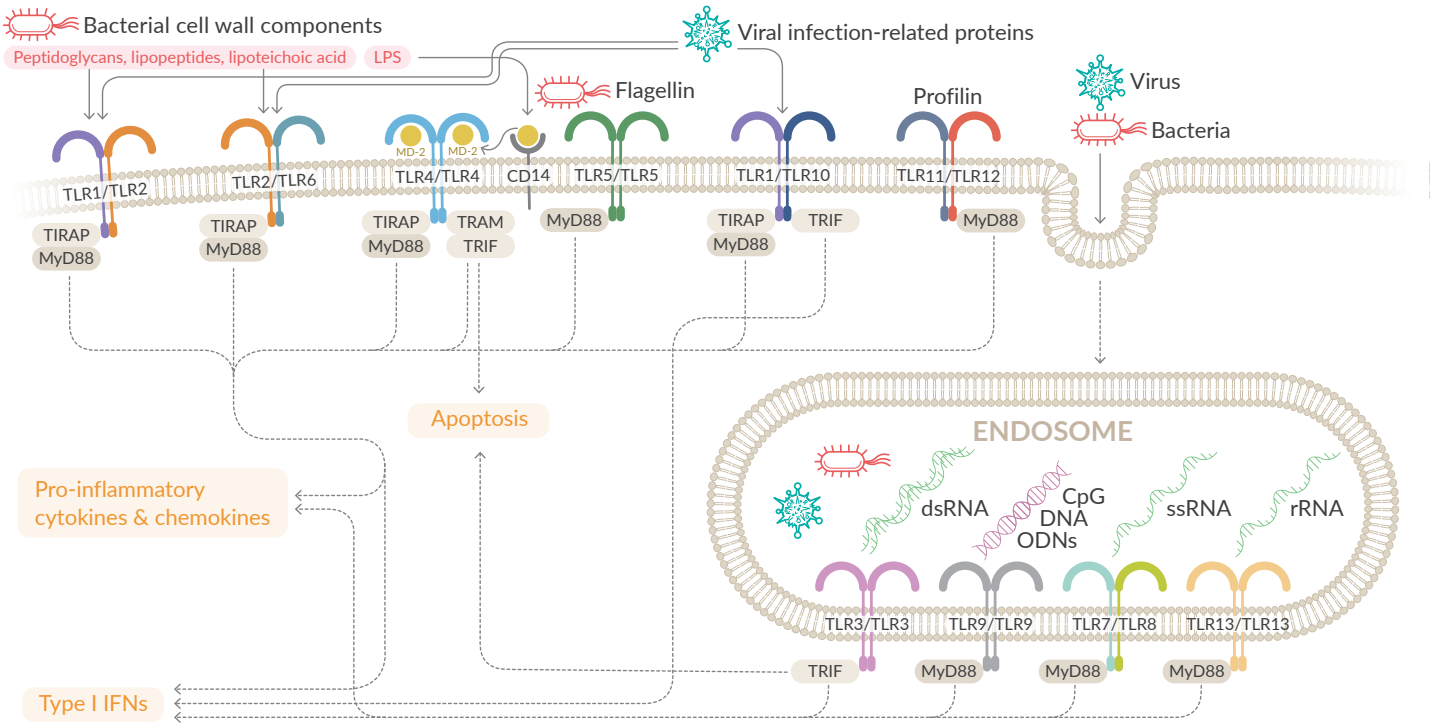
Discover more at www.caymanchem.com/customsynthesis

Read our News article to discover more and browse our wide selection of lipids for lipid-based nanoparticle research at **www.caymanchem.com/lipidbaseddrugdelivery**

TOOLS TO STUDY AUTOIMMUNITY

Toll-Like Receptor Signaling

Detection of viral-associated molecular patterns by TLRs induces IFN signaling as part of the innate response to viral infection. However, prolonged or excessive TLR signaling can lead to destructive inflammation and autoimmunity. In some patients with severe COVID-19, expression of genes encoding certain TLRs, as well as the adaptor MyD88, is elevated.



TLR localization and signaling.

MyD88 and TLR Antibodies

Item No.	Product Name
32250	MyD88 (N-Term) Rabbit Monoclonal Antibody
13587	Toll-Like Receptor 2 Monoclonal Antibody (Clone TL2.1)
13589	Toll-Like Receptor 4 Monoclonal Antibody (Clone HTA125)
13591	Toll-Like Receptor 7 Polyclonal Antibody
13592	Toll-Like Receptor 8 Monoclonal Antibody (Clone 44C143)

See all TLR antibodies at www.caymanchem.com

TLR1/2 Antagonists

Item No.	Product Name
27029	C29
15244	CU CPT 22

TLR4 Antagonists

Item No.	Product Name
18512	TLR4-C34
13871	TAK-242
13615	CAY10614
33099	T-5342126

TLR8 Antagonists

Item No.	Product Name
29815	CU-115
28723	CU-CPT9b
25349	CU-CPT8m
28722	CU-CPT9a

Read the article on Toll-like Receptors: Immune Signaling Sentinels to learn more about how TLRs sense a variety of ligands to induce IFN and pro-inflammatory signaling. **www.caymanchem.com/TLRs**

STING Signaling

STING signaling is another innate immune defense pathway that is triggered by SARS-CoV-2 infection and leads to production of IFNs, which could contribute to development of autoimmune diseases. Several STING agonists, including the cyclic dinucleotides (CDNs) 2'2'-cGAMP and 2'3'-cGAMP, have been found to inhibit SARS-CoV-2 infection in cellular models.

Designer STING Agonists

FEATURED PRODUCT

diABZI STING Agonist-1 (hydrochloride) - Item No. 28054

A STING agonist that decreases the level of SARS-CoV-2 RNA in primary human respiratory cells and in two different mouse models of infection, reducing lung inflammation. diABZI STING agonist-1 was also found to be effective against the SARS-CoV-2 South African variant B.1.351.

STING Agonists

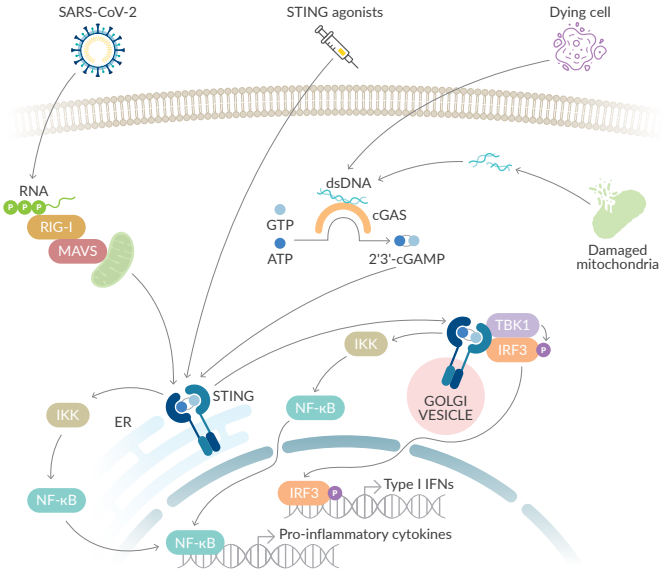
Item No.	Product Name
34088	diABZI STING Agonist-2
34082	diABZI STING Agonist-3
30140	MSA-2
32521	STING Agonist 12b

See all STING agonists at www.caymanchem.com

LEARN MORE

Read our News article to learn more about how STING agonists inhibit SARS-CoV-2 replication.

www.caymanchem.com /STINGagonistSARS-CoV-2



STING activators induce IFN and pro-inflammatory cytokine production.

CDNs and Negative Controls

Item No.	Product Name
22419	2'2'-cGAMP (sodium salt)
19887	2'3'-cGAMP (sodium salt)
17966	3'3'-cGAMP (sodium salt)
33886	5'-pApA (sodium salt)
33889	5'-pGpG (sodium salt)
17753	Cyclic di-AMP (sodium salt)
17144	Cyclic di-GMP (sodium salt)
22485	Cyclic di-IMP (sodium salt)
33890	Cyclic di-UMP (sodium salt)

STRUCTURE-BASED DRUG DESIGN SERVICES

Our structure-based drug design (SBDD) services are supported by medicinal chemistry, computer-aided drug design, and protein production services, as well as expertise in biophysical characterization, X-ray structure determination, and *in silico* docking analysis.

Discover more at www.caymanchem.com/structuralbiology

LEARN MORE

View our virtual poster to learn more about how Cayman scientists have used *in silico* screening and surface plasmon resonance studies to characterize the binding of various agonists to human STING variants.

www.caymanchem.com/hSTINGagonists

TOOLS TO STUDY EXCESSIVE INFLAMMATION

Platelet Activation, Coagulation, and Thrombosis in COVID-19

Coagulopathy can lead to life-threatening complications such as thrombosis in patients with COVID-19. Elevated plasma levels of thromboxane B_2 (TXB_2), fibrinogen, and C-reactive protein (CRP) have been associated with increased platelet activation and aggregation, coagulation, and inflammation in patients with COVID-19. Cayman offers a variety of research tools to study these factors in COVID-19.

CRP and TXB_2 Quantification

C-Reactive Protein (human) ELISA Kit - Item No. 10011236

- Measure CRP from human plasma
- Rapid results in <3 hours

Thromboxane B_2 ELISA Kit - Item No. 501020

- Measure TXB_2 levels down to 5 pg/ml
- Colorimetric readout

Thromboxane B_2 Express ELISA Kit - Item No. 10004023

- Measure TXB_2 levels down to 45 pg/ml
- Rapid results in <4 hours

Fibrinogen Antibodies

Item No.	Product Name
18033	Fibrinogen (α chain) Polyclonal Antibody
18793	Fibrinogen (α chain) Monoclonal Antibody

Inducers of Platelet Aggregation

Item No.	Product Name
21230	2-Methylthioadenosine diphosphate (sodium salt)
13188	Thrombin (human)

Antiplatelet Compounds

Antiplatelet compounds inhibit activation and aggregation of platelets, preventing formation of blood clots.

Purinergic $P2Y_{12}$ Receptor Antagonists

Item No.	Product Name
21002	(S)-(+)-Clopidogrel (sulfate)
14278	Prasugrel
15425	Ticagrelor

See all $P2Y_{12}$ antagonists at www.caymanchem.com

Glycoprotein IIb/IIIa Inhibitors

Item No.	Product Name
21578	Eptifibatide
23392	Tirofiban (hydrochloride hydrate)

Phosphodiesterase Inhibitors

Item No.	Product Name
15035	Cilostazol
18189	Dipyridamole
17217	Trequinsin (hydrochloride)

See all phosphodiesterase inhibitors at www.caymanchem.com

Anticoagulants

Anticoagulants block the coagulation cascade through inhibition of thrombin, factor Xa, and vitamin K.

Thrombin Inhibitors

Item No.	Product Name
23035	Bivalirudin
17133	Dabigatran
15160	PPACK (trifluoroacetate salt)

Factor Xa Inhibitors

Item No.	Product Name
15427	Apixaban
24033	Fondaparinux (sodium salt)
16043	Rivaroxaban

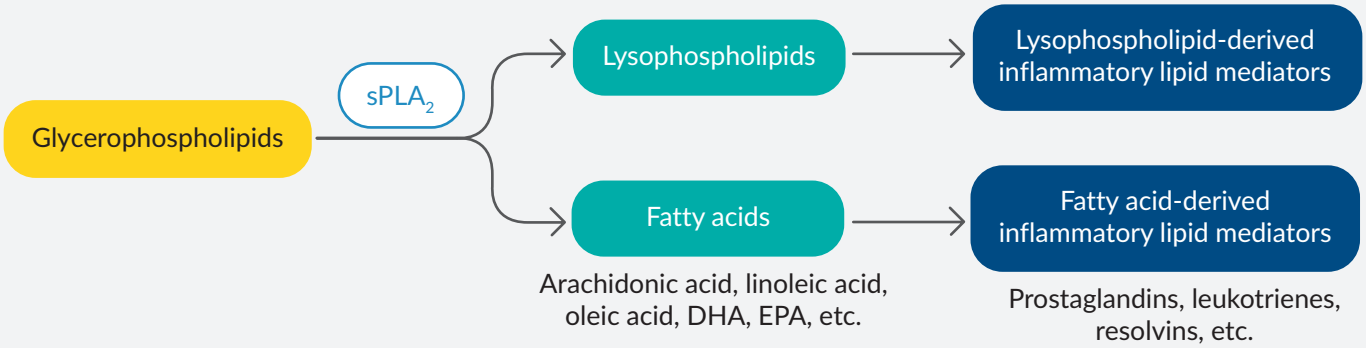
Vitamin K Antagonists

Item No.	Product Name
30060	Phenindione
31730	Phenprocoumon
13531	(–)-Warfarin

See all inhibitors of blood coagulation factors at www.caymanchem.com

SPOTLIGHT ON $sPLA_2$

Secretory PLA_2 ($sPLA_2$) enzymes are significantly upregulated in animal models of acute lung injury and in patients with acute respiratory distress syndrome. Elevated $sPLA_2$ Type IIA levels are associated with COVID-19 disease severity and can predict COVID-19 mortality. Cayman offers a variety of assay kits, proteins, antibodies, and small molecule inhibitors to study the role of $sPLA_2$ in COVID-19 pathophysiology.



$sPLA_2$ Assay Kits

Item No.	Product Name
765001	$sPLA_2$ Assay Kit
501380	$sPLA_2$ (human Type IIA) ELISA Kit
10004883	$sPLA_2$ (Type V) Inhibitor Screening Assay Kit

Antibodies and Blocking Peptide

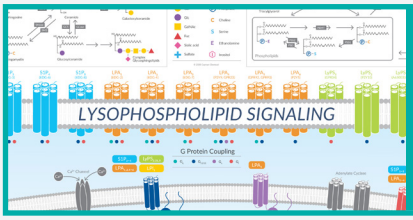
Item No.	Product Name
160500	$sPLA_2$ (human Type IIA) Monoclonal Antibody (Clone SCACC353)
160502	$sPLA_2$ (human Type IIA) Polyclonal Antiserum
160510	$sPLA_2$ (human Type V) Monoclonal Antibody (Clone MCL-3G1)
160512	$sPLA_2$ (mouse Type V) Polyclonal Antibody
360512	$sPLA_2$ (mouse Type V) Blocking Peptide

$sPLA_2$ Inhibitors

Item No.	Product Name
13181	CAY10590
14902	Luffariellolide
17973	LY311727
18267	LY315920
17277	$sPLA_2$ Inhibitor
62750	Thioetheramide-PC
17631	YM-26734

Proteins

Item No.	Product Name
10009563	$sPLA_2$ (human, recombinant Type V)
60500	$sPLA_2$ (Type III)



Request the Lysophospholipid Signaling Poster

Explore how lysophospholipids are synthesized and transduce signals through their specific GPCRs to initiate downstream signaling cascades.

www.caymanchem.com/lysophospholipidposter

BIOMARKER DEVELOPMENT SERVICES

Cayman's Biomarker Development group performs preclinical bioanalytical screening projects for drug discovery and diagnostics using multiple platforms. We offer a diverse suite of services in assay development and biomarker profiling and have decades of industry expertise in assay and methods development, sample preparation, and analysis.

Discover more at www.caymanchem.com/bioanalysis

Inflammatory Lipid Mediators

During the eicosanoid storm, cellular debris and other activation signals trigger production of pro-inflammatory lipid mediators. In contrast, specialized pro-resolving mediators (SPMs) can counter pro-inflammatory cytokine production and help clear inflammation. Changes to the lipidome documented in the lungs of patients with severe COVID-19 include elevated levels of SPMs as well as arachidonic acid and its various metabolites, such as 12-HETE and 15-HETE.

Read the article on Resolving Inflammation in COVID-19 to learn how resolvins and sEH inhibitors may help alleviate symptoms of COVID-19.
www.caymanchem.com/resolvinginflammation

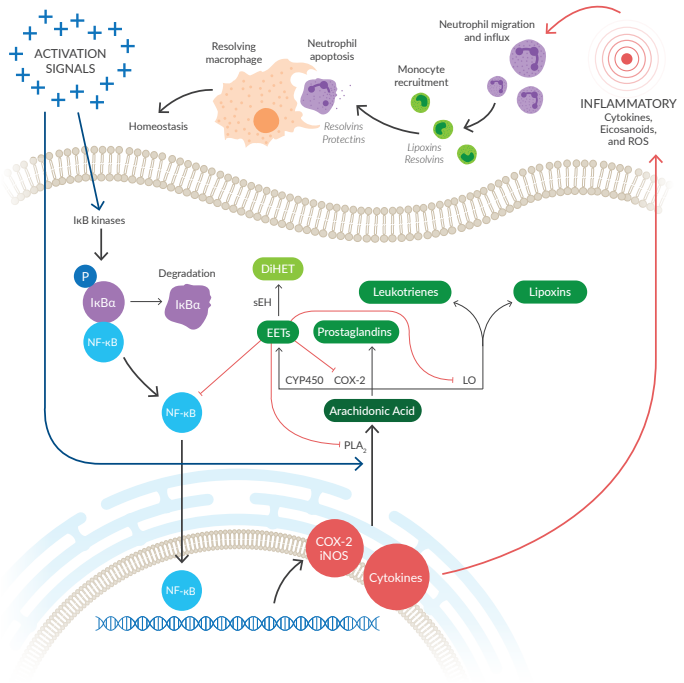
SPM Quantification

Item No.	Product Name
590410	Lipoxin A_4 ELISA Kit
590415	15-*epi* Lipoxin A_4 ELISA Kit
501920	Lipoxin B_4 ELISA Kit
501150	Maresin 1 ELISA Kit
500380	Resolvin D1 ELISA Kit
501120	Resolvin D2 ELISA Kit

Arachidonic Acid Metabolite Quantification

Item No.	Product Name
534721	15(S)-HETE ELISA Kit
500390	Cysteinyl Leukotriene ELISA Kit
520111	Leukotriene B_4 ELISA Kit
501070	Leukotriene C_4 ELISA Kit
501060	Leukotriene E_4 ELISA Kit
512031	Prostaglandin D_2 ELISA Kit
514010	Prostaglandin E_2 ELISA Kit - Monoclonal

See all assay kits for inflammatory lipid mediator detection at www.caymanchem.com



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

ASSAY DEVELOPMENT SERVICES

Leverage our team of experts for assay design, development, validation, and manufacturing. We can build quantitative assays on a variety of analysis and detection platforms to suit your specific needs.

Discover more at www.caymanchem.com/assayservices

VISIT CAYMAN'S NEW LIPID RESOURCE CENTER

Resolvins

Item No.	Product Name
10012554	Resolvin D1
10007279	Resolvin D2
13834	Resolvin D3
10007848	Resolvin E1
13827	Resolvin E2
29590	Resolvin E4

Lipoxins

Item No.	Product Name
90410	Lipoxin A_4
90420	Lipoxin B_4

Other SPMs

Item No.	Product Name
10878	Maresin 1
16369	Maresin 2
10010390	Protectin D1

See all resolvins, lipoxins, and other SPMs at www.caymanchem.com

Prostaglandins

Item No.	Product Name
12010	Prostaglandin D_2
14010	Prostaglandin E_2

See all prostaglandins at www.caymanchem.com

Leukotrienes

Item No.	Product Name
20110	Leukotriene B_4
20210	Leukotriene C_4
20310	Leukotriene D_4
20410	Leukotriene E_4

See all leukotrienes at www.caymachem.com

Oxylipin Mixtures for Mass Spectrometry

Item No.	Product Name
20666	Arachidonic Acid Oxylipin LC-MS Mixture
21393	EPA Oxylipin LC-MS Mixture
33596	Oxylipins MaxSpec® Discovery Mixture 1
33597	Oxylipins MaxSpec® Discovery Mixture 2

See all oxylipin mixtures for mass spectrometry at www.caymanchem.com

Request the Specialized Pro-Resolving Mediators Poster

www.caymanchem.com/SPMposter

Request the Arachidonic Acid Cascade Poster

www.caymanchem.com/AAposter

LIPIDOMICS SERVICES

Cayman offers lipid synthesis, purification, and characterization services backed by state-of-the-art chromatography/mass spectrometry systems and data analysis software, enabling us to offer targeted and untargeted lipidomics services to meet your specific project needs.

Discover more at www.caymanchem.com/lipidomics

LEARN MORE

Read our News article to learn more about how Cayman's Lipidomics Services team used their targeted eicosanoid and oxylipin panels to help researchers at the University of Rochester detect biomarkers of inflammation in COVID-19.

www.caymanchem.com/COVID-19biomarkers

- **Learn more about lipid roles in biology, health and disease, and pharmaceutical development**
- **Explore resources and literature**
- **Browse our large collection of lipids and standards**

www.caymanchem.com/lipids

The Cytokine Storm and NETosis

Detecting Elevated Cytokines

Some patients with COVID-19 develop a hyperinflammatory cytokine storm that can lead to tissue damage. Cytokines involved in this response can include IL-1β, IL-6, IL-7, IL-10, G-CSF, CXCL10, MCP-1/CCL2, and TNF-α.

Single-Plex Cytokine Detection Assays

Item No.	Product Name
583301	Interleukin-1α (human) ELISA Kit
583311	Interleukin-1β (human) ELISA Kit
501030	Interleukin-6 (human) ELISA Kit
589201	TNF-α (human) ELISA Kit

See all cytokine detection assay kits at www.caymanchem.com

Kinase Inhibitors

Kinases are integral to inflammatory signaling pathways. JAKs function downstream of IL-6 to regulate cytokine release and inflammation. TLR7/8 signals through BTK to induce NF-κB-mediated production of pro-inflammatory cytokines.

JAK Inhibitors

Item No.	Product Name
16707	Baricitinib
11598	CP 690,550
11609	Ruxolitinib
16289	TG101348

BTK Inhibitors

Item No.	Product Name
19899	Acalabrutinib
16274	Ibrutinib
28924	Zanubrutinib

See all kinase inhibitors at www.caymanchem.com

LEARN MORE

Read our News article to learn more about kinase signaling in inflammation and the cytokine storm.

www.caymanchem.com/cytokinestorm

NETosis

Excessive neutrophil infiltration and NETosis can lead to increased inflammation and thrombosis. Levels of the NET markers myeloperoxidase and citrullinated histone H3 are elevated in sera of patients with COVID-19.

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
601070	Neutrophil (mouse) Isolation Kit

See all NETosis assay kits at www.caymanchem.com

LEARN MORE

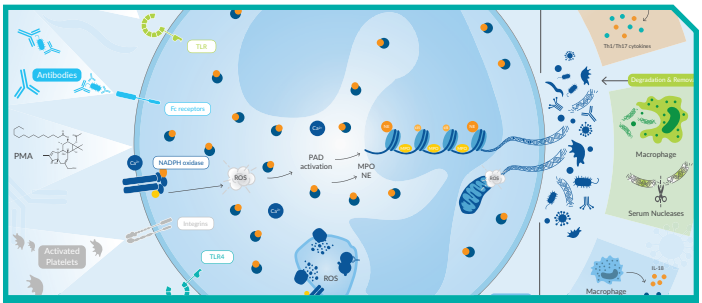
Read the article on Casting NETs in COVID-19 to learn about how NETs are being examined as a complicating factor in the severity of the disease.

www.caymanchem.com/SARS-CoV-2NETs

NETosis SERVICES

Our experts can detect NET formation and screen for modulators of NETosis using freshly isolated neutrophils *ex vivo* for high-content imaging and NET-associated enzyme activity assays.

Discover more at www.caymanchem.com/bioanalysis



Request the Neutrophil Biology Poster

www.caymanchem.com/neutrophilposter

TOOLS TO STUDY MITOCHONDRIAL DYSFUNCTION

Mitochondrial dysfunction and damage have been observed in patients with the post-viral syndrome ME/CFS, which is characterized by generalized fatigue. Growing evidence suggests that SARS-CoV-2 impairs mitochondrial function in immune cells. As modulation of mitochondrial function has been shown to relieve fatigue in patients with ME/CFS, it may show similar benefits in patients with Long COVID.

Mitochondrial Function and Damage Assays

Item No.	Product Name
700410	ATP Detection Assay Kit - Luminescence
701600	Mitochondrial ROS Detection Assay Kit
600800	Oxygen Consumption Rate Assay Kit
700470	Pyruvate Assay Kit
701310	TMRE Mitochondrial Membrane Potential Assay Kit

See all mitochondrial biology assay kits at www.caymanchem.com

Iron Chelators

Iron overload, which can contribute to mitochondrial dysfunction, lipid peroxidation, ferroptotic cell death, and inflammation, has been observed in some patients with COVID-19.

Item No.	Product Name
16753	Deferasirox
20387	Deferiprone
14595	Deferoxamine (mesylate)

See all metal chelators at www.caymanchem.com

LEARN MORE ABOUT FERROPTOSIS

www.caymanchem.com/ferroptosis

CELLULAR METABOLISM SERVICES

Cayman scientists can provide a detailed view of cellular metabolic function *via* analysis of mitochondrial toxicity, function, and biogenesis, as well as glycolysis, metabolic substrate utilization, oxidative stress, and more.

Discover more at www.caymanchem.com/cellmetabolism

Mitochondrial Support Nutrients

Various antioxidants, cofactors, vitamins, and mitochondrial metabolites have been shown to reduce fatigue, including in patients with ME/CFS.

Item No.	Product Name
81025	Curcumin
70935	(−)-Epigallocatechin Gallate
20261	N-acetyl-L-Cysteine
16078	NADH (sodium salt hydrate)
10005169	Quercetin (hydrate)
19677	Ubiquinol

AMPK Activators

Direct and indirect activators of AMPK, a metabolic regulator, have been studied for their impacts on metabolism and mitochondrial biogenesis.

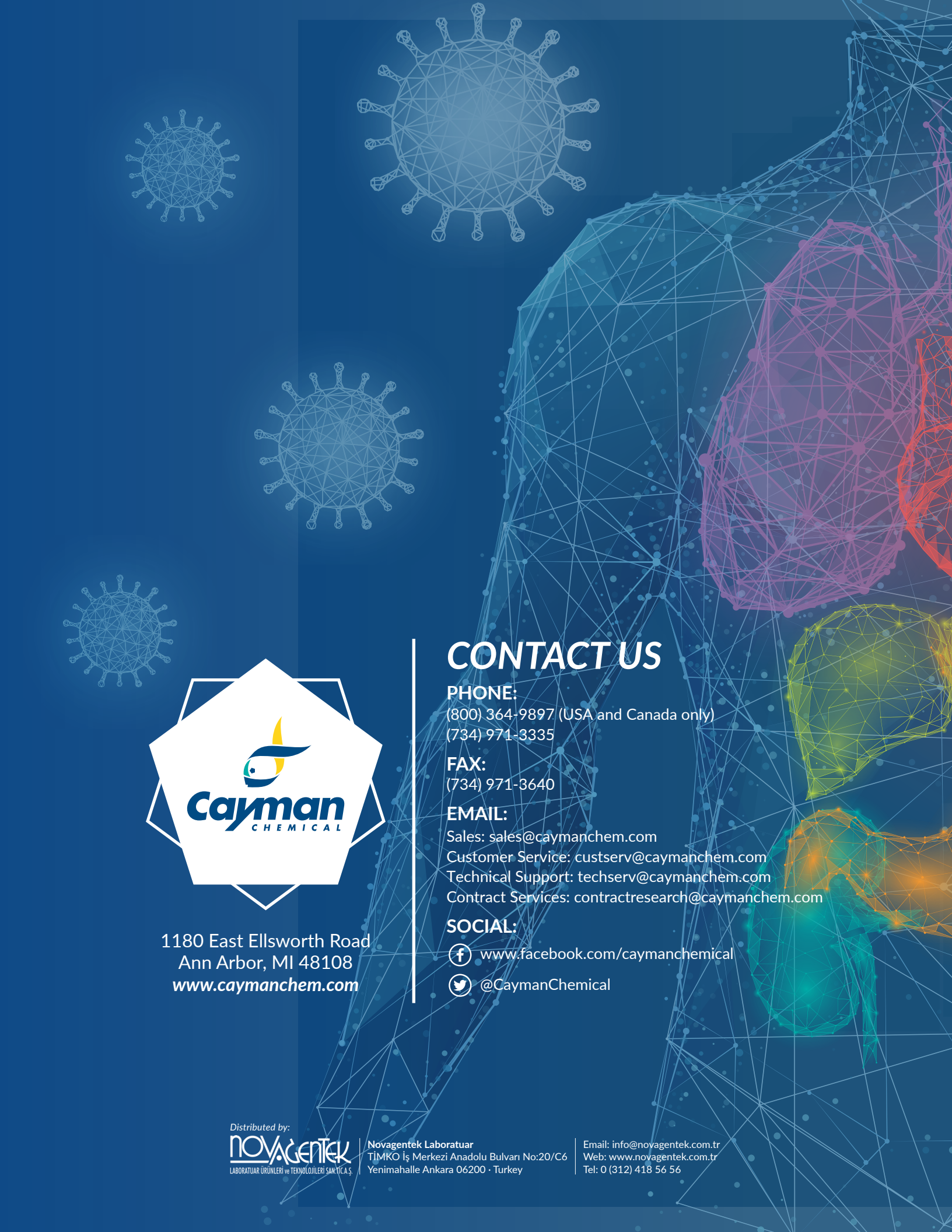
Item No.	Product Name
10010241	AICAR
13118	Metformin (hydrochloride)
10028	Pioglitazone (potassium salt)
71740	Rosiglitazone

See all AMPK activators at www.caymanchem.com

PDHK Inhibitors

Inhibition of PDHKs, which negatively regulate the pyruvate dehydrogenase complex, reduces the conversion of pyruvate to lactate.

Item No.	Product Name
19282	AZD 7545
18911	CAY10703
10006148	Leelamine
19182	VER-246608



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