

DRUGBANK WHITE PAPER

# COVID-19: Finding the Right Fit

Identifying Potential Treatments  
Using a Data-Driven Approach

The effects of COVID-19 have reverberated across the globe since late 2019, and have resulted in an influx of new research and data being produced on potential novel candidates to treat the virus. There is a vast amount of research that uses data-driven approaches to identify potential therapies for the virus, and much of the research that has been done has used data from resources like DrugBank. This paper will give an overview of COVID-19, ongoing research, and how data-driven drug repurposing using data from DrugBank is giving life to high-potential investigative treatments for this worldwide outbreak.

## COVID-19 OUTBREAK SUMMARY

Coronavirus disease 2019 (named COVID-19 on February 11, 2020 by the World Health Organization (WHO) [3,6]) was first identified in Wuhan, China near the end of 2019 [3]. It is caused by the virus known as SARS-CoV-2 (previously called 2019-nCoV). This name was chosen because the virus is related to the coronavirus that caused the SARS outbreak of 2003. The two viruses are different despite their genetic similarity [2]. COVID-19 is believed to be less lethal but much more infectious than SARS-CoV [4]. Until the recent outbreak, this virus had not been identified in humans [8].

The first death from COVID-19 occurred in a 61 year old male who had purchased goods from a seafood market in Wuhan. Several other cases of the disease were diagnosed and traced back to the seafood market at the end of 2019 and beginning of 2020 [7,9].

On January 30, 2020, the WHO identified the spread of SARS-CoV-2 to be a *Public Health Emergency of International Concern*. By this time, the virus had spread to all 31 provinces in China, with about 7700 cases reported across China and a death toll of 170. The outbreak has rapidly progressed, spreading to 75 countries worldwide, with cases identified in Asia, Europe, North and South America, Australia, and Africa.

As of March 4, 2020, the total number of confirmed cases of COVID-19 has risen to 95,075 with 3,252 total deaths and 51,156 recovered cases [5]. These numbers are subject to change with ongoing infection and recovery from COVID-19.

**Influenza (i.e. the flu) is more infectious than SARS-CoV-2, but the reported mortality rate of COVID-19 is about 3.4%, which exceeds the standard 1% mortality rate of the flu [10].**

## CLARIFICATION:

**SARS-CoV-2, previously called 2019-nCoV, is the causative virus of coronavirus disease (COVID-19) [1]**

## ABBREVIATIONS

**ACE2:** Angiotensin Converting Enzyme 2

**β-CoV:** Betacoronavirus

**COVID-19:** Coronavirus Disease

**HIV:** Human Immunodeficiency Virus

**MERS:** Middle East Respiratory Syndrome

**MERS-CoV:** Middle East Respiratory Syndrome Coronavirus

**RNA:** Ribonucleic Acid

**SARS:** Severe Acute Respiratory Syndrome

**SARS-CoV:** Severe Acute Respiratory Syndrome Coronavirus

**SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus 2

**2019-nCoV:** 2019 Novel Coronavirus

About 80% of those infected with SARS-CoV-2 are expected to recover without hospitalization [4]. The risk of serious illness resulting from SARS-CoV-2 is increased in elderly patients with pre-existing conditions, such as heart failure and diabetes [4]. Because this virus has not been previously identified in humans, research into prevention and treatment of COVID-19 is underway [10].

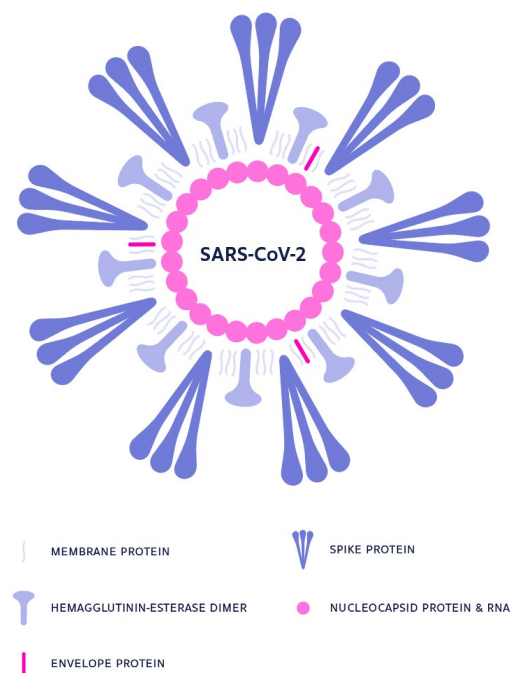
## WHAT IS SARS-COV-2?

SARS-CoV-2 is an enveloped RNA virus belonging to the genus betacoronavirus (β-CoV). Other notable members of this genus include SARS-CoV and MERS-CoV [11,12]. The spike (S) protein of SARS-CoV-2 forms a trimer which then attaches to angiotensin converting enzyme 2 (ACE2) in the epithelial cells of the lungs, kidney, and small intestine; endothelial cells of the veins and arteries; and arterial smooth muscle cells [12,13].

The virus is spread through respiratory droplets from coughs and sneezes within approximately 6 feet or 1.8 metres and also by viral particles resting on surfaces [16,17]. SARS-CoV-2 is not expected to be an airborne virus [17].

The average incubation period of COVID-19 is 5.2 days [14]. After incubation, patients generally present with pneumonia, fever, cough, myalgia, dyspnea, and fatigue [15]. Less commonly, they may develop headache, hemoptysis, and diarrhea [15]. During an infection, there is an increase in pro-inflammatory cytokines such as interleukin-2, interleukin-7, interleukin-10, granulocyte colony-stimulating factor, interferon  $\gamma$ -induced protein-10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1 $\alpha$ , and tumor necrosis factor- $\alpha$  which may promote disease severity [15].

Chinese researchers recently discovered that SARS-CoV-2 had diverged into 2 strains, L-type and S-type, though information surrounding this mutation is controversial in the literature. The L-type strain of the virus is not only more transmissible than the S-type, but also the more predominant of the two [18]. It accounts for about 70% of cases and may impact the development of vaccines and therapies for COVID-19 [18].



## How Researchers Use DrugBank To Find Antiviral Candidates

In exploring novel therapies for COVID-19 researchers are leveraging artificial intelligence to aid in the discovery of potential candidates. Many are working in the drug repurposing space, using data from DrugBank and other data sources to narrow their funnel of potential treatments.

Drug repurposing (also commonly referred to as drug repositioning) is a drug development strategy used to identify novel uses for existing approved and investigational drugs outside of their original indication. This strategy offers numerous advantages over traditional drug development pipelines. Unlike traditional drug development, which risks failure in preclinical or early-stage clinical trials due to safety concerns, the process of drug repurposing mitigates this risk by utilizing drugs that have demonstrated safety records from previous trials. Drug repurposing is also significantly more efficient and cost effective than traditional drug development since pre-clinical and early-stage clinical trials do not need to be repeated[19].

In the past, drug repurposing often occurred serendipitously due to observed off-target (or previously unknown on-target) effects. For example, sildenafil is a phosphodiesterase

inhibitor that helps dilate blood vessels which was originally investigated for use as a cardiac agent in the treatment of angina pectoris. Patients in clinical trials noted a significant incidence of unwanted erections, and in 1996 sildenafil was patented and marketed instead for the treatment of erectile dysfunction under its now familiar alias: Viagra [20,21].

With the advances in artificial intelligence and machine learning, drug repurposing has shifted from being something serendipitous to a technologically-focused data-driven practice enhanced by comprehensive drug and chemical databases, including DrugBank.

Using structured data from DrugBank, researchers looking to find novel therapies for COVID-19 can incorporate AI methods, such as deep learning, into their drug repurposing research. More specifically, they can incorporate input data like crystal structures, and homology models of proteins and co-crystallized ligand fragments in order to predict the structures of drugs that will act as targets to these proteins.

Machine learning models learn the latent representations of structures to generate structures of antiviral drugs. Insilico Medicine's generative chemistry platform provides a comprehensive set of AI tools for training machine learning models on protein structure data in order to generate relevant antiviral structures. Protein structure data can be represented in the form of sequences (string) representations, graph representations, or in 3D spaces. Natural language processing (NLP), graph embedding, and computer vision can be used to train models to learn protein structures based on these representations respectively.

By leveraging machine learning techniques, researchers looking for novel therapies can be confident that drug repurposing efforts will be significantly more efficient, reducing the time and cost burden on researchers. By combining AI/ML and DrugBank's structured data, researchers can quickly navigate potential novel candidates, use data-driven decision making to narrow their research, and more efficiently find effective treatments for viruses like SARS-CoV-2 [25].

There are a number of specific use cases and examples of current research in drug repurposing related to COVID-19 treatments. In all of the cases below, the research includes the use of DrugBank's data.

Nguyen, et al. author of Potentially highly potent drugs for 2019-nCoV, **developed a structural-based drug repositioning (SBDR) ML model to screen 1465 approved drugs from DrugBank.** They found that the 3CL protease was 96% similar between SARS-CoV and SARS-CoV-2, and with this knowledge constructed a 3D putative structure of the SARS-CoV-2 3CL protease to perform a drug-target binding assay using DrugBank's data [22].



Like Nguyen, et al., researcher, Long Chen, **determined eight credible open reading frames (ORFs) with high homology to SARS-CoV-2 by analyzing the coronavirus genome and calculating binding parameters using SeeSAR.** From there, they used DrugBank to screen against seven different drugs that were selected based on DrugBank's sequence search module [23].



Using SeeSAR along with drug information for 2525 FDA-approved drugs pulled from the DrugBank database, Arya, et al., conducted virtual *in silico* screening to **identify molecules with the ability to inhibit any SARS-CoV-2 proteins essential for the viral reproductive cycle** [24].



Another study looking at novel candidates for COVID-19, used **high-throughput computational screening of a library of 8,000 experimental and approved drugs and small molecules obtained from DrugBank** to identify four molecules with high binding capacity for SARS-CoV-2's main protease [25].



DrugBank's data was also used by Junmei Wang, and Hosseini and Amanlou, in two studies that conducted virtual screenings. Wang focused on **"two-step hierarchical virtual screenings to identify repurposing drugs targeting the [SARS-CoV-2] protease,"** and tested the SARS-CoV-2 crystal structure against a series of datasets including approved, investigational, and experimental drugs. Unlike Wang, Hosseini and Amanlou focused only on approved drugs, and conducted virtual screening on 1615 FDA-approved drugs pulled from DrugBank [26,27].



The final example of a research study using DrugBank's data is the Khan et al. study that **tested a library of 123 existing antivirals available on DrugBank against two potential SARS-CoV-2 target proteins** [28].



The examples above highlight the multitude of ways in which DrugBank's data is utilized to improve and optimize drug discovery and repurposing. Further, the cases illustrate how drug information datasets like DrugBank have been and continue to be an indispensable tool for these processes. Drug repurposing is one of the most efficient ways to effectively respond to urgent health threats like the SARS-CoV-2 outbreak - hence research into promising treatment candidates will likely continue to focus on this method.



## Promising Drug Treatments For COVID-19

Although there is no known cure for coronavirus, healthcare providers are attempting to repurpose antivirals approved to treat other viral infections such as influenza, HIV, and Ebola. Interestingly, oseltamivir (Tamiflu) has shown some promise in slowing down SARS-CoV-2 despite the fact that oseltamivir was designed to target enzymes specific to the influenza virus. Scientists are hopeful that an investigational drug with a broad antiviral spectrum called remdesivir (marketed by Gilead) will be effective against coronaviruses [34]. While it was tested against Zaire Ebolavirus with no success, remdesivir was effective in blocking the replication of various coronaviruses in *in vitro* studies and animal models [28]. Remdesivir is currently being studied in Phase III trials and has been used successfully in one US patient. Gilead is aiming to conduct a large-scale clinical study consisting of patients with COVID-19 residing in China and other countries [29]. Remdesivir is also being investigated in a U.S. clinical trial as a breakthrough experimental treatment for COVID-19.

A rapid advice guideline was developed in December 2019 to address the need for a structured approach to the management of SARS-CoV-2. Information from guidelines addressing the management of similar respiratory illnesses such as SARS and MERS, as well as guidelines from the World Health Organization and the National Health Commission of the People's Republic of China was used to create this guideline. At present time there is weak evidence for treatment with inhaled interferon- $\alpha$  and oral lopinavir/ritonavir (Kaletra). Kaletra is being explored as combination therapy with several other medications including ribavirin, which inhibits RNA synthesis; umifenovir, which inhibits membrane fusion; and certain reverse transcriptase inhibitors [36].

Given that SARS-CoV-2 is a single stranded RNA  $\beta$ -CoV, some scientists recommend focusing on treatments that will target enzymes and machinery directly involved in its replication. Although antiretrovirals (e.g. Kaletra) used to treat HIV have been used and are currently being investigated for the treatment of SARS-CoV-2, it should be noted that this particular virus does not rely on reverse transcriptase which is a key target for antiretrovirals [35].

Favipiravir, or favilavir, was the first antiviral approved by the National Medical Products Administration of China for the treatment of COVID-19 after it demonstrated efficacy and an acceptable tolerability profile in a clinical trial that consisted of 70 patients with the disease [33,41]. Although specific details regarding the clinical trial are not currently available, the antiviral is an accepted experimental treatment for COVID-19 in both Japan and China [30,31]. Marketing for the drug was approved in February 2020, and Zhejiang Hisun

Pharmaceutical Company has begun mass production of the drug in response to the SARS-CoV-2 outbreak [28,30].

Ritonavir is currently being investigated in clinical trials in combination with other drugs, including danoprevir, oseltamivir, umifenovir, and darunavir [31,32].

Chloroquine, an anti-malarial drug with anti-inflammatory properties, was authorized by China's National Health Commission for the treatment of pneumonia associated with COVID-19. It was effective against SARS-CoV-2 *in vitro* and showed moderate clinical efficacy in multiple clinical trials across China in patients with COVID-19 [31,32].

Other drugs currently being investigated in laboratory testing and clinical trials include darunavir (in combination with cobicistat), galidesvir, and pifrenidone [31,32].

## Vaccines Under Development For COVID-19

Like other communicable diseases, preventing COVID-19 is far more effective than delivering treatment after infection [36]. Since vaccines are a cornerstone of disease prevention, various pharmaceutical companies are actively collaborating to pioneer vaccines for the prevention of COVID-19. Moderna Therapeutics has developed mRNA-1273, a vaccine currently under investigation in Phase I clinical trials. Moderna is also partnering with the National Institutes of Health (NIH) on a study commencing this April to assess the safety of its novel vaccine.

INO-4800, an experimental vaccine being developed by Inovio Pharmaceuticals, is in the preclinical stages of investigation. Inovio is collaborating with Beijing Advaccine Biotechnology to launch trials shortly examining its effectiveness [34]. A third international company involved in the development of an experimental vaccine is CureVac. Headquartered in Germany, CureVac is working with The Coalition for Epidemic Preparedness Innovations to design a manufacturing technology for the rapid production of vaccines. GlaxoSmithKline and Clover Biopharmaceuticals, a company based in China, are working together to develop a viral protein based vaccine. It is expected to be studied in clinical trials following the current preclinical study phase [34].

Finally, Johnson & Johnson, Regeneron Pharmaceuticals, Sanofi, and Vir Biotechnology are also seeking to develop vaccines for the prevention of COVID-19 [33].

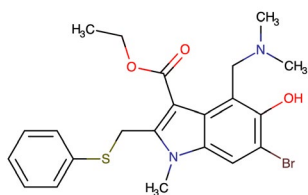
# Investigative Treatments

There are a number of high-potential investigative treatments for COVID-19 being explored. Below is an overview of the candidates being explored as treatments.

DB13609

## Umifenovir

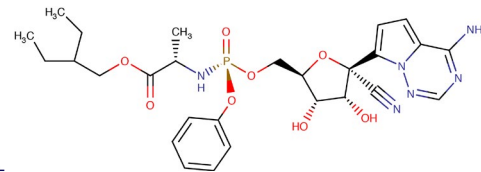
Umifenovir is an indole-based, hydrophobic, dual-acting direct antiviral/host-targeting agent used for the treatment and prophylaxis of influenza and other respiratory infections [49]. It has been in use in Russia for approximately 25 years and in China since 2006. Its invention is credited to a collaboration between Russian scientists from several research institutes 40-50 years ago, and reports of its chemical synthesis date back to 1993 [49]. Umifenovir's ability to exert antiviral effects through multiple pathways has resulted in considerable investigation into its use for a variety of enveloped and non-enveloped RNA and DNA viruses. This dual activity may also confer additional protection against viral resistance, as the development of resistance to umifenovir does not appear to be significant. Umifenovir is currently being investigated as a potential treatment and prophylactic agent for COVID-19 caused by SARS-CoV-2 infections in combination with both currently available and investigational antiviral therapies.



DB14761

## Remdesivir

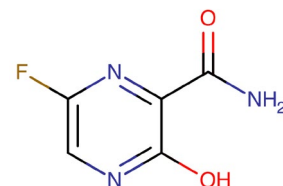
Remdesivir, or GS-5734, is an adenosine triphosphate analog first described in the literature in 2016 as a potential treatment for Ebola [39]. In 2017, its activity against the coronavirus family of viruses was also demonstrated [40]. Remdesivir is also being researched as a potential treatment for SARS-CoV-2, the coronavirus responsible for COVID-19 [40].



DB12466

## Favipiravir

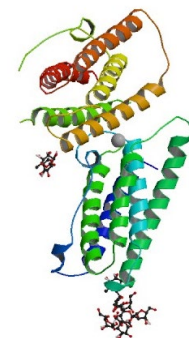
Favipiravir has been approved in Japan since March 2014 for the treatment of resistant cases of influenza, and has more recently gained traction in both Japan and China as an experimental treatment for SARS-CoV-2 [41]. In a clinical trial involving 70 patients, the antiviral demonstrated efficacy in treating SARS-CoV-2 and was well tolerated (more specific details regarding the clinical trial have not been released) [41,43]. Marketing for the drug was approved in February 2020, and Zhejiang Hisun Pharmaceutical Company has begun mass production of the drug in response to the SARS-CoV-2 outbreak [41,43].



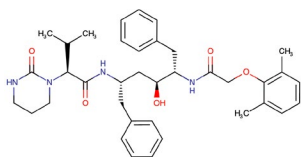
DB00068

## Interferon Beta

Interferon- $\beta$  is a cytokine disease-modifying agent initially approved to treat certain forms of Multiple Sclerosis (MS). Type 1  $\beta$ -interferons regulate the immune system, conferring protection against bacterial and viral replication. Interferon- $\beta$  was initially approved by the FDA in 1993. Some *in vitro* studies have determined that it can effectively clear other types of coronavirus, including SARS-CoV of 2003 and MERS-CoV of 2016 [44,45,46,47]. *In vivo* findings differ and report varying levels of success [46,50]. These findings may not translate to efficacy in the treatment of SARS-CoV-2 of 2019 in humans; however, genetic similarities between the viruses may be the basis for the development of future therapies. Human trials are not yet underway for treating SARS-CoV-2 with interferon- $\beta$ .

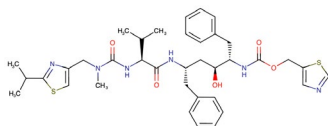


## DB01601 Lopinavir

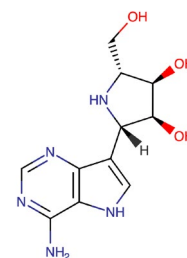


Lopinavir/ritonavir is a combination product marketed under the brand name Kaletra. It is an HIV-1 protease inhibitor that was first approved in the United States in 2000 for the treatment of HIV-1 infection, often in combination with other antiretrovirals. [36,53] Historically, low-level evidence has suggested that the combination provided benefit in the treatment of previous coronavirus outbreaks, such as SARS-CoV and MERS-CoV, and it may be particularly useful in the treatment of early SARS-CoV-2 infections [37].

## DB00503 Ritonavir

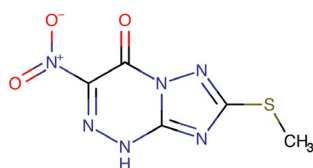


## DB11676 Galidesivir



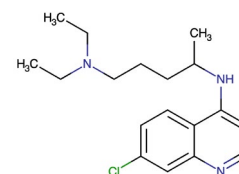
Galidesivir is an adenosine analogue that has been investigated for use against Zaire Ebolavirus [59]. *In vitro*, it displayed broad-spectrum antiviral activity against various negative- and positive-sense RNA viruses [60]. This drug has demonstrated antiviral action against other coronaviruses [33]. Phase 1 clinical trials have begun to determine the safety of this drug in humans [61]. Because of its activity against other coronaviruses, it may be studied as a potential therapy for COVID-19.

## DB15622 Triazavirin



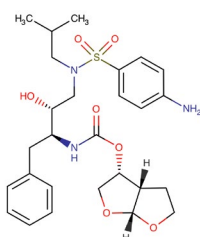
Triazavirin is an antiviral originally developed in Russia that has shown efficacy against influenza A and B, including the H5N1 strain [54,56]. It appears that triazavirin has shown promise in reducing influenza disease severity and associated complications [55]. Given the similarities between SARS-CoV-2 and H5N1, health officials are investigating triazavirin as an option to combat SARS-CoV-2 [56].

## DB00608 Chloroquine



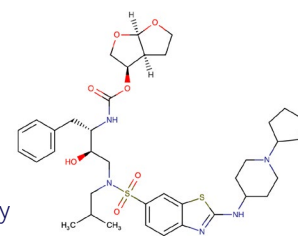
Chloroquine is currently undergoing clinical trials in China as a potential treatment for COVID-19 [59]. Chloroquine has been demonstrated to increase the pH of endosomes and inhibit glycosylation of ACE2, preventing viral entry into cells [58,59]. Studies *in vitro* have shown inhibition of infection at concentrations seen in patients taking chloroquine [58,59].

## DB01264 Darunavir



Darunavir is a protease inhibitor used with other HIV protease inhibitor drugs as well as ritonavir for the management of HIV-1 infection. As a second generation protease inhibitor, darunavir is designed to combat resistance to standard HIV therapy. It was initially approved by the FDA in 2006. Preliminary results from *in vitro* studies indicate that darunavir combined with umifenovir, an antiviral used to treat the flu in Russia and China, is effective in suppressing SARS-CoV-2 [49]. Another *in vitro* study also supports the use of darunavir in SARS-CoV-2 treatment [50]. Clinical trials in humans are underway that combine darunavir and cobicistat (a boosting agent), and are expected to conclude in August 2020 and determine the efficacy of this combination in clearing SARS-CoV-2 [52]. It is currently unclear whether the *in vitro* effects of darunavir combined with boosting agents will translate to clinical effects in humans [46], but clinical trials may provide further insight [35].

## DB15623 TMC-310911



TMC-310911 (also known as ASC-09) is a novel investigational protease inhibitor that is structurally similar to the currently available darunavir [62]. It has been investigated for use in HIV-1 infections. It may offer advantages over existing HIV therapies, such as a broader *in vitro* resistance profile as compared to other approved protease inhibitors [62].

# Staying up to date.

While this paper is not conclusive and research is ongoing, it provides evidence for the value of using data-driven approaches to find effective therapies for COVID-19. Ultimately, combining the power of artificial intelligence and machine learning tools with the structured data in Drugbank will allow researchers to more efficiently repurpose drugs for the treatment of this outbreak.

COVID-19 is still under investigation and there is no definitive solution to the outbreak at this time. The DrugBank database is updated regularly to reflect current research. Stay up to date regarding investigational treatments for COVID-19 by visiting [www.drugbank.ca](http://www.drugbank.ca).

## DISCLAIMERS:

1. This list of potential candidates is not exhaustive, and research in this area is constantly evolving.
2. This paper is not synonymous with medical advice. If you suspect you have COVID-19, please contact a medical professional.
3. Because of the COVID-19 outbreak, you should exercise frequent hand washing with soap and water, cover your mouth when you cough or sneeze, stay home if you feel ill, and avoid touching your face, eyes, and mouth.



## REFERENCES

- Rothan HA, Byrareddy SN: The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun.* 2020 Feb 26:102433. doi: 10.1016/j.jaut.2020.102433.
- World Health Organization (WHO). "Naming the coronavirus disease (covid-2019) and the virus that causes it." [https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-\(covid-2019\)-and-the-virus-that-causes-it](https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it). Accessed 2020 Mar 4.
- World Health Organization (WHO). "Rolling updates on Coronavirus disease (COVID-19)." <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen>. Accessed 2020 Mar 4.
- World Health Organization (WHO). "Q&A on coronaviruses (COVID-19)." <https://www.who.int/news-room/q-a-detail/q-a-coronaviruses>. Accessed 2020 Mar 4.
- Johns Hopkins. "Coronavirus COVID-2019 Global Cases." <https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9cfe>. Accessed 2020 Mar 4.
- CDC. "Coronavirus Disease 2019." <https://www.cdc.gov/coronavirus/2019-ncov/index.html>. Accessed 2020 Mar 4.
- European Center for Disease Control. "Event background: Covid-19." <https://www.ecdc.europa.eu/en/novel-coronavirus/event-background-2019>. Accessed 2020 Mar 4.
- European Center for Disease Control. "Covid-19." <https://www.ecdc.europa.eu/en/novel-coronavirus-china>. Accessed 2020 Mar 4.
- Al Jazeera. "China reports first death from mysterious outbreak in Wuhan." <https://www.aljazeera.com/news/2020/01/china-reports-death-mysterious-outbreak-wuhan-200111023325546.html>. Accessed 2020 Mar 4.
- World Health Organization (WHO). "WHO Director-General's opening remarks at the media briefing on COVID-19 - 3 March 2020." <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---3-march-2020>. Accessed 2020 Mar 4.
- Chan JF, Lau SK, To KK, Cheng VC, Woo PC, Yuen KY: Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. *Clin Microbiol Rev.* 2015 Apr;28(2):465-522. doi: 10.1128/CMR.00102-14.
- Salata C, Calistri A, Parolin C, Palu G: Coronaviruses: a paradigm of new emerging zoonotic diseases. *Pathog Dis.* 2019 Dec 1;77(9). pii: S1739327. doi: 10.1093/femspd/ftaa006.
- Chen Y, Guo Y, Pan Y, Zhao ZJ: Structure analysis of the receptor binding of 2019-nCoV. *Biochem Biophys Res Commun.* 2020 Feb 17. pii: S0006-291X(20)30339-9. doi: 10.1016/j.bbrc.2020.02.071.
- Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xiang X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Li M, Wu, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JTK, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z: Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med.* 2020 Jan 29. doi: 10.1056/NEJMoa2001316.
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020 Feb 15;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5. Epub 2020 Jan 24.
- CDC: How COVID-19 Spreads. 4 Mar. 2020. <https://www.cdc.gov/coronavirus/2019-ncov/about/transmission.html>. Accessed 4 Mar. 2020.
- WHO: Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). 24 Feb. 2020. <https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf>. Accessed 4 Mar. 2020.
- Tang X, Wu C, Li X, Song Y, Yao X, Wu X, Duan Y, Zhang H, Wang Y, Qian Z, Cui J, Lu J: On the origin and continuing evolution of SARS-CoV-2. *National Science Review.*
- Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, Doig A, Guilliams T, Latimer J, McNamee C, Norris A, Sanseau P, Cavalla D, Pirmohamed M: Drug repurposing: progress, challenges and recommendations. *Nat Rev Drug Discov.* 2019 Jan;18(1):41-58. doi: 10.1038/nrd.2018.168. Epub 2018 Oct 12.
- Ban TA: The role of serendipity in drug discovery. *Dialogues Clin Neurosci.* 2006;8(3):335-44.
- Goldstein I, Burnett AL, Rosen RC, Park WP, Stecher VJ: The Serendipitous Story of Sildenafil: An Unexpected Oral Therapy for Erectile Dysfunction. *Sex Med Rev.* 2019 Jan;7(1):115-128. doi: 10.1016/j.jsxmr.2018.06.005. Epub 2018 Oct 6.
- Nguyen D, Gao K, Chen J, Wang R, Wei G: Potentially highly potent drugs for 2019-nCoV. Preprint at <https://www.biorxiv.org/content/10.1101/2020.02.05.936013v1>. (2020). doi: <https://doi.org/10.1101/2020.02.05.936013>
- Chen L: Genomics functional analysis and drug screening of 2019 novel coronavirus in Wuhan, China. Preprint at <https://osf.io/kcuja/>. (2020). doi: 10.31219/osf.io/kcuja.
- Arya R, Das A, Prashar V, Kumar M: Potential inhibitors against papain-like protease of novel coronavirus (SARS-CoV-2) from FDA approved drugs. Preprint at [https://chemrxiv.org/articles/Potential\\_Inhibitors\\_Against\\_Papain-Like\\_Protease\\_of\\_Novel\\_Coronavirus\\_COVID-19\\_from\\_FDA\\_Approved\\_Drugs/11860011/2\\_02020](https://chemrxiv.org/articles/Potential_Inhibitors_Against_Papain-Like_Protease_of_Novel_Coronavirus_COVID-19_from_FDA_Approved_Drugs/11860011/2_02020).
- Zhavoronkov A, Aladinskiy V, Zhebrak A, Bogdan Z, Terentiev V, Bezrukov DS, Polykovskiy D, Shayakhmetov R, Filimonov A, Orekhov P, Yan Y, Popova O, Vanhaelen Q, Aliper A, Yvanenkov Y: Potential COVID-2019 3C-like Protease Inhibitors Designed Using Generative Deep Learning Approaches. Preprint from [https://chemrxiv.org/articles/Potential\\_2019-nCoV\\_3C-like\\_Protease\\_Inhibitors\\_Designed\\_Using\\_Generative\\_Deep\\_Learning\\_Approaches/11829102/2\\_02020](https://chemrxiv.org/articles/Potential_2019-nCoV_3C-like_Protease_Inhibitors_Designed_Using_Generative_Deep_Learning_Approaches/11829102/2_02020).
- Wang J: Fast Identification of Possible Drug Treatment of Coronavirus Disease-19 (COVID-19) Through Computational Drug Repurposing Study. Preprint from [https://chemrxiv.org/articles/Fast\\_Identification\\_of\\_Possible\\_Drug\\_Treatment\\_of\\_Coronavirus\\_Disease\\_19\\_COVID-19\\_Through\\_Computational\\_Drug\\_Repurposing\\_Study/11875446\\_02020](https://chemrxiv.org/articles/Fast_Identification_of_Possible_Drug_Treatment_of_Coronavirus_Disease_19_COVID-19_Through_Computational_Drug_Repurposing_Study/11875446_02020).
- Hosseini FS, Amanlou M: Simeprevir, Potential Candidate to Repurpose for Coronavirus Infection: Virtual Screening and Molecular Docking Study. Preprint at <https://www.preprints.org/manuscript/202002.0438/v1>. (2020). doi: 10.20944/preprints202002.0438.v1.
- Khan RJ, Jha RK, Amara GM, Jain M, Singh E, Pathak A, Singh RP, Muthukumarjan J, Singh AK: Targeting Novel Coronavirus 2019: A Systematic Drug Repurposing Approach to Identify Promising Inhibitors Against 3C-like Proteinase and 2'-O-Ribose Methyltransferase. Preprint at [https://chemrxiv.org/articles/Targeting\\_Novel\\_Coronavirus\\_2019\\_A\\_Systematic\\_Drug\\_Repurposing\\_Approach\\_to\\_Identify\\_Promising\\_Inhibitors\\_Against\\_3C-like\\_Proteinase\\_and\\_2-O-Ribose\\_Methyltransferase/11888730/1\\_02020](https://chemrxiv.org/articles/Targeting_Novel_Coronavirus_2019_A_Systematic_Drug_Repurposing_Approach_to_Identify_Promising_Inhibitors_Against_3C-like_Proteinase_and_2-O-Ribose_Methyltransferase/11888730/1_02020).
- Rees, Victoria. "Mechanism of action revealed for remdesivir, potential coronavirus drug." *Drug Target Review.* 3 March 2020. <https://www.drugtargetreview.com/news/56798/mechanism-of-action-revealed-for-remdesivir-potential-coronavirus-drug/>. Accessed 4 March 2020.
- Grady, Denis. "Gilead to Expand Coronavirus Drug Trials to Other Countries." *New York Times.* 26 February 2020. <https://www.nytimes.com/2020/02/26/health/coronavirus-gilead-drug-trials.html>. Accessed 4 March 2020.
- "Coronavirus Treatment Could Lie in Existing Drugs." *Genetic Engineering & Biotechnology News.* <https://www.genengnews.com/news/coronavirus-treatment-could-lie-in-existing-drugs/>. Accessed 4 March 2020.
- "How to Conquer Coronavirus: Top 35 Treatments in Development." *Genetic Engineering & Biotechnology News.* <https://www.genengnews.com/a-lists/how-to-conquer-coronavirus-top-35-treatments-in-development/>. Accessed 4 March 2020.
- Duddu, Praveen. "Coronavirus treatment: Vaccines/drugs in the pipeline for Covid-19." *Clinical Trials Arena.* 4 March 2020. <https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/>. Accessed 4 March 2020.
- Garde, Damian. "A detailed guide to the coronavirus drugs and vaccines in development." *Stat.* 2 March 2020. <https://www.statnews.com/2020/03/02/coronavirus-drugs-and-vaccines-in-development/>. Accessed 2020 Mar 4.
- Pappas, Stephanie. "Is there a cure for the new coronavirus?" *LiveScience.* 4 March 2020. <https://www.livescience.com/can-coronavirus-be-cured.html>. Accessed 2020 Mar 4.
- Harrison, Charlotte. "Coronavirus puts drug repurposing on the fast track." *Nature.* 27 February 2020. <https://www.nature.com/articles/d41587-020-00003-1>. Accessed 2020 Mar 4.
- Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, Fang C, Huang D, Huang LQ, Huang Q, Han Y, Hu B, Hu F, Li BH, Li YR, Liang K, Lin LK, Luo LS, Ma J, Ma LL, Peng ZY, Pan YB, Pan ZY, Ren XQ, Sun HM, Wang Y, Wang YY, Weng H, Wei CJ, Wu DF, Xia J, Xiong Y, Xu HB, Yao XM, Yuan YF, Ye TS, Zhang XC, Zhang YW, Zhang YG, Zhang HM, Zhao Y, Zhao MJ, Zi H, Zeng XT, Wang YY, Wang XH: A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res.* 2020 Feb 6;7(1):4. doi: 10.1186/s40779-020-0233-6.
- Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, Siegel D, Perron M, Bannister R, Hui HC, Larson N, Strickley R, Wells J, Stuthman KS, Van Tongeren SA, Garza NL, Donnelly G, Shurtleff AC, Rettner CJ, Gharaibeh D, Zamani R, Kenny T, Eaton BP, Grimes E, Welch LS, Gomba L, Wilhelmsen CL, Nichols DK, Nuss JE, Nagle ER, Kugelmann JR, Palacios G, Doerffler E, Neville S, Carrá E, Clarke MO, Zhang L, Lew W, Ross B, Wang Q, Chun K, Wolfe L, Babusis D, Park Y, Stray KM, Trancheva I, Feng JY, Barauskas O, Xu Y, Wong P, Braun MR, Flint M, McMullan LK, Chen SS, Fearnis R, Swaminathan S, Mayers DL, Spiropoulos CF, Lee WA, Nichol ST, Cihlar T, Bavari S: Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature.* 2016 Mar 17;531(7594):381-5. doi: 10.1038/nature17180. Epub 2016 Mar 2.
- Sheahan TP, Sims AC, Graham RL, Menachery VD, Galinski LE, Case JB, Leist SR, Pyrc K, Feng JY, Trancheva I, Bannister R, Park Y, Babusis D, Clarke MO, Mackman RL, Spahn JE, Palmiotti CA, Siegel D, Ray AS, Cihlar T, Jordan R, Denison MR, Baric RS: Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med.* 2017 Jun 28;9(396). pii: 9/396/eaal3653. doi: 10.1126/scitranslmed.aal3653.
- de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, Scott D, Cihlar T, Feldmann H: Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci U S A.* 2020 Feb 13. pii: 1922083117. doi: 10.1073/pnas.1922083117.
- Focus Taiwan. "Taiwan synthesizes anti-viral drug favilavir for COVID-19 patients." <https://focustaiwan.tw/scitech/202003020012>. Accessed 2020 Mar 4.
- Clinical Trials Arena. "Coronavirus treatment: Vaccines/drugs in the pipeline for Covid-19." <https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/>. Accessed 2020 Mar 4.
- Dunleavy, Brian P. "China approves antiviral favilavir to treat coronavirus." <https://www.upi.com/HealthNews/2020/02/17/China-approves-antiviral-favilavir-to-treat-coronavirus/5291581953892/>. Accessed 2020 Mar 4.
- McCarty MF, DiNicolantonio JJ: Nutraceuticals have potential for boosting the type 1 interferon response to RNA viruses including influenza and coronavirus. *Prog Cardiovasc Dis.* 2020 Feb 12. pii: S0033-0620(20)30037-2. doi: 10.1016/j.pcad.2020.02.007.
- Sahin AR, Erdogan A, Mutlu Agaoglu P, Dineri Y, Cakirci AY, Senel ME, et al. 2019 Novel Coronavirus (COVID-19) Outbreak: A Review of the Current Literature. *EJMO* 2020;4(1):1-7.
- World Health Organization (WHO). "Landscape analysis of therapeutics as of 17 February 2020." [https://www.who.int/blueprint/priority-diseases/key-action/Table\\_of\\_therapeutics\\_Appendix\\_17022020.pdf?ua=1](https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1). Accessed 2020 Mar 4.
- Hensley LE, Fritz LE, Jahrling PB, Karp CL, Huggins JW, Geisbert TW: Interferon-beta 1a and SARS coronavirus replication. *Emerg Infect Dis.* 2004;10(2):317-319. doi: 10.3201/eid1002\_030482
- Al Ghamdi M, Alghamdi KM, Ghandooria Y, Alzahrani A, Salah F, Alsulami A, Bawayan MF, Vaidya D, Perl TM, Sood G: Treatment outcomes for patients with Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV) infection at a coronavirus referral center in the Kingdom of Saudi Arabia. *BMC Infect Dis.* 2016 Apr 21;16:174. doi: 10.1186/s12879-016-1492-4.
- Blaising J, Polyak SJ, Pecheur EL: *Arbidol as a broad-spectrum antiviral: an update.* *Antiviral Res.* 2014 Jul;107:84-94. doi: 10.1016/j.antiviral.2014.04.006. Epub 2014 Apr 24
- Ng, Eric. "Coronavirus: are cocktail therapies for flu and HIV the magic cure? Bangkok and Hangzhou hospitals put combination remedies to the test. 2020 Feb 4." <https://www.scmp.com/business/companies/article/3048888/could-cocktail-therapies-hiv-and-flu-be-magic-cure-new>. Accessed 2020 Mar 4.
- Chang Y, Tung Y, Lee K, Chen T, Hsiao Y, Chang H, Hsieg T, Su C, Wang S, Yu J, Shih S, Lin Y, Lin Y, Tu YE, Tung C, Chen C: Potential Therapeutic Agents for COVID-19 Based on the Analysis of Protease and RNA Polymerase Docking. Preprint from <https://www.preprints.org/manuscript/202002.0242/v1>. (2020). doi: 10.20944/preprints202002.0242.v1.
- "Efficacy and Safety of Darunavir and Cobicistat for Treatment of Pneumonia Caused by 2019-nCoV (DACO-nCoV)." <https://www.clinicaltrials.gov/ct2/show/NCT04252274>. Accessed 2020 Mar 4.
- "FDA Approved Drug Products: Kaletra Oral Tablets." [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/021251s058,021906s053lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021251s058,021906s053lbl.pdf). Accessed 2020 Mar 4.
- Kiselev OI, Deeva EG, Mel'nikova TI, Kozeletskaia KN, Kiselev AS, Rusinov VL, Charushin VN, Chupakhin ON: [A new antiviral drug Triazavirin: results of phase II clinical trial]. *Vopr Virusol.* 2012 Nov-Dec;57(6):9-12.
- MacDonald, Bryan. "China tests Russian anti-viral drug which might treat coronavirus as Moscow warns of possible 'mass outbreak'." <https://www.rt.com/russia/480037-china-tests-russian-drug-coronavirus/>. Accessed 2020 Mar 4.
- Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, Seidah NG, Nichol ST: Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virology.* 2005 Aug 22;339:269-271. doi: 10.1016/S0042-6822-05-01047-9.
- Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G: Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020 Mar;30(3):269-271. doi: 10.1038/s41422-020-0282-0. Epub 2020 Feb 4.
- Gao J, Tian Z, Yang X: Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends.* 2020 Feb 19. doi: 10.5582/bst.2020.01047.
- Tchesnokov EP, Feng JY, Porter DP, Gotte M: Mechanism of Inhibition of Ebola Virus RNA-Dependent RNA Polymerase by Remdesivir. *Viruses.* 2019 Apr 4;11(4). pii: v11040326. doi: 10.3390/v11040326.
- Westover JB, Mathis A, Taylor R, Wandersee L, Bailey KW, Sefing EJ, Hickerson BT, Jung KH, Sheridan WP, Gowen BB: *Galidesivir limits Rift Valley fever virus infection and disease in Syrian golden hamsters.* *Antiviral Res.* 2018 Aug;156:38-45. doi: 10.1016/j.antiviral.2018.05.013. Epub 2018 Jun 1.
- "BioCryst Initiates Phase 1 Clinical Trial of Galidesivir. Press Release. 2019 Jan 27." <http://ir.biocryst.com/node/19526/pdf>. Accessed 2020 Mar 4.
- "TMC-310911." <https://aidsinfo.nih.gov/drugs/549/tmc-310911/0/professional>. Accessed 2020 Mar 4.