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COVID-19: How R&D Responded

& What we Learned for Future Outbreaks

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RESEARCH SUPPORT SERVICE

March, 2020

Intelligence Brief Question

What is the COVID-19 outbreak and how has it been tackled?

The COVID-19 pandemic is impacting the entire world in an unprecedented way. Collecting information on the COVID-19-causing virus, called the SARS-CoV-2 virus, how it changes, and how it acts will be crucial to understand how to developed strategies to manage the outbreak and ultimately tackle the virus.

In Part 2 of this Intelligence Brief, we take a deep dive into SARS-CoV-2 virus genetics and the strategies and tools that fueled the identification of new therapies. We also look into some of the latest research and treatments being developed.

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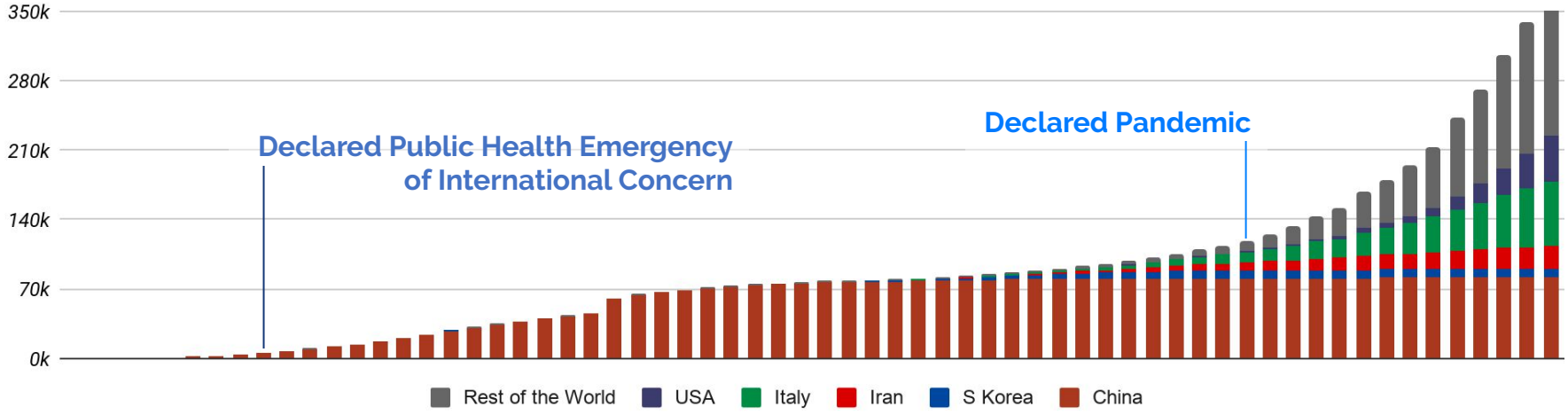
Executive Summary

The COVID-19 pandemic is already being described as the ***worst public health crisis in a generation***.

In the first 30 days of 2020, it went from ~50 confirmed cases to ~10,000 cases, mostly in China. It was then declared to be a public health emergency of international concern by the World Health Organization (WHO). Since then, it has jumped to more than **400,000 confirmed cases** across 193 countries and regions and **~18,000 fatalities**.

The current growth rate has the pandemic doubling in number of infected people every 7 days; the same applies for fatalities. What started as a Chinese problem quickly became a global crisis, with governments scrambling to contain the disease, gather key resources, and develop a cure.

COVID-19 confirmed cases evolution according to the European CDC



Executive Summary

What is the SARS-CoV-2 Virus?

SARS-CoV-2 is a positive-sense single-stranded RNA virus from the severe acute respiratory syndrome–related coronavirus species.

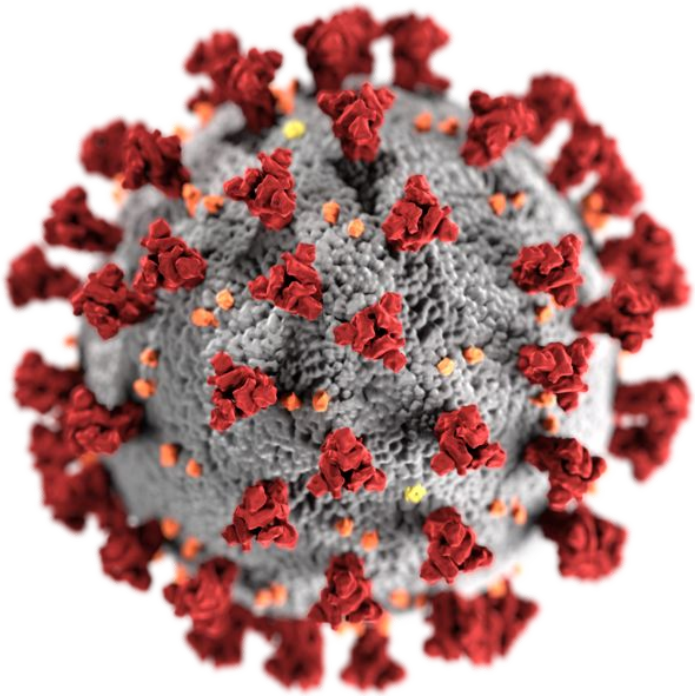
It emerged in China in December 2019, in a wet market of Wuhan.

Early studies demonstrated that SARS-CoV-2 binds a **membrane receptor** called human angiotensin converting enzyme 2 (hACE2).

hACE2 is expressed in different organs, such as the **lung, heart, kidney, and gastrointestinal tract.**

Once the virus binds and enters the host cell through the receptor, it **bypasses the host cell mechanisms and replicates**.

Cellular damage results either from the **virus that controls the host cell's mechanisms** or the **immune cells that kill the infected host cells, resulting in massive cell death**.



SARS-CoV-2 - Source: CDC

Executive Summary

Diagnosis:

Current guidelines from the WHO are for patients to be screened for the virus with a polymerase chain reaction (PCR)-based test (NAAT - nucleic acid amplification test).

Some initial studies reported that the approved assays had a sensitivity of 60-80%, often requiring a second test due to possible false negatives, particularly for suspect cases.

As such, computed tomography (CT) imaging is also often performed. As a chest CT scan with contrast takes about 40 minutes to perform, it has been utilized as a primary diagnostic tool to sort out suspected cases and predict severe complications such as acute respiratory diseases.

Manual NAAT-based tests are typically slow, requiring specialized equipment and personnel. They are not performed at the point of care (POC), potentially resulting in a turnaround time of several days for the results. Automated semi-POC or POC tests eliminate several of the pain points but are still typically slow and require expensive equipment.

The WHO's Global Research Forum that aims to identify research gaps and priorities for COVID-19 identified the development of a rapid point-of-care diagnostics for use at the community level as an immediate research need.

Executive Summary

There has been a strong response in regard to diagnosis development. **There are currently 96 manual and 30 automated NAAT assays commercialized, with at least 20 more in development.** The FDA just approved the first rapid near-POC NAAT assay from Cepheid on March 22, which can return results in just 40 minutes, but still requires specialized equipment that runs only one test at a time.

Only a fraction of automated NAAT assays are near point of care, with the majority still requiring lab processing. One notable exception is the **NINAAT from Self-Diagnostics**, initially developed for STDs, measuring less than 10 cm and returning results in just 30 minutes.

The greatest hope for rapid diagnostic test kits relies on immunoassays that detect the presence of anti-SARS-CoV-2 antibody levels (IgG and/or IgM). So far, there are over 70 such kits being commercialized, mostly from Chinese companies, with several others in development.

New assays need to be approved by each country's health authorities (a process that is a lot faster than drug approval under emergency status) and ramp up production to meet the current millions per day required around the world, which explains the shortage still felt by several countries.

A POC NAAT - NINAAT - *Self Diagnostics*

A rapid immunoassay - OnSite SARS-CoV-2 IgG/IgM Rapid Test, *CTK Biotech, Inc.*

A lab-based near-POC automated kit - QIAstat-Dx Respiratory Panel, *QIAGEN GmbH*

Executive Summary

Treatment:

There is no approved treatment for COVID-19. The current standard of treatment is to manage symptoms.

Several existing and new therapies are being investigated for treatment and prevention of COVID-19 - **we showcase 35 and highlight 2 in this report.**

Several of the world's major pharma and biotech companies have answered the call for a treatment with several antiviral drugs, vaccines, immunotherapies (mAB), and even cell therapies currently being developed.

One of the most promising drugs has been the antiviral drug **Remdesivir** from Gilead - initially developed for the Ebola virus. The drug has shown good antiviral activity against single stranded RNA viruses such as coronaviruses, inhibiting virus proliferation.

The number of COVID-19 studies registered so far:

468
Registered within the Chinese CT database

125
Registered within the FDA

REGENERON abbvie BAYER gsk GlaxoSmithKline SANOFI janssen PHARMACEUTICAL COMPANIES OF Johnson&Johnson GILEAD

Some of the companies currently working on a vaccine or therapy for COVID-19.

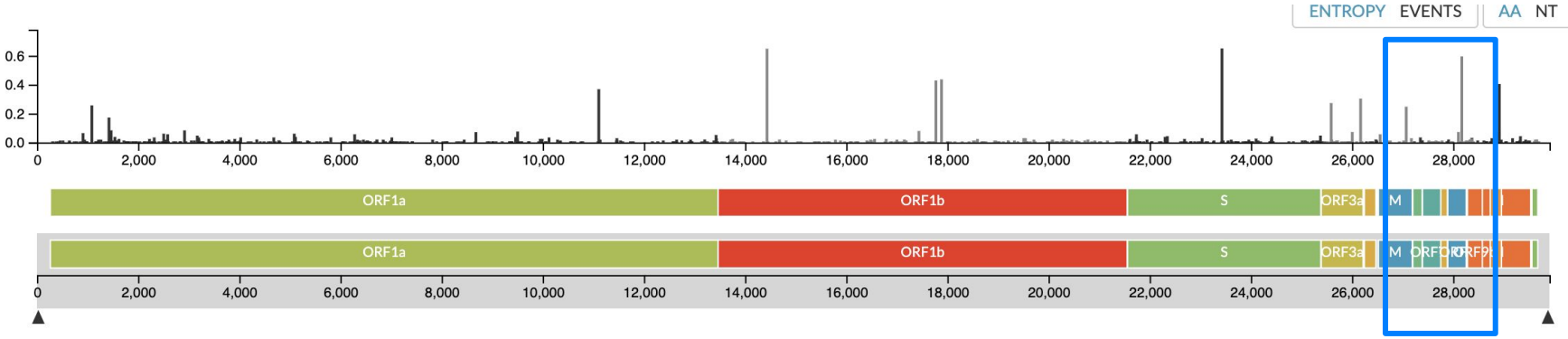
Executive Summary

Latest research in genomic information:

For the first time ever during a global outbreak, scientists are extensively using computational protein modeling and machine learning algorithms to identify viral protein targets and to predict which FDA-approved antiviral drug molecules can interact with SARS-CoV-2 proteins.

Major findings include:

1. A high sequence similarity (>99%) between all sequenced SARS-CoV-2 genomes available. This means that **a drug or vaccine would likely cover all of the strains thus far known.**
2. The spike protein (a major capsid) is highly similar to SARS-CoV, which means that **drugs and vaccines directed to SARS could be repurposed to target SARS-CoV-2.**
3. Despite the low heterogeneity of the SARS-CoV-2 genomes, at least two hyper-variable genomic hotspots were found (one is in the viral ORF8-encoded protein).



The genomic diversity plotted over the whole genome (numbers indicate nucleotide position) for all the 303 sequenced SARS-CoV-2 strains so far. One major variable region is ORF8. This region is thought to be involved in the suppression of the human immune system (blocking interferon gamma production). **Click here to access the interactive genomic database NextStrain.**

Executive Summary

The speed at which research moves against outbreaks has ramped up. Here's how the SARS-CoV-2 pandemic will have implications on future outbreaks:

1. Machine learning approaches identified possible antiviral drugs **within 2 weeks** of the publication of the first genome sequence. Several studies combined identified over **30 possible drug candidates**: The repurposing of FDA-approved drugs allows that some drugs can immediately be tested in patients and can immediately benefit treatment of the outbreak.

2. This is the first time that during an outbreak open access paper repositories are being used. All the newest, high-impact research is **immediately published** on sites such as bioRxiv before peer review. This increases the speed at which other scientists can build on findings dramatically.

3. Updates on genomic databases with tools to visualize and download genome and protein sequences are almost instantaneous, and the **newest sequencing tools** allow genome sequencing within a day. This greatly aids the mapping of mutations that might block the mode of action of certain drugs and can be analyzed *in silico*.

Latest in Research

A. Bioinformatics & genomics

Genomic origin and variability of SARS-CoV-2 strains

Genomic study indicates that a drug and vaccine is possible[1]

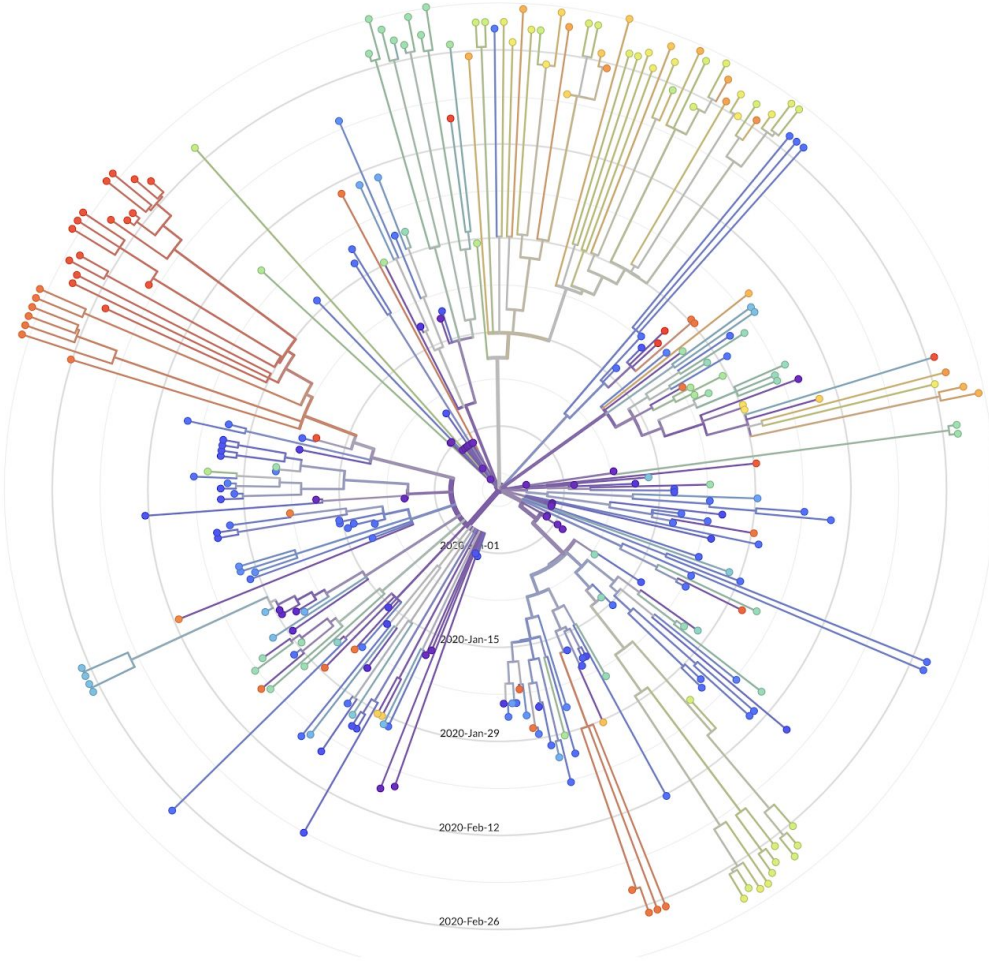
Full genomic SARS-CoV-2 sequences have been released (**n = 1111**) by the worldwide scientific community in order to understand the evolutionary origin and molecular characteristics of this virus.

Major conclusions:

1. There is high sequence similarity (>99%) between all sequenced SARS-CoV-2 genomes available. This means that **a drug or vaccine would likely cover all of the strains thus far known.**
2. Genomic analysis indicates that the SARS-CoV-2 originated in bats, the closest BCoV sequence sharing 96.2% sequence identity. This confirms a zoonotic origin of SARS-CoV-2. It has not been confirmed that the virus reservoir is in bats as of yet.
3. The spike protein (a major capsid) is highly similar to SARS-CoV, which means that **drugs and vaccines directed at SARS could be repurposed to target SARS-CoV-2.** The similarity to SARS-CoV also led to renaming nCoV to SARS-CoV-2
4. Despite the low heterogeneity of the SARS-CoV-2 genomes, at least two hyper-variable genomic hotspots were found (one is in the viral ORF8-encoded protein).

Origin of sequenced SARS-CoV-2 strains

Nextstrain



China
Hubei
Beijing
Anhui
Jiangxi
Chongqing
Hangzhou
Sichuan
Yunnan
Jiangsu
Shandong
Zhejiang
Fujian
Guangdong
Shanghai
Hong Kong
Taiwan
Taoyuan
Aichi
Tokyo
Saitama
Nara
Osaka
Kyoto
Kanagawa
Gyeonggi
Chungcheongnam
Seoul
South Korea
Selangor
Kathmandu
Kerala
Iran
Kuwait
Tbilisi
Thanh Hoa
Vinhphuc

Brussels
Liège
Bavaria
Baden-Wuerttember
North Rhine Westph
Netherlands
Utrecht
Overijssel
Gelderland
Limburg
Drenthe
North Brabant
Flevoland
South Holland
North Holland
Luxembourg
Zielonogorskie
Basel
Bern
Zurich
Aargau
Geneva
Vaud
Ticino
Graubünden
Schwyz
Comunitat Valencia
Italy
Lazio
Lombardy
Usti nad Labem
Northern Ireland
England
Wales
Dublin
Limerick
Scotland

Red River Delta
Quangning
Sihanoukville
Nonthaburi
Singapore
Queensland
New South Wales
Victoria
Wellington
Otago
Auckland
Riyadh
Europe
Central Hungary
Baranya
Copenhagen
Bretagne
Ile de France
Auvergne-Rhône-Alp
Pays de la Loire
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Bretagne
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Normandie
Grand Est
Auvergne Rhone Alp
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Galicia
Madrid
Flanders
Leuven
Couthuin
Kessel-Lo
Holsbeek
Sint-Niklaas
Kraainem
Huldenberg

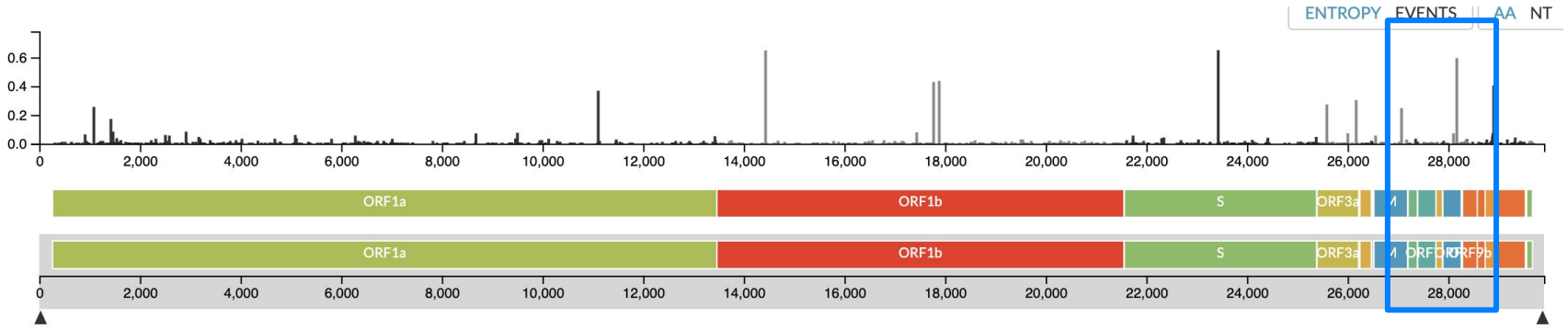
Småland
Helsinki
Finland
Portugal
Lagos
Kinshasa
KwaZulu-Natal
Santiago
Talca
Sao Paulo
Espirito Santo
Bahia
Rio de Janeiro
Distrito Federal
Amazonas State
Panama City
Mexico City
USA
Connecticut
Texas
Utah
Arizona
California
Illinois
Wisconsin
Minnesota
Massachusetts
New York
Washington
British Columbia
Ontario
Grand Princess
United Kingdom
Diamond Princess
Castilla y León

AG showing the sequenced SARS-CoV-2 variants (realtime) known so far. Strains are separated per region but could also be separated by genome type. **Click here to access the interactive genomic database NextStrain.**

Genomic variability of SARS-CoV-2 strains

Nextstrain

Low variability is advantageous to drug discovery and vaccine development efforts; as it means that a drug or vaccine would likely cover all of the strains thus far known.



The genomic diversity plotted over the whole genome (numbers indicate nucleotide position) for all the 1111 sequenced SARS-CoV-2 strains so far (3/24/20). **One major variable region is ORF8.** This region is thought to be involved **in the suppression of the human immune system (blocking interferon gamma production). Click here to access the interactive genomic database NextStrain.**

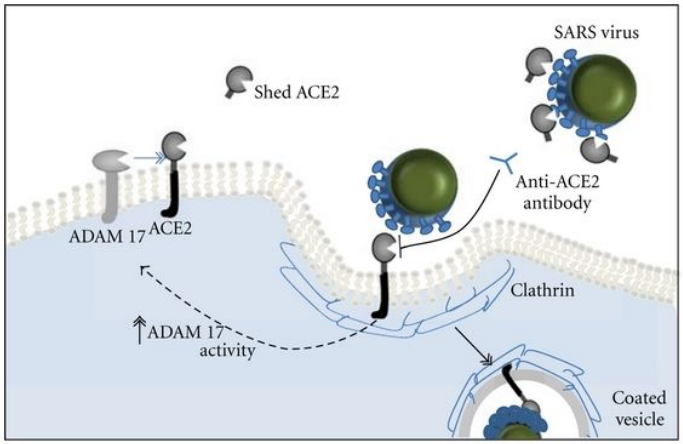
B. Characterizing the virus

Virus binding sites in human lungs

Human SARS-CoV-2 human transmission is driven by the interactions of the spike protein (S-protein) with human receptors. ACE2 was the main suspect receptor for SARS-CoV-2 because of the fact that SARS-CoV used this as a receptor to enter human lung cells.

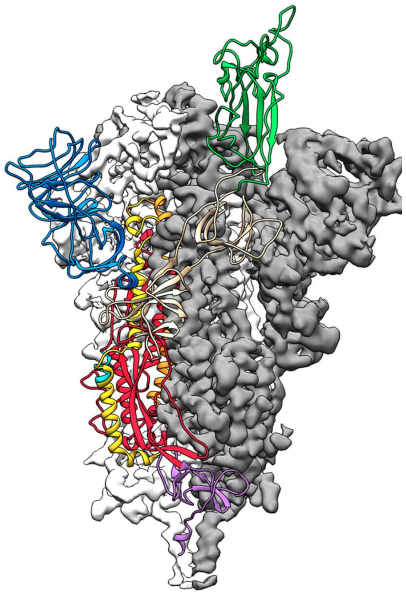
Major scientific findings:

1. Previously, several *in silico* predictions have identified ACE2 as the main receptor to be targeted by SARS-CoV-2[2].
2. ACE2 is mainly expressed on a small portion of alveolar cells called AT2[3].
3. The cellular protease TMPRSS2 is used for SARS-CoV-2 priming and entry[4].
4. Alignment of spike proteins of SARS-CoV and SARS-CoV-2 show conserved ACE2 binding region[5].

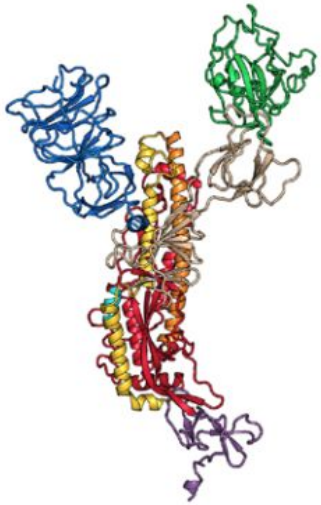


ACE2 is a receptor on human cells that binds SARS-CoV and SARS-CoV2 virus particles. Upon binding, the virus can enter through clathrin-coated vesicles. This can be blocked by anti-ACE2 antibodies (shown in the image) or compounds that block TMPRSS2 priming, preventing viral entry[5].

Structure of the spike protein of SARS-CoV-2 solved



SARS-CoV-2



ARS-CoV

Shown here is the structural comparison between the structure of the spike protein of SARS-CoV and SARS-CoV-2. As expected by earlier studies, the proteins are extremely similar.

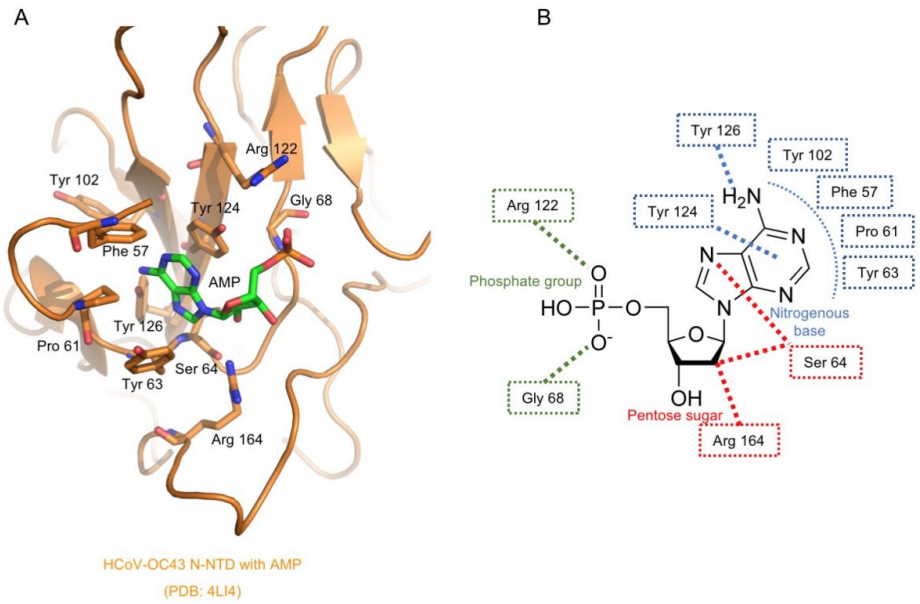
This is the 3D molecular structure of the SARS-CoV-2 spike protein. The protein takes on two different shapes, called conformations—one before it infects a host cell (shown here), and another during infection[7].

The McLellan group was the first to publish the structure of the spike protein. The authors used cryogenic electron microscopy (cryo-EM). A second research group published a similar structure study a few days after McLellan's[6].

Knowing the exact structure of the protein will allow a better prediction of potential drugs and binding partners as well as aid vaccine development.

Structure of the SARS-CoV-2 nucleocapsid protein solved

Authors Kang *et al.* solved the crystal structure for the SARS-CoV-2 nucleocapsid protein, further characterizing the virus biology. The authors demonstrated a unique RNA binding site in the protein that will aid the development of drugs that can interfere specifically with SARS-CoV and SARS-CoV-2[8].



The left panel shows a detailed cryo-EM structure of the ribonucleotide binding pocket of the nucleocapsid protein that is specific to SARS-CoV and SARS-CoV-2. Modeled in the structure is a ribonucleotide (AMP). The right panel shows a more simple illustration of the AMP binding pocket and its interaction with certain peptide residues in the protein.

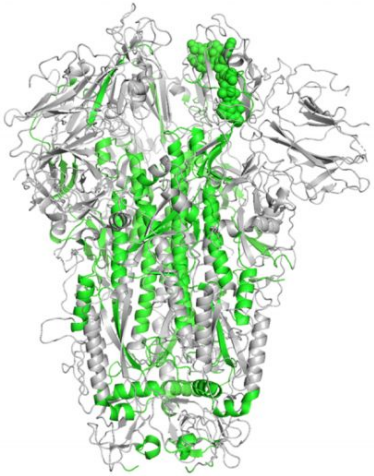
Understanding the structure of viral proteins will allow targeting and future treatment of current and potential future coronavirus outbreaks.

C. Vaccine development: Computational target identification

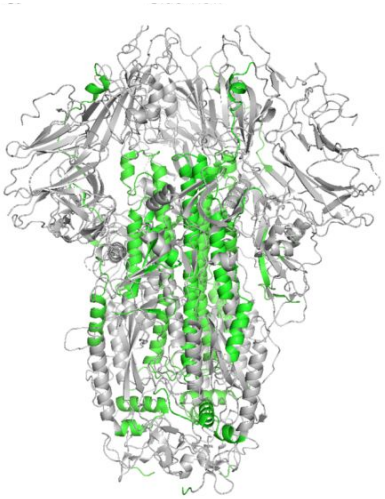
Preliminary identification of potential SARS-CoV-2 vaccine targets

Ahmed *et al.* used the high similarity between SARS-CoV and SARS-CoV-2 and conservation in surface proteins to predict B and T cell epitopes in the immunogenic in the spike (S) protein and nucleocapsid (N) of SARS-CoV-2[9].

As no mutation has been observed in these identified epitopes among the available SARS-CoV-2 sequences, immune targeting of these epitopes may potentially offer protection against SARS-CoV-2. For the T cell epitopes, a population coverage analysis of the associated MHC alleles was performed and a set of epitopes that is estimated to provide broad coverage was proposed.



Location of T cell epitopes on S-protein

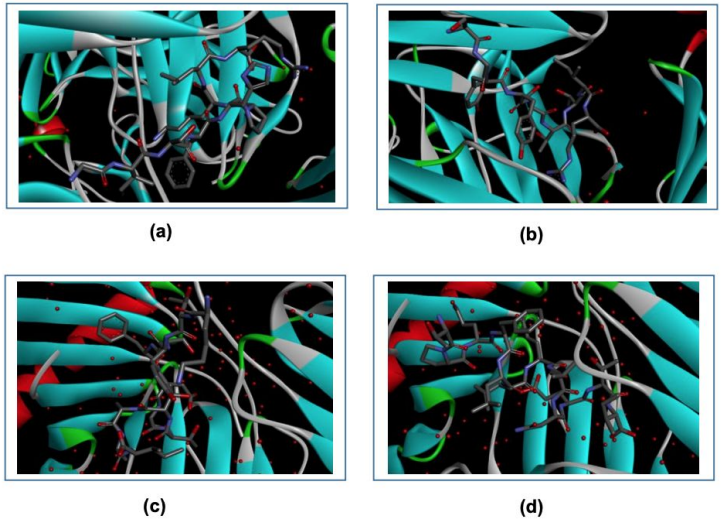


Location of B cell epitopes on S-protein

Epitope-based *in silico* vaccine design to identify vaccine candidates

Sarkar *et al.* used reverse vaccinology and immunoinformatics to design possible epitope-based subunit vaccines against the SARS-CoV-2 virus. The group identified several possible epitopes and used molecular dynamics simulations, *in silico* codon adaptation to check biological stability and find effective mass production strategies[10].

Two proteins, the SARS-CoV2 nucleocapsid phosphoprotein and surface glycoprotein, were identified as potent antigens. Four *in silico* peptide vaccine epitopes were docked in a computer model to show their effective interaction with the human immune system's antigen-presenting molecules MHC-I and MHC-II.



The best poses of interactions between the selected epitopes from the two proteins and their respective receptor:

a) The interaction between QLESKMSGK and MHC class-I

b) The interaction between GVLTESNKK and MHC class-I

c) The interaction between LIRQGTDYKHWP and MHC class-II

d) The interaction between TSNFRVQPTESI and MHC class-II.

D. Cure development

Cure development strategies - Academic publications

Academic research summary

On January 28, 2020, an Australian group managed to culture the SARS-CoV-2 virus. A video of the successful culturing of the virus can be found here. Their protocols were shared publicly so that scientists could start working on a cure and vaccine[11].

Currently, several groups are working on *de novo* drug discovery:

1. Machine learning algorithms to predict drug combinations based on *in silico* analysis[12,13]
2. Testing approved drugs that work against similar viruses using computational models[14,15]
3. Vaccine target predictions based on homology searches and initial antibody identification for passive immunization[16,17]

Previously and against SARS/MERS, **classical drug screening was performed,** taking up long times before treatment combinations were established.

This is one of the **first times machine learning has been used** to this extent to predict the effectiveness of certain drug regimens.

Machine learning algorithms to predict drug combinations against viral protease

The SARS-CoV-2 viral protease is highly conserved with the SARS coronavirus protease (96.1%). Gao *et al.* reported a series of compounds that they have found by machine learning to target the viral protease[12]. The authors found that besides SARS antivirals, HIV-1 drugs might be able to target the virus as well.

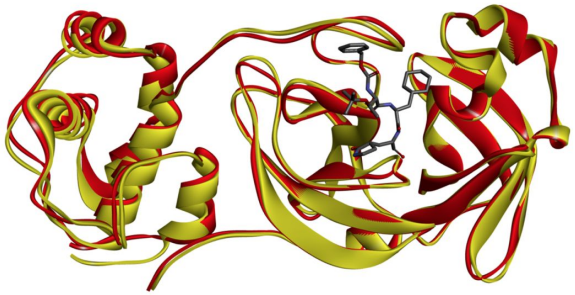


Illustration of the similarity between SARS-CoV-2 protease in gold and SARS-CoV 3CL protease in red. The anti-SARS inhibitor in dark color indicates the binding site[12]

ID	3DALL	3DMT	LS-BP	2DFP	logP	logS	Synthesizability
MSU3298	-10.56	-9.09	-9.87	-8.77	4.96	-5.69	3.25
MSU2313	-9.71	-8.28	-9.54	-7.14	3.24	-4.65	3.44
MSU3245	-9.55	-9.75	-8.98	-8.42	5.44	-6.26	3.10
MSU1221	-9.54	-9.38	-7.28	-5.34	4.93	-5.40	2.86
MSU3079	-9.47	-7.69	-8.98	-8.52	5.36	-6.68	3.82
MSU3054	-9.35	-8.15	-8.15	-8.15	6.28	-6.68	3.33
MSU7200	-9.31	-9.10	-7.06	-7.00	3.59	-5.28	2.08
MSU3258	-8.96	-7.75	-9.23	-7.19	5.40	-5.54	3.79
MSU2879	-8.87	-7.37	-5.70	-8.59	4.27	-5.33	2.50
MSU3289	-8.87	-8.11	-8.74	-8.51	5.11	-4.81	2.87
MSU2947	-8.86	-8.02	-9.48	-9.07	6.47	-6.44	2.64
MSU3519	-8.85	-7.87	-9.22	-6.98	5.58	-5.58	4.69
MSU3137	-8.85	-8.44	-8.25	-8.75	5.12	-6.02	4.04
MSU3134	-8.85	-7.05	-8.63	-8.68	5.12	-5.81	4.02
MSU3085	-8.85	-8.00	-7.87	-9.39	5.16	-6.21	3.13
lopinavir	-7.78	-8.13	-5.67	-5.55	4.33	-4.76	3.90
ritonavir	-8.44	-8.07	-5.14	-4.96	5.91	-5.30	4.19

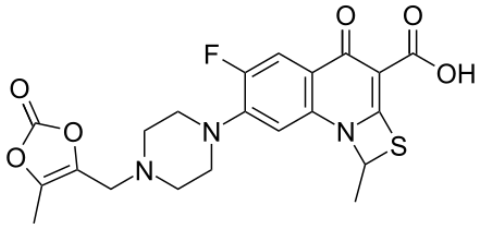
Top 15 leads predicted by machine learning. **Antiviral drugs lopinavir and ritonavir are among 8000 predicted compounds that should bind the viral protease.** The numbers in the table indicate scores from different models that were tested (3DALL, 3DMT, etc.) The synthesizability indicates how easy it is to make the drug (the lower the better)[12].

Machine learning algorithms to predict drug combinations against viral protease

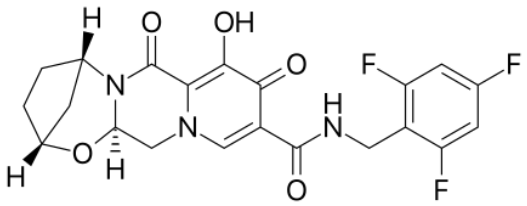
Authors Li *et al.* confirm that the SARS-CoV-2 viral protease is highly conserved with the SARS coronavirus protease (96.1%). The authors simulated the docking of 690 molecules with possible binding capacity with SARS-CoV main protease, (most of them were dyes, toxins, and antitumor drugs with strong side effects)[14].

About 50 molecules were left after excluding these molecules, and marketable drugs were selected for further kinetic and biochemical analysis.

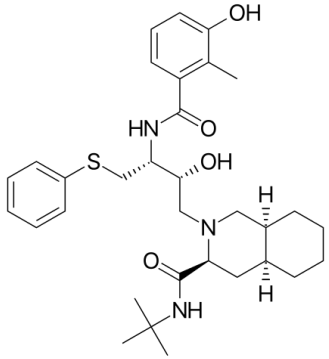
Finally, 4 molecules were identified, including No. 6651 molecule (Prulifloxacin), No. 6589 molecule (Bictegravir), No. 0097 molecule (Nelfinavir), and No. 6626 molecule (Tegobuvi). These could be used as monotherapy, or potentially as multivalent therapy strategies.



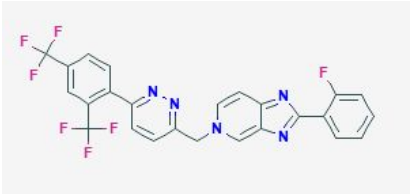
Prulifloxacin (Fluoroquinolone)
Not FDA approved



Bictegravir (HIV)
Approved



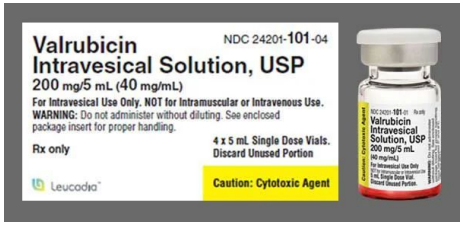
Nelfinavir (HIV) Approved



Tegobuvir (Hep C) Not FDA approved

Computational docking to predict drug combinations against viral protease

Liu & Wang reported ten compounds that they have found by computation docking to target the viral protease. **The authors found several approved drugs that may be tested for their efficacy against SARS-CoV-2[18].**



Name	H-bond counts	Vital residues taking part in H-bond formation	Medical indications according to DrugBank
Colistin	9	THR24, THR25, THR26	Antibiotic
Valrubicin	7	THR24, THR25, THR26, ASN28, ASN119	Anthracycline, antitumor
Icatibant	6	ASN28, ASN119	Hereditary angioedema
Bepotastine	5	THR25, THR26, ASN119	Rhinitis, uriticaria/puritus
Epirubicin	4	ASN28, ASN119	Antitumor
Epoprostenol	4	ASN119	Vasodilator, platelet aggregation
Vapreotide	3	THR24, ASN28, ASN119	Antitumor
Aprepitant	3	ASN28, ASN119	Nausea, vomiting, antitumor
Caspofungin	3	ASN119	Antifungal
Perphenazine	2	ASN28, ASN119	Antipsychotic

The authors used the amount of H-bonds formed with the viral protease as a metric to define possible candidates.

A drug-target interaction deep learning model to predict drugs against multiple viral protein

Ram Back *et al.* used a drug-target interaction deep learning model to predict which known antiviral drugs would work against the SARS-CoV-2 viral proteins[19].

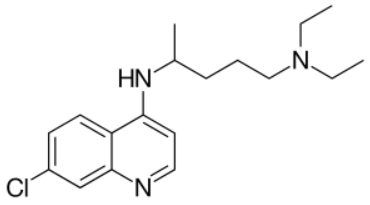
The algorithm sorted these drugs based on their predicted nanomolar affinity. Now that the virus can be cultured, these combinations can be tested *in vitro*.

Drug type	Function	Examples
Protease	viral protein that cuts other proteins	Atazanavir, Efavirenz, Ritonvir, Dolutegravir, Asunaprevir
RNA polymerase	viral enzyme that synthesizes viral RNA	Grazoprevir, Ganciclovir, Atazanavir, Daclatasvir, Acyclovir
Methyltransferase	viral protein that methylates viral RNA	Atazanavir, Efavirenz, Boceprevir
EndoRNAse	viral enzyme that cuts RNA	Efavirenz, Atazanavir, Ritonavir, Danoprevir, Grazoprevir
Exonuclease	viral protein that cuts DNA	Simeprevir, Efavirenz, Danoprevir, Ganciclovir, Penciclovir
Helicase	viral protein that helps folding of RNA/DNA	Simeprevir, Atazanavir, Grazoprevir, Asunaprevir, Telaprevir

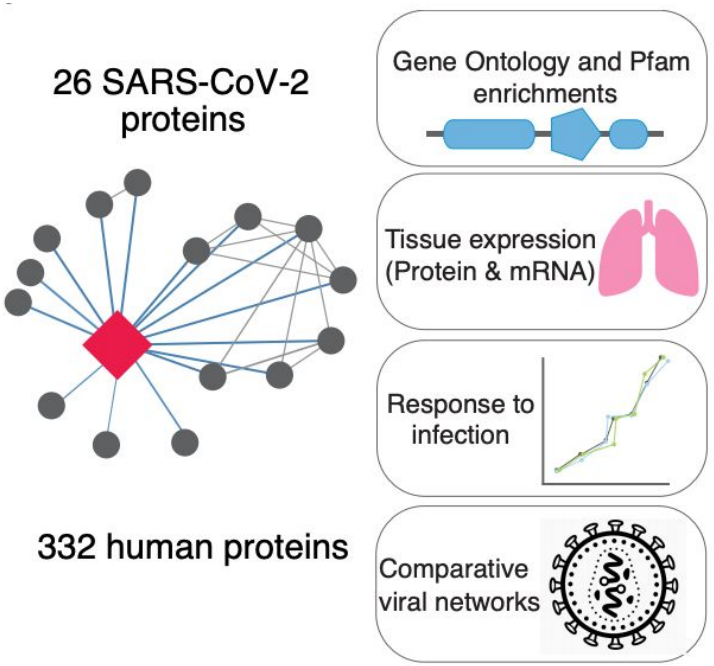
A massive protein-protein interaction mapping effort reveals potential (FDA-approved) drug candidates

Gordon *et al.* expressed most viral proteins and mapped how they bind to human proteins. Their study revealed 67 druggable human proteins and 69 drug candidates[30].

The authors used mass spectrophotometry and protein binding assays to map all the protein binding events between viral proteins and human proteins.



Interestingly, Chloroquine (earlier indicated as drug candidate) came out of this analysis as well.



In total, 26 SARS-CoV-2 were expressed and found to interact with 332 different human proteins. Results were filtered by looking at candidates that are expressed in lung tissue, during infection and by looking at other viral comparative networks.

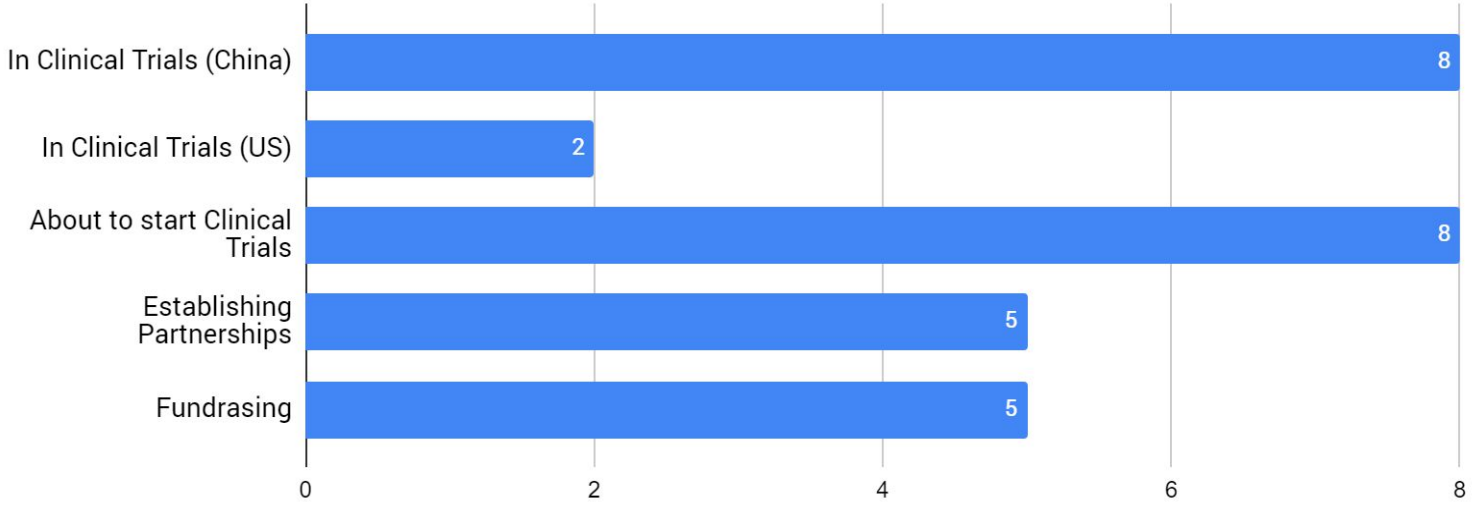
This massive high-throughput collaboration effort identified **69 potential FDA-approved drugs** that could go directly into Phase-I to test its efficacy against SARS-CoV-2 infection.

E. Drug development: Experimental leads & trials

Potential cures in development / Clinical trials

There has been an unprecedented response from both academic and pharmaceutical players to this crisis[20,21]. At least 34 different entities have announced they are developing potential therapies, with several already in clinical trials. The majority are US- (several collaborating with foreign players) and Chinese-based companies, and the therapies include both adaptation of previously developed vaccines for coronaviruses as well as novel approaches such as mRNA-based vaccines, AB therapies, and different novel vaccines. Two of the earliest developments to start clinical trials in Wuhan were Gilead Sciences' Remdesivir and the combination therapy of Abidol and Darunavir led by the research team of Prof. Lanjuan Li with Pharmstandard. We provide a brief overview of both these drugs as well as a short list of the main initiatives in place in the following pages.

Status of some of the 34 treatments in development[22-25]



Gilead Sciences

About Gilead

Gilead Sciences, Inc., is an American biotechnology company that researches, develops, and commercializes drugs. The company focuses primarily on antiviral drugs used in the treatment of HIV, hepatitis B, hepatitis C, and influenza, including Harvoni and Sovaldi.

Headquarter: Foster City, California, United States **Website:** www.gilead.com

Summary

Doctors in Washington State gave Remdesivir to the first coronavirus patient in the United States after his condition worsened and pneumonia developed when he'd been in the hospital for a week. His symptoms improved the next day.

Two clinical trials will take place in Wuhan, China, the center of the outbreak; 500 patients will receive the drug, and comparison groups will get a placebo.

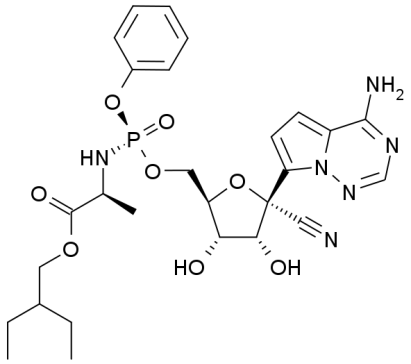
Remdesivir receives orphan drug designation by the FDA on March 24th.

Gilead Sciences

Clinical development[20,26,27]

- **Clinical usage:** Remdesivir has been recently recognized as a promising antiviral drug against a wide array of RNA virus infections (including SARS/MERS-CoV5) in cultured cells, mice, and nonhuman primate (NHP) models. It is currently under clinical development for the treatment of Ebola virus infection.

- **How does it work?**: Remdesivir is an adenosine analogue, which incorporates into nascent viral RNA chains and results in pre-mature termination. Remdesivir also inhibited virus infection efficiently in a human cell line, human liver cancer Huh-7 cells, which is sensitive to SARS-CoV-2.



Li Lanjuan Lab at Zhejiang University

About Li Lanjuan

Li Lanjuan is a Chinese epidemiologist, hepatologist, and professor at Zhejiang University School of Medicine. She is an academician of the Chinese Academy of Engineering and serves as the director of the State Key Laboratory for Diagnosis and Treatment of Infectious Diseases. She developed Li-NBAL, an artificial liver support system that is widely used to sustain the lives of people suffering from acute liver failure, and she won multiple national awards for her roles in combating the SARS, H1N1, and H7N9 epidemics.

Institute: First Affiliated Hospital of Zhejiang University **Field:** Epidemiology

Summary

The research team of Li Lanjuan, one of China's leading scientists in the fight against the novel coronavirus, announced a major breakthrough on Feb 4, China's Changjiang daily reported. Preliminary tests showed that two drugs - Abidol (Umifenovir) and Darunavir – can effectively inhibit the virus in vitro cell experiments, according to Li, who is also a professor at Zhejiang University[28].

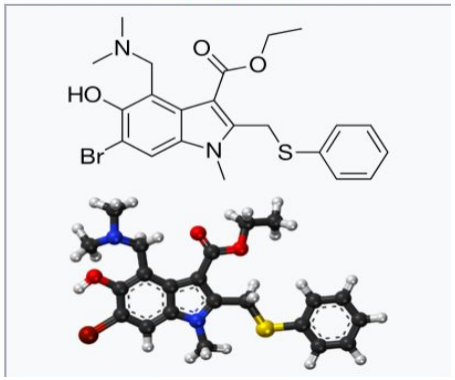
However, previewed articles about this finding haven't been published yet.

Li Lanjuan Lab at Zhejiang University

Abidol (Umifenovir)

Umifenovir is an antiviral treatment for influenza infection used in Russia and China. The drug is manufactured by **Pharmstandard.** Although some Russian studies have shown it to be effective, it is not approved for use in Western countries. It is not approved by the FDA for the treatment or prevention of influenza. Chemically, Umifenovir features an indole core, functionalized at all but one position with different substituents. The drug is claimed to inhibit viral entry into target cells and stimulate the immune response.

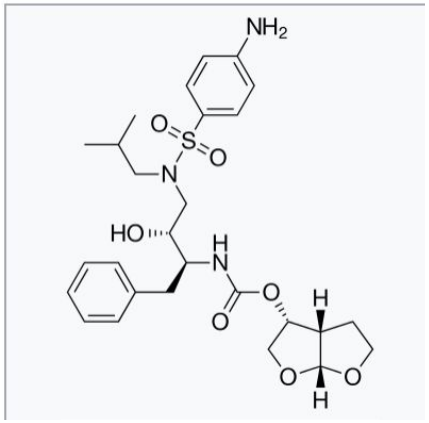
Umifenovir



Darunavir

Darunavir (DRV), sold under the brand name **Prezista** among others, is an antiretroviral medication used to treat and prevent HIV/AIDS. It is generally recommended for use with other antiretrovirals. It is often used with low doses of Ritonavir or Cobicistat to increase Darunavir levels. Darunavir was approved for medical use in the United States in 2006. It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system.

Darunavir



Potential therapies in development

Treatments in development

Country	Institute	Drug	Stage
US	AbbVie	Kaletra - Antiviral protease inhibitor	Clinical trial in China
US	AIM ImmunoTech	Ampligen - Immune modulator	Pursuing approval for trials in China
UK	Altimmune	Intranasal vaccine	Clinical test planned in August
Austria	APEIRON Biologics	APN01	Clinical trial in China
China	Ascletis Pharma	Ganovo - Antiviral protease inhibitor	Clinical trial in China
China	Bayer and numerous Chinese manufacturers	Chloroquine phosphate - Antiviral / Anti-inflammatory	Clinical trial in China
China	Beijing Staidson, Biopharma, and InflaRx	IFX-1 - mAB	Clinical trials approved by China
US	Biocryst	Galidesivir - RNA polymerase disruptor	Animal trials

Potential therapies in development

Treatments in development

Country	Institute	Drug	Stage
US	BioXyTran	BXT-25 - ARDS drug	Exploring partnering with international drug companies
US	Celularity and Sorrento Therapeutics	CYNK-001 - NK cell therapy	In contact with leading scientists and local Chinese experts for clinical trials
China	Chugai Pharmaceutical and Zhejiang Hisun Pharmaceutical	Tocilizumab - mAB	Clinical trials registered in China
Australia	CSL and the University of Queensland	Vaccine	Fundraising
Germany	CureVac	mRNA-based vaccine	Fundraising
US	CytoDyn	Leronlimab (PRO 140) - mAB	Clinical trials in China

Potential therapies in development

Treatments in development

Country	Institute	Drug	Stage
China	Fujifilm Holdings and Zhejiang Hisun Pharmaceutical	Favipiravir - RNA polymerase inhibitor	Clinical trials in China
Canada	Generex Biotechnology	Ii-Key peptide - Vaccine	Fundraising
US	Gilead Sciences	Remdesivir - Nucleotide prodrug	Clinical trials in China and US
China	GlaxoSmithKline and Clover Biopharmaceuticals	SARS-CoV-2 S-Trimer - Protein-based vaccine	Partnership
China	iBio and Beijing CC-Pharming	Plant-derived vaccine	Planning clinical tests
Canada	ImmunoPrecise Antibodies	Vaccines and coronavirus-neutralizing antibodies	Planning

Potential therapies in development

Treatments in development

Country	Institute	Drug	Stage
China	Incyte, Shanghai Hengrui Pharmaceutical	Camrelizumab and thymosin (mAB)	Clinical trials registered in China
US	Innovation Pharmaceuticals	Brilacidin - Novel antibiotic	Partnership agreement
China	Inovio Pharmaceuticals and Beijing Advaccine Biotechnology	INO-4800 - Vaccine	Clinical trials in China
UK	Janssen Pharmaceutical Cos. (Johnson & Johnson)	Prezcobix - Vaccine	Clinical trials in China
US and Italy	LineaRx (Applied DNA Sciences) and Takis Biotech	Linear DNA vaccine	Seeking commercial partners

Potential therapies in development

Treatments in development

Country	Institute	Drug	Stage
US	Moderna	mRNA-1273 - Vaccine	Clinical trials in the US
US	NanoViricides	Nanoparticle-based antiviral therapy	Preparing testing
US	Novavax	Vaccine	Planning for clinical test in May or June
US and Canada	Q Biomed and Mannin Research	Drug to treat vascular diseases in people with COVID-19	Fundraising
US	Regeneron Pharmaceuticals	REGN3048 and REGN 3051 - mAB	Partnership, clinical trials in the US

Potential therapies in development

Treatments in development

Country	Institute	Drug	Stage
France	Sanofi	Recombinant DNA vaccine	Partnership
US	Tonix Pharmaceuticals Holding	TNX-1800 - Vaccine	Partnership
US	Vaxart	Vaccine based on proprietary VAAST™ Platform	Planning on nonclinical tests
US and China	Vir Biotechnology and WuXi Biologics	mAB treatment	Apply for regulatory approvals to be commercialized

Actions to take

It is unlikely that new compounds in non-FDA approved drugs will become available before 2021. It is therefore more likely that companies will focus on FDA-approved drug candidates for some more immediate relief for the pandemic.

1. Standard Operating Procedures (SOPs) should be created for viral culturing and drug testing.
2. Antiviral libraries should be tested as quickly as possible. There are solid techniques to test higher-order interactions between drug combinations[29].
3. As many combinations and regimens as possible should be tested, with a focus on drugs that have worked against SARS-CoV (due to the high genomic similarity).
4. Drugs that have not been approved yet should be pushed into preclinical and clinical trials where possible.

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New opportunity: Artificial intelligence

Summary: Rapid drug discovery using computational methods

Using computational modeling and machine learning to learn how the virus works and how it can be neutralized

For the first time ever during a global outbreak, scientists are extensively using computational protein modeling and machine learning algorithms to identify viral protein targets and to predict which FDA-approved antiviral drug molecules can interact with SARS-CoV-2 proteins.

Major examples of computational and machine learning methods:

1. The binding receptors for SARS-CoV-2 were predicted first by computational modeling (Human ACE2)[1,2]
2. Machine learning algorithms were used to predict drug combinations based on *in silico* analysis[3,4]
3. Several FDA-approved antiviral drugs were predicted to bind to SARS-CoV-2 viral proteins[5,6]
4. Vaccine targets were predicted based on homology searches[6]

Machine learning approaches and the lessons we learn from using these now are universally applicable to any outbreak in the future. The more data is generated, the better the algorithms can be trained.

AI strategies

Prediction and diagnosis

- BlueDot early warning[7] on Dec. 31st
- Metabiota Track Epidemics[8]

Cure strategy development

- Alibaba and Baidu AI is accelerating vaccine and drug R&D[9]
- Insilico Medicine uses AI to identify molecules that could fight coronavirus[10]
- Benevolent AI used AI to search for existing approved drugs that might be helpful in limiting the virus's infection[11]
- Deargen used deep learning to find various available antiviral drugs that could be investigated as a potential treatment[11]

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Professional Summary:

João Guerreiro is one of PreScouter's Lead Scientists and Technical Directors. He helps clients design and define the projects and leads the PreScouter Scholar Team toward successful deliveries, ensuring PreScouter projects meet both clients' and scholars' expectations. He is also responsible for developing new initiatives and products as one of PreScouter's Lead R&D Scientist. Prior to joining PreScouter, João worked as a freelance life science consultant. As an academic, João performed research in the fields of stem cells, gene therapy, and tissue engineering at the Massachusetts Institute of Technology in the US, the University College, London, in the UK, and the University of Lisbon in Portugal. He holds a PhD in Bioengineering Systems and a Masters in Biological Engineering.

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Yaying earned his PhD in Materials Science and his MS in Electrical and Computer Engineering from Duke University. Before that, he earned a BS in Materials Physics from the University of Science and Technology, Beijing, in China. During Yaying's PhD tenure, he built expertise in nanomaterial synthesis, energy devices, advanced manufacturing, and telecommunications. At PreScouter, Yaying leads projects in the energy industry.

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Subject Matter Expert

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Maikel Boot is a Postdoctoral Fellow at the Rego Lab in the department of Microbial Pathogenesis at the Yale University School of Medicine. His research focuses on mapping the consequences of bacterial cell-to-cell variation of the causative agent of tuberculosis, *Mycobacterium tuberculosis*, on macrophage infection. He uses live-cell super-resolution microscopy (3D-SIM) to study long-term mycobacterial-macrophage infections. Maikel has been a part-time consultant at PreScouter for roughly two years and has worked on several projects as a research scholar or team leader. He enjoys puzzles, challenges and working together with other people to solve those. Besides his work at Yale, Maikel is a Fellow at Yale's Jonathan Edward College and current Chair of the Yale Postdoctoral Organization, leading a team of volunteers that organize 180+ events for 1250 Postdocs at Yale University. In his free time he enjoys listening to music and going to concerts.

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Professional Summary:

Luyao (Sunshine) Zhang is a tenure-tracked Assistant Professor in Business Management at East China Normal University in Shanghai, China. She has an abiding passion for interdisciplinary collaborations, especially related to Artificial Intelligence (Machine Learning), Fintech (Cryptocurrency and Blockchain), and Big Data (from all industries). She is also keenly interested in seeking creative solutions to challenging problems and transferring in-depth insights into practical impacts. She is a part-time consultant at PreScouter and works with industry pioneers on big-data paradigm shifts and digital transformations. She has dedicated herself to services with empathy, which she believes is one critical cornerstone of any civil society. She has served many local and international communities. She is the Ambassador for Startup Genome in Shanghai and was the Founding President for Dance Illumination, an NPO aiming at promoting diverse dance histories.

Subject Matter Expert

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Yiran Cao has a combined education background in chemistry and business. Her research is focused on physical chemistry and surface science. She utilizes cyclic voltammetry with the use of rotating disk electrode and OLEMS to enhance insight of the kinetic impact of bromide on the chloride oxidation reaction. Her prior experiences include different management functions in MNCs and high-growth startups/unicorns, as well as international relations between China and Europe. She's passionate about technology and interdisciplinary collaboration, especially in the sectors of artificial intelligence, healthcare, and sustainability, with extensive knowledge and understanding in innovative trends and digital ecosystem in China and abroad.

Subject Matter Expert

Sophie Ramas, PhD in Developmental Biology (Goethe University, Frankfurt am Main, DE)

Professional Summary:

Sophie Ramas is a postdoctoral researcher in the Pharmacology department of Pr. Dr. Offermanns at the Max Planck Institute for Heart and Lung Research (Bad Nauheim, Germany). Her work focuses on the biological function of receptors in pancreatic beta cell functions, by combining in vitro and in vivo models. Her former work on zebrafish cardiovascular development during her PhD enabled her to strengthen a strong knowledge in molecular and cellular biology and genetic engineering.

In addition to her lab work, she has recently joined the PreScouter program as a scholar researcher. Combining lab work and consulting projects fulfills her scientific career. She is passionate about Life Science, always trying to improve her work efficiency. Interdisciplinary collaborating work is, for her, critical to a successful project.

Sophie is the mother of two children and successfully manages to balance her work, her family life, and swimming thanks to her organizational skills and her ability to adapt to different work environments.

Next Steps

SOME POSSIBILITIES THAT PRESCOUTER CAN OFFER FOR CONTINUATION OF OUR RELATIONSHIP

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- ☑ TECHNOLOGY & PATENT LANDSCAPING
- ☑ MARKET RESEARCH & ANALYSIS
- ☑ TRENDS MAPPING
- ☑ REVIEW BEST PRACTICES
- ☑ PATENT COMMERCIALIZATION STRATEGY
- ☑ DATA ANALYSIS & RECOMMENDATIONS
- ☑ ACQUIRE NON-PUBLIC INFORMATION
- ☑ SUPPLIER OUTREACH & ANALYSIS
- ☑ CONSULT WITH INDUSTRY SUBJECT MATTER EXPERTS
- ☑ INTERVIEWING COMPANIES & EXPERTS

WE CAN ALSO DO THE FOLLOWING

- ✔ **CONFERENCE SUPPORT:** Attend conferences of interest on your behalf.
- ✔ **WRITING ARTICLES:** Write technical or more public facing articles on your behalf.
- ✔ **WORKING WITH A CONTRACT RESEARCH ORGANIZATION:** Engage with a CRO to build a prototype, test equipment or any other related research service.

For any requests, we welcome your additional questions and custom building a solution for you.

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