COVID Drug Strategies

Since the emergence of COVID-19, the biopharma industry has been working tirelessly to develop both preventive and therapeutic interventions.

SARS-CoV-2 is part of the coronavirus family. Although viruses in this family vary in terms of disease caused and how they pass from host to host, their basic structure is the same. Coronaviruses are made up of three key parts;

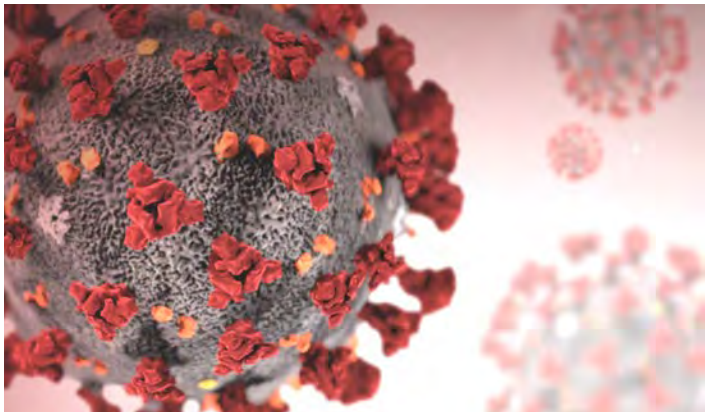
- Genetic information contained in RNA
- A viral envelope
- Spike proteins

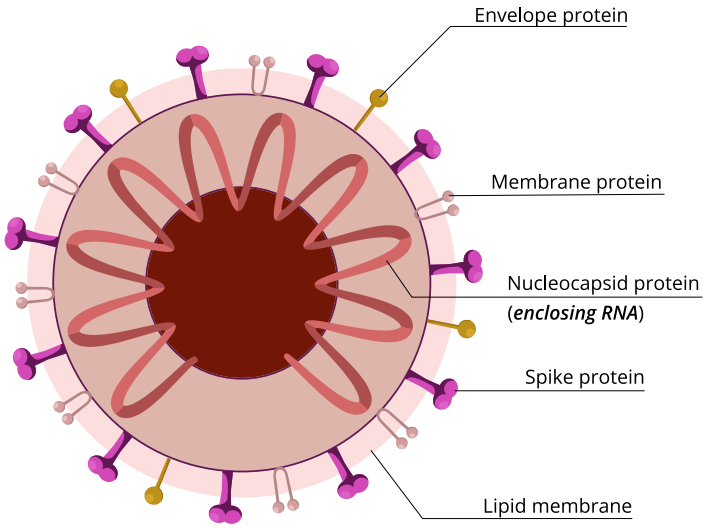
We consider four drug development strategies;

- 1: Block Viral Replication
- 2: Prevent Cell entry
- 3: Reduce Immune response
- 4: Drug Repurposing

1: Block Viral Replication.

Despite our limited knowledge of SARS-CoV-2, pathogenic coronaviruses have been widely studied since the SARS coronavirus outbreak of 2003 and the MERS outbreak which began in 2012. While there are differences in both infectivity and mortality rates between SARS/MERS and the current SARS-CoV-2 virus, the genome size (30 kb) and organisation of replicase-transcriptase and structural protein Orfs used in all three viruses is highly conserved. Therefore, SARS and MERS research has already helped in identifying potential viral and host drug targets to block coronavirus replication.





2: Prevent Cell Entry.

Cell entry of coronaviruses depends on binding of the viral spike (S) proteins to cellular receptors and on S protein priming by host cell proteases. Unravelling which cellular factors are used by SARS-CoV-2 for entry might provide insights into viral transmission and reveal therapeutic targets. SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming.

3: Reduce Immune Response.

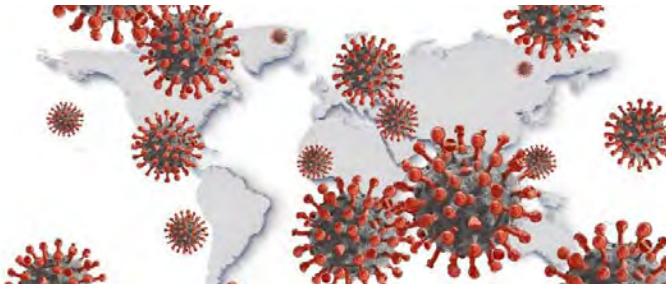
The severity and outcome of COVID-19 might be associated with the excessive production of proinflammatory cytokines; "cytokine storm," leading to an acute respiratory distress syndrome. Immune - modulatory or immune - suppressive treatments such as Hydroxychloroquine, Interleukin (IL)-6 and IL-1 antagonists, might be considered as treatment choices for COVID-19, particularly in severe disease.

4: Drug Repurposing.

Leverage drugs and biomolecules previously reported to have activity against related coronaviruses.

COVID-19 Treatment Strategies

SARS-CoV-2 and severe acute respiratory syndrome–associated coronavirus (SARS-CoV) have >90% sequence identity in their essential enzymes and share the same entry receptor. Their close genetic relationship suggests that drugs effective against SARS-CoV (and potentially other coronaviruses) might be effective against SARS-CoV-2.



Analysis - Four Ways of Treating COVID 19

Some of the drugs being developed to attack the disease and the SARS-CoV-2 virus that causes it.

Strategy 1 - Block Viral Replication

Drug	Action	Company/Lab	Status
Remdesivir	Disrupt viral RNA synthesis	U. of North Carolina Vanderbilt University Gilead Sciences	Clinical trials
EIDD-2801	Disrupt viral RNA synthesis	Emory University U. of North Carolina Vanderbilt University Ridgeback Biotherapeutics	Clinical trials
Danoprevir-Ritonavir	Inhibit viral protease enzyme	Ascletis Pharma	Clinical trials
RNAi Experimental Compounds	Block viral RNA synthesis	Alnylam Pharmaceuticals Vir Biotechnology	Early Research

Strategy 2 - Prevent Entry Into Cells

Drug	Action	Company/Lab	Status
APNO1	Decoy cell receptor	Apeiron Biologics	Clinical trials
Multiple Human Antibody Cocktail	Antibodies neutralize virus	Regeneron	Clinical trials planned for Summer
Monoclonal Antibody Candidates	Antibodies neutralize virus	Vir Biotechnology Biogen WuXi Biologics	Clinical trials planned
TAK-888	Modified antibodies against virus	Takeda	Preclinical

COVID-19 Treatment Strategies

Strategy 3 - Reduce Hyperimmune Response and Acute Respiratory Distress

Drug	Action	Company/Lab	Status
Kevzara (sarilumab)	Antibodies block IL-6 immune cell signal	Regeneron Sanofi	Clinical trials
Actemra (tocilizumab)	Antibodies block IL-6 immune cell signal	Genentech BARDA*	Clinical trials
Remestemcel-L	Stem cells modulate immune system	Mesoblast NIH**	Clinical trials
Xeljanz (tofacitinib)	Inhibit inflammatory cells	Pfizer	Clinical trials

*U.S. Biomedical Advanced Research and Development Authority
**National Institutes of Health

Strategy 4 - Drug Repurposing Treatments/Combinations in Development

Candidate	MoA/Indication	Status/Clinical Trials	Sponsor/ Producer
Kaletra (lopinavir/ ritonavir) Combinational therapy	HIV protease inhibitor HIV-1 infection	> 10 latest stages clinical studies (Including combinations with other drugs) NCT04321174 NCT04255017 NCT04307693	AbbVie
COVID-19 antibody therapy	antibody	Development stage	AbCellera Eli Lilly
TMC-310911 (ASC-09)	Stem cells modulate immune system	Mesoblast NIH**	Clinical trials
Ganovo (Danoprevir)	Hepatitis C virus protease inhibitor Hepatitis C	Phase 4 Clinical Study In combination with other drugs NCT04291729	Ascletis, The Ninth Hospital of Nanchang
Galidesivir (BCX4430)	Nucleoside RNA polymerase inhibitor Yellow Fever	Advanced development stage	BioCryst Pharmaceuticals

COVID-19 Treatment Strategies

Candidate	MoA/Indication	Status/Clinical Trials	Sponsor/ Producer
BOLD-100	Inhibit stress-induced upregulation of GRP78 Cancer drug	Suggested	Bold Therapeutics
Leronlimab (PRO 140) Humanized monoclonal antibody	Binds to CCR5 HIV, cancer	Initiation of Phase 2 Clinical Study	CytoDyn Inc.
Ivermectin	Anti-parasitic drug	Preclinical study	Doherty Institute Monash University in Australia
Fingolimod	Sphingosine 1-phosphate receptor modulator Multiple sclerosis	Phase 2 Clinical Study in China NCT04280588	First Affiliated Hospital of Fujian Medical University
Thalidomide	MoA is not fully understood	Phase 2 Clinical Trials in China NCT04273581 NCT04273529	First Affiliated Hospital of Wenzhou Medical University
Remdesivir (GS - 5734)	Block RNA polymerase Ebola	Orphan Drug Designation for Gilead 9 clinical studies worldwide NCT04323761 NCT04257656 NCT04315948	Gilead Sciences
Truvada (emtricitabine + tenofovir) Combinational therapy	Non-nucleoside reverse transcriptase inhibitors HIV infection	In preparation	Gilead Sciences
Triazavirin	inhibits RNA synthesis	Phase 3 Clinical Study in China ChiCTR2000030001	Health commission of Heilongjiang province
Baricitinib	JAK/NAK inhibitor Rheumatic Disease	Phase 3 Clinical Study in Italy NCT04320277	Hospital of Prato
Prezista/ Prezcobix (darunavir + cobicistat)	Protease inhibitor HIV infection	Phase 3 Clinical Studies NCT04304053 in Spain	Janssen Pharmaceuticals Fundacio Lluita
Combinational therapy		3Cclinical tStudies in China NCT04252274 ChiCTR2000030259 ChiCTR2000029541	Contra la SIDA, Medical Institutions in China
Chloroquine	Endosomal acidification fusion inhibitor Anti-malarial	> 10 studies worldwide > 10 Clinical Studies in China ChiCTR2000029609 NCT04261517	Medical institutions worldwide
Azithromycin	Antibiotic	> 10 trials in combination with other drugs NCT04322396 NCT04321278 NCT04322123	Medical institutions worldwide
Remestemcel-L Mesenchymal stromal cell (MSC)	Migrate to the site of inflammation to reduce the production of pro-inflammatory cytokines. Indication: Acute Graft versus Host Disease	Phase III Clinical Trials NCT04371393	Mesoblast, Inc. / Icahn School of Medicine at Mount Sinai

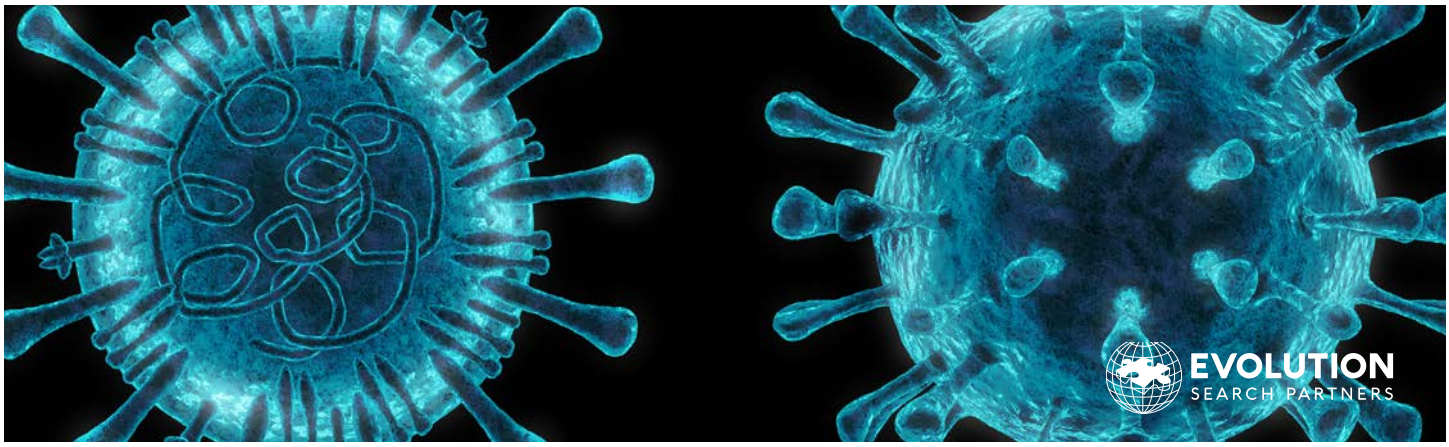
COVID-19 Treatment Strategies

Candidate	MoA/Indication	Status/Clinical Trials	Sponsor/ Producer
Favipiravir (T-705)	Block RNA polymerase Flu drug	Approved in China Clinical studies in China, Japan, and Italy ChiCTR2000029996 ChiCTR2000030894	Produced by Fujifilm Toyama Chemical
Kevzara (sarilumab) Monoclonal antibody	Anti - IL-6 Rheumatoid arthritis	Phase 2, 3 Clinical Study NCT04315298	Regeneron Pharmaceuticals, Sanofi
EIDD-2801	Block RNA polymerase	Suggested	Ridgeback Biotherapeutics Developed by Emory University
Activase	Tissue plasminogen activator Stroke drug	Suggested	Ridgeback Biotherapeutics Developed by Emory University
Actemra (tocilizumab) Monoclonal antibody	anti-IL-6R Rheumatoid arthritis	Approved in China 5 Clinical Studies in Denmark, Italy, China NCT04317092 NCT04331795	Roche, Medical institutions worldwide
Umifenovir (Arbidol)	Membrane fusion inhibitor	Latest stages clinical studies in China (Including combinations with other drugs) ChiCTR2000029621 NCT04260594	Ruijin Hospital, Other institutions in China
TAK-888 (Plasma-derived antibodies)	Polyclonal hyperimmune globulin (H-IG)	Development stage	Takeda
Ruxolitinib (Jakafi, Jakavi)	Inhibitor of Janus-associated kinases (JAK1 and JAK2) Myelofibrosis	Clinical Study in China Ruxolitinib combined with stem cell therapy ChiCTR2000029580 Tongji Hospital, Hubei, China	Tongji Hospital, Hubei, China Manufacturer - Incyte Corporation
Camostat mesylate (Foypan)	inhibit SARS-CoV-2 Spike protein-initiated membrane fusion	Phase 1, 2 Clinical Study in Germany NCT04321096	University of Aarhus Manufactured in Japan
Nafamostat mesylate (Fusan)	inhibit SARS-CoV-2 Spike protein-initiated membrane fusion Acute pancreatitis	Completed preclinical study in Japan	University of Tokyo
Hydroxychloroquine (Plaquenil)	Endosomal acidification fusion inhibitor Anti-malarial Rheumatoid arthritis treatment	> 10 Clinical Studies worldwide 10 Clinical Studies in China NCT04321278 NCT04261517 ChiCTR2000029868	

Summary

Challenges

- The issue of hyperinflammation versus viral replication.
- The timing for immunomodulation therapy.
- The pharmacokinetics of oral medications in crucially ill patients.
- Impaired clearance of the drugs.



Summary

Ending the pandemic and preventing its return is assumed to require an effective vaccine and antiviral drugs. None of the approaches discussed are cures. The drugs under development may reduce COVID-19 severity when symptoms first arise. It is hoped that combination therapy may help by limiting symptoms and prevent hospital admissions.

References

- Kindrachuk, J et al. Coronaviruses: An Overview of Their Replication and Pathogenesis Methods Mol Biol.
- Lu R, Zhao X , Li J , et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020; 395: 565-574
- US Biomedical Advanced Research & Development Authority
- National Institute of Health
- Scientific American

EVOLUTION
SEARCH PARTNERS

Evolution Search Partners are a boutique search firm operating globally across USA, Europe and APAC, providing 'business critical' teams to the Biomanufacturing and Cell Gene Therapy sector.

With 25 years acclaimed international Biotechnology experience, we offer strong global networks, exceptional technical and business acumen, and operate as an experienced, competent, trustworthy search partner.

Online: www.evolutionexec.com **Email: info@evolutionexec.com**