SARS-CoV-2 (previously 2019-nCoV or Wuhan coronavirus) caused an unprecedented fast-spreading worldwide pandemic. Although currently with a rather low mortality rate, the virus spread rapidly over the world using the modern world’s traffic highways. The coronavirus (CoV) family members were responsible for several deadly outbreaks and epidemics during the last decade. Not only governments but also the scientific community reacted promptly to the outbreak, and information is shared quickly. For example, the genetic fingerprint was shared, and the 3D structure of key proteins was rapidly solved, which can be used for the discovery of potential treatments. An overview is given on the current knowledge of the spread, disease course, and molecular biology of SARS-CoV-2. We discuss potential treatment developments in the context of recent outbreaks, drug repurposing, and development timelines.

SARS-CoV-2 OUTBREAK IN WUHAN

In December 2019, an outbreak of pneumonia of an unknown cause was reported in Wuhan, in Hubei province, China. It was speculated that the first patient caught the infection from a seafood market that also traded wild animals. The causing agent was quickly identified as a novel coronavirus (CoV). The CoV responsible for the outbreak is now called SARS-CoV-2. The respiratory illness caused by SARS-CoV-2 is called COVID-19. The symptoms of the SARS-CoV-2 infection range from asymptomatic to mild to severe to death. It soon became clear that person-to-person transmission was also occurring, as was the case with the previous human CoV. In an unprecedented documented speed, the SARS-CoV-2 travels around the globe, and as of May 15th led to >4.5 million infections and 300,000 fatalities. Based on the previous experience with the SARS-CoV outbreak at the beginning of this century, very stringent measures were taken by the Chinese government, and several multimillion-inhabitant cities were isolated and put under quarantine in order to slow the pandemic spread. Different hosts of the SARS-CoV-2 are proposed, including snails, bats, and pangolins.

CoVs are a large family of zoonotic viruses and their outbreaks are common to humans, although major outbreaks have been experienced in animals, especially in cattle. Under the electron microscope, they exhibit formations that are reminiscent of the solar corona. The common cold is often caused by human CoVs. They are single-stranded enveloped positive RNA viruses and stand out because of their rather large genome. As with viruses in general, the structure is rather simple. SARS-CoV-2 is generally less pathogenic than SARS-CoV, much less pathogenic than the Middle East respiratory syndrome MERS-CoV, but more pathogenic than practically harmless HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63. The reported case-fatality rate of COVID-19 is ≤3% and is thus rather low as compared with SARS (30%, Table 1). However, the transmission rate (TR) (number of newly infected people per infected person) of 2.5 to 3 is high and accounts

The Bigger Picture

Challenges and opportunities:

- The SARS-CoV-2 pandemic has changed our world in just half a year: a large number of people have died from the virus-induced pneumonia COVID-19, and the global economy is at an unprecedented low with unknown near- and long-term consequences.

- The coronavirus pandemic needs a two-pronged approach: a short-term solution to find a drug to treat the massive number of seriously ill patients, and long-term development of preventive and curative drugs for future coronavirus outbreaks.

- De novo drug discovery takes years to move from idea and/or pre-clinic to market release and is not a short-term solution for the current SARS-CoV-2 pandemic. Drug repurposing is perhaps the only short-term solution, and vaccination is a middle-term solution.
for the danger of the current pandemic. For comparison, the TR of the yearly common cold is less than 1.4.

Advice guidelines for diagnosis and treatment of SARS-CoV-2 infected pneumonia have been shared rapidly.3

What are the issues and chances for a rapid approval of a new medicine to treat COVID-19? In principle, there are several potential strategies to pharmacologically fight COVID-19: vaccines, monoclonal antibodies, oligonucleotide-based therapies, peptides, interferon therapies, small-molecule drugs, or natural medicines (e.g., traditional Chinese medicine [TCM]). The timelines for de novo development of a small-molecule drug are historically >6–7 years, and in the best case less than 2 years. Vaccines can be developed much faster, but rapid development in the range of 1–2 years is very challenging. Antibodies to support the body’s immune system are also a strategy to combat viral diseases. Again, the typical development timelines are several years. Therefore, is there a hope for a drug to come rapidly to the market? A strategy that is promising in the current situation is drug repurposing. Drug repurposing aims to discover novel indication areas for already approved drugs.4 The overwhelming advantage of drug repurposing is the potential for much faster market approval because of the already extensive knowledge of the drug’s behavior in humans.

An expert opinion on the potential for repurposing existing antiviral agents to treat COVID-19, some of which are already clinically evaluated, was recently given.5 Here, we discuss molecular targets of the SARS-CoV-2, some of the known small molecules, and the potential for repurposing existing drugs.

MOLECULAR BIOLOGY AND TARGETS

Despite the rather large size of the RNA virus genome of ~30,000 bases, the SARS-CoV-2 genome encodes for few proteins (Figure 1): the structural spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein, which are needed to produce a structurally complete viral particle. Additionally, the SARS-CoV-2 genome encodes 16–17 non-structural proteins (ns1 to ns17), such as 3-chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), helicase, and RNA-dependent RNA polymerase (RdRp).

3CLpro

Both the virus-encoded proteases 3CLpro and PLpro are involved in the processing of the two viral polyproteins in a coordinated manner, and thus comprise important drug targets. The structure, function, and inhibition of CoV 3CLpro (also called...
Mpro) has been recently comprehensively reviewed. The 3CLpro is a cysteine protease that cleaves and processes the viral polyproteins. SARS-CoV-2 and SARS-CoV share 96% sequence identity in their 3CLpro. On the basis of the rapidly published virus sequence data, a homology model was created. Moreover, an X-ray structure of the C3Lpro covalently bound to a peptidomimetic acrylester (1) is now available (Figure 2, PDB ID 6LU7).

Because of the high sequence similarity of different CoV 3CLpros, a lot of previously described inhibitors can be considered to be of great use in the current SARS-CoV-2. A majority of inhibitors of the 3CLpro are covalent in nature, binding to the active-site cysteine (Scheme 1). Different electrophilic warheads are known, including α-halocarbonyl, acrylamides, sulfanyl chlorides, aldehydes (2), isatines (3), or α-ketoheteraromates (4). Many of the molecules are rather large and are based on extensive amide chemistry, mimicking part of the peptide substrate of the protease. Moreover, their selectivity toward other potential targets in the human body has not been established.
Interestingly, some compounds binding to the active site of the 3CLpro—using a noncovalent mechanism—have been established. A high-throughput screening (HTS) identified pyrazolidinone (5), which displayed 1,3,5-triaryl substitution patterns, as SARS-CoV 3CLpro inhibitors.\textsuperscript{11} Nitroanilides (6), derived from the drug niclosamide were also found to inhibit 3CLpro.\textsuperscript{12} \(\alpha\)-aminoacylamides were identified by an HTS, and a strong stereochemical effect was noted. The simple one-pot accessible scaffold by an Ugi-four component condensation was the key to rapidly generate structure activity relationship (SAR) for the putative P2-P1 and P1 subgroups. An optimized version ML188 (7) was designated as the probe status (Figure 3). A P3 truncated version of 8 allowing for significant molecular weight (MW) reduction without diminishing potency was developed as a second probe ML300 (9) with potent enzyme inhibition and cellular activity. These compounds comprise rare examples of a noncovalent SARS-CoV 3CLpro inhibitor of moderate MW with good enzyme and antiviral inhibitory activity. However, these molecules suffer from extensive metabolism and rapid clearance. Nonetheless, they are a promising starting point for further drug development.\textsuperscript{13}

Even if such compounds cannot be rapidly developed to cope with the current situation, their development is highly warranted to be prepared for likely future CoV outbreaks. It is noteworthy that different computational approaches, including machine learning, have been published to propose approved drugs potentially binding to 3CLpro (drug repurposing).\textsuperscript{14,15} One such approach virtually screened commercial medicines in the DrugBank database for binding into the active site of Mpro.\textsuperscript{16} Ten different commercial medicines were proposed that might form hydrogen
In vitro DMPK and ancillary pharmacology:

**ML188**
- **SID 99350510, MW=433**
- 3CLpro IC$_{50}$ = 1.5 μM
- LE=0.25
- cLogP=4.6, LELP=18
- 
  | Compound | PPB Fu (h, r) | $C_{h_{app}}$ (h, r) | CYPs (μM) |
  |----------|--------------|----------------|-----------|
  | 7        | 3.3%, 2.6%   | 20.69 mL/min/kg | >30 (1A2), 9.1 (2C9), >30(2D6), 1.7 (3A4) |
  | racemic  |              |                | Eurofins Profiler Screen: |
  |          |              |                | No significant activity |
  | ML300    |              |                |                       |
  | SID 99289112, MW=431 | 3CLpro IC$_{50}$ = 4.11 ± 0.24 μM |
  | LE=0.24  | cLogP=3.2, LELP=13 |

**ML300**
- **SID 99289112, MW=431**
- 3CLpro IC$_{50}$ = 4.11 ± 0.24 μM
- LE=0.24
- cLogP=3.2, LELP=13
- 
  | PPB Fu (h, r): 4.8%, 10.6% |
  | $C_{h_{app}}$ (h, r): 20.67 mL/min/kg |
  | CYPs (μM): 7.7 (1A2), 7.2 (2C9), 8.4 (2D6), 4.6 (3A4) |
  | Eurofins Profiler Screen: |
  | Melatonin MT1 75% inhibition (10μM) |
bonds to key residues within the binding pocket of SARS-CoV-2 3CLpro, which might have higher mutation tolerance than lopinavir or ritonavir.

Flavonoids (10–14) are plant-derived natural products with diverse reported biological activities, and they have been shown to be also able to inhibit the 3CLpro (Figure 4).17,18 The broad-spectrum and established use of plant-based medicines to combat infectious diseases in TCM is the basis of several currently ongoing clinical trials in China. One of the largest among them assesses shuanghuanglian, a Chinese herbal medicine that contains extracts from the dried fruit lianqiao (Forsythiae fructus), which is purported to have been used for treating infections for more than 2,000 years.

Several approved HIV protease inhibitors (15, 16, and 18) were previously repurposed for the treatment of SARS (Scheme 2).19–21 They were hypothesized to inhibit the SARS-CoV 3CLpro: HIV protease is an Asp protease and differs considerably from the Cys protease 3CLpro, but it also shares some common elements, such as a tetrahedral transition state and receptor pockets to recognize the amino acid side chains of the substrates. Given that SARS-CoV-2 and SARS-CoV share very high identical sequence in their 3CLpro, these HIV protease inhibitors are currently again repurposed for the treatment of COVID-19 (Chinese Clinical Trial Registry: ChiCTR2000029539).22–24

PLpro
The coronaviral PLpro is another attractive antiviral drug target because it is essential for CoV replication. The structure, function, and inhibition of the SARS-CoV PLpro has been extensively reviewed.25 Although the primary function of PLpro and 3CLpro is to process the viral polyprotein in a coordinated manner, PLpro

Figure 3. Non-covalent Probes Binding to the Active Site of the 3CLpro
Above: co-crystal structure of probe ML188 bound to SARS-CoV (PDB: 3V3M). The homology and the 3D structural similarity of SARS-CoV (green graphic) and SARS-CoV-2 (pink graphic) 3CLpro are very high. Shown is a close up view into the ML188-binding site (cyan sticks). Shown on the bottom is synthesis and some molecular, drug metabolism and pharmacokinetic (DMPK), and pharmacology data of the probes ML188 and ML300.

Figure 4. Flavonoids Inhibiting 3CLPro as They Occur in Liang Quiao, the Seeds of the Forsythiae fructus Plant Used in the TCM Shuanghuanglian
has the additional function of stripping ubiquitin and ISG15 from host-cell proteins to help CoV to evade the host innate immune responses. Therefore, it was recently argued that targeting PLpro with antiviral drugs might have an advantage in not only inhibiting viral replication but also inhibiting the dysregulation of signaling cascades in infected cells that might lead to cell death in surrounding, uninfected cells. Different compounds forming a covalent bond to the active-site Cys112 have been described, including epoxyketones, α-halo-ketones, alkynes, aldehydes, trifluoromethyl ketones, α,β-unsaturated ketone, activated esters, or vinyl sulfones.

Disulfiram (19), an approved drug for the treatment of chronic alcohol dependence, has a great potential for drug repurposing because it has been shown to inhibit PLpro of MERS-CoV and SARS-CoV. The antimetabolites 6-mercaptopurine (20) and 6-thioguanine (21) are additional drugs inhibiting PLpro (Scheme 3).

Potent naphthyl methylamine hits (e.g., 22) which have been structurally characterized and have been subsequently optimized toward better metabolic stability were identified from an HTS campaign. The naphthyl methylamines work through a noncovalent mechanism and show a rather drug-like appearance (Figure 5).
Spike Glycoprotein

The envelope-anchored S protein mediates CoV entry into host cells by first binding to a host receptor and then fus ing viral and host membranes. The SARS-CoV-2 S protein was solved by cryoelectron microscopy and just released,\textsuperscript{30} knowing the Å-resolution structure of the SARS-CoV-2 spike will allow for additional protein engineering efforts that could improve antigenicity and protein expression for vaccine development. Moreover, the Å-resolution detail will enable the design and screening of small molecules with fusion-inhibiting potential.

It is the affinity between the viral receptor-binding domain (RBD) and the host receptor in the initial viral attachment step that primarily determines which host is susceptible to SARS-CoV infection. The SARS-CoV-2 entry through receptor binding was elucidated independently by several groups.\textsuperscript{31,32} On the basis of the rich knowledge about SARS-CoV and the sequence homology, it was suggested that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as its receptor (Figure 6). It uses the SARS-CoV receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells.\textsuperscript{31,32} The interplay of the ACE receptor in cardiovascular diseases (with the well-known drug class of ACE inhibitors) and as the docking point for SARS-CoV-2 cellular infection is a current point of intense debate and research.\textsuperscript{33}

It was found that several critical residues in SARS-CoV-2 RBM (particularly Gln493) provide favorable interactions with human ACE2, consistent with SARS-CoV-2’s capacity for human cell infection.
On the basis of the extensive modeling of the virus-human receptor interactions, it was also predicted that a single N501T mutation might significantly enhance the binding affinity between SARS-CoV-2 RBD and human ACE2 and thus potentially lead to much more virulent bodies.31,32 The emergency and evolution of novel mutations at the 501 position in SARS-CoV-2-infected and Covid-19 patients have to be closely monitored.34

Mutations in the S protein are the ones causing the zoonosis, and as a result, not all of them will lead to their binding to ACE2. Therefore, drugs targeting the
S protein-ACE2 interaction might not apply to some of the future CoVs. On the other hand, the spike-shaped protein on the surface of the viruses causing SARS, MERS, and COVID-19 provides a tantalizing target for antibodies or other compounds, which could prevent CoVs from invading human cells. The virus’ S protein seems to emerge as the consensus target antigen.

**RdRp**

The RdRp enzyme allows the viral genome to be transcribed into new RNA copies by using the host cell’s machinery. RdRp inhibitors are emerging as a new strategy to fight viral infections. RNA polymerase inhibitors are promising agents to fight Covid-19. RdRp proteins of SARS-CoV-2 and SARS-CoV share 96% sequence identity. Favipiravir (24) is an approved RNA polymerase inhibitor for the treatment of the influenza pandemic. It has been shown not only to be active in influenza but also active against other RNA viruses (Figure 7). Favipiravir is a prodrug, which is metabolized in cells into the active purine-mimicking nucleotide favipiravir-ribofuranosyl-5-triphosphate that inhibits the RNA replication and thus the viral progression. Interestingly, it does not inhibit host DNA and RNA synthesis and inosine 5'-monophosphate dehydrogenase (IMPDH) activity. Favipiravir reportedly demonstrated efficacy with minor side effects in an ongoing 70-patient clinical trial in Shenzhen, Guangdong province. The drug’s generic version received approval by the health authorities in China.

The broad-spectrum antiviral drug remdesivir together with chloroquine effectively inhibit the recently emerged novel CoV (SARS-CoV-2) in vitro. Remdesivir (25) reduced SARS-CoV-2 infection of monkey kidney cells with an EC50 of 0.77 μM. The compound is in late-stage clinical development and has been recently described to inhibit multiple RNA viruses on a cellular level, including Ebola and SARS. The presumed mode of action of the adenosine analog prodrug remdesivir is pre-mature RNA synthesis termination by incorporation into nascent viral RNA chains. Galidesivir (26) is another antiviral drug under clinical development with potential in COVID-19 treatment (Figure 7). It is an adenosine analog and is currently developed for Ebola virus disease and Marburg virus disease. It also shows broad-spectrum antiviral activity against RNA virus families including CoVs.
Multiple other RdRp inhibitors are described in the literature, for example, broad-spectrum antiviral 6'-bis fluorinated aristeromycin analog (27).44 Chloroquine (28) is an existing anti-malaria medicine also used to treat several other diseases. It blocked virus infection with an EC₅₀ of 1.13 μM.40,41 Its mode of action is unclear. However, chloroquine inhibits endosomal acidification and thus could stop the release of viral DNA into the cytoplasm. It is under assessment in more than 100 patients at over ten hospitals in Beijing and Guangdong province. Plans for an additional study in Hunan province are underway.

**Other Viral Proteins**
The role of the other SARS-CoV-2 N proteins as drug-discovery targets is less clear. For the assembly of the replication and/or transcription complexes, there is a vast interaction network described between the non-structural proteins. Similarly, viral particle assembly requires orchestrated interaction between N, S, M, and E proteins. All these interactions can be potential targets, but the structural information is currently minimal. Resolution of the protein and complex structures will provide new unique drug targets. For example, the crystal structure of SARS-CoV-2 N protein RNA-binding domain was just published and will give structural insight as a potential drug target.45 It is rapidly detected by antibodies in serum, plasma, and peripheral blood, and might therefore serve to develop specific diagnostics.

**Host Targets**
Using methods of machine learning-enabled scientific literature analysis, the biotech company BenevolentAI proposed the AP2-associated protein kinase 1 (AAK1) as a host target to fight SARS-CoV-2. AAK1 is the key enzyme of receptor-mediated endocytosis, which is the major mechanism of most viruses to enter their host cells.
Thus, they predict the approved (for rheumatoid arthritis) kinase inhibitor baricitinib to reduce the ability of the virus to infect lung cells (Figure 8).

OUTLOOK

The recent emergence of the Wuhan CoV (SARS-CoV-2) has put the world on alert. The rapid worldwide spread and the high human-to-human transmissibility, combined with the inability to contain the pandemic, is causing an increasing death toll and also considerable paralysis of the world economy. The COVID-19 could decrease and disappear or could be established worldwide in the human population and reoccur seasonally in future mutations through zoonosis from one of the animal reservoirs. However, it is very likely that in the upcoming years, we will see more outbreaks from CoV and other viruses. The basic, translational, and public health research communities have to prepare for this much better. The outbreak has emphasized the urgent need for renewed efforts to develop broad-spectrum antiviral agents to combat CoVs. On the positive side, much new information of the virus biology and the spread was immediately shared, whereas, on the negative side, many past opportunities to develop antivirals against CoVs were not taken, despite a large number of promising approaches and compounds. The past decade has shown that CoV outbreaks are regularly reoccurring with more or less health effect on human and livestock. It remains to be hoped that the current pandemic will slow down and end as predicted in summer. Furthermore, it turns out that containment measures are not effective to avoid more severe spread. It remains to be seen whether efficient and long-lasting immunity will develop in the infected population with regard to future outbreaks and whether pharmacological measures can be rapidly developed to be able to treat severely sick people.

ACKNOWLEDGMENTS

Research in the Dömling laboratory is sponsored through ITN “Accelerated Early stage drug discovery” (AEGIS, grant agreement 675555), the National Institute of Health (NIH) (2R01GM097082-05), the European Lead Factory (IMI) (grant agreement 115489), the Qatar National Research Foundation (NPRP6-065-3-012), Co-funds Alert (grant agreement 665250), Prominent (grant agreement 754425), and KWF Kankerbestrijding grant (grant agreement 10504). L.G. is grateful for a CSC stipend. Both authors are grateful to Micky Tortorella (GBH) for helpful discussions.

AUTHOR CONTRIBUTIONS

A.D. and L.G. wrote the manuscript.

REFERENCES

1. Lai, C.C., Shih, T.P., Ko, W.C., Tang, H.J., and Hsueh, P.R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Int. J. Antimicrob. Agents 55, 105924.

2. Liu, P., Chen, W., and Chen, J.P. (2019). Viral metagenomics revealed Sendai virus and coronavirus infection of Malayan pangolins (Manis javanica). Viruses 11, 979.

3. Jin, Y.H., Cai, L., Cheng, Z.S., Cheng, H., Deng, T., Fan, Y.P., Fang, C., Huang, D., Huang, L.Q., Huang, Q., et al. (2020). A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil. Med. Res. 7, 4.

4. Pushpakom, S., Iorio, F., Eyers, P.A., Escott, K.J., Hopper, S., Wells, A., Doig, A., Guilhamm, T., Latimer, J., McNamee, C., et al. (2019). Drug repurposing: progress, challenges and recommendations. Nat. Rev. Drug Discov. 18, 41–58.

5. Li, G., and De Clercq, E. (2020). Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat. Rev. Drug Discov. 19, 149–150.

6. Pillaiyur, T., Manickam, M., Namasiyam, Y., Hayashi, Y., and Jung, S.H. (2016). An overview of severe acute respiratory syndrome–coronavirus (SARS-CoV) 3CL protease inhibitors: peptidomimetics and small molecule chemotherapy. J. Med. Chem. 59, 6595–6628.

7. Martin, S. (2020). Homology models of Wuhan coronavirus 3CLpro protease. ChemRxiv. https://doi.org/10.26434/chemrxiv.11637294.v1.

8. Jin, Z., Du, X., Xu, Y., Deng, Y., Liu, M., Zhao, Y., Zhang, B., Li, X., Zhang, L., Peng, C., et al. (2020). Structure of M^{\text{pro}} from COVID-19 virus and discovery of its inhibitors. Nature. https://doi.org/10.1038/s41586-020-2223-y.

9. Yang, S., Chen, S.J., Hsu, M.F., Wu, J.D., Tseng, C.T.K., Liu, Y.F., Chen, H.C., Kuo, C.W., Wu, C.S., Chang, L.W., et al. (2006). Synthesis,
crystal structure, structure–activity relationships, and antiviral activity of a potent SARS coronavirus 3CL protease inhibitor. J. Med. Chem. 49, 4971–4980.

10. Chen, L.R., Wang, Y.C., Lin, Y.W., Chou, S.Y., Chen, S.F., Liu, L.T., Wu, Y.T., Kuo, C.J., Chen, T.S., and Juang, S.H. (2005). Synthesis and evaluation of sunitinib derivatives as effective SARS coronavirus 3CL protease inhibitors. Bioorg. Med. Chem. Lett. 15, 3058–3062.

11. Ramajayam, R., Tan, K.P., Liu, H.G., and Liang, P.H. (2010). Synthesis and evaluation of pyrazolone compounds as SARS-coronavirus 3C-like protease inhibitors. Bioorg. Med. Chem. 18, 7849–7856.

12. Shie, J.J., Fang, J.M., Kuo, C.J., Kuo, T.H., Liang, P.H., Huang, H.J., Yang, W.B., Lin, C.H., Chen, J.L., Wu, Y.T., and Wong, C.H. (2009). Discovery of potent anilide inhibitors against the severe acute respiratory syndrome 3CL protease. J. Med. Chem. 48, 4469–4473.

13. Jacobs, J., Grun-Tokars, Y., Zhou, Y., Tawfik, D.S., Mallalane, S.A., Chase, P., et al. (2013). Discovery, synthesis, and structure-based optimization of a series of N-(tert-butyl)-2-(N-arylamido)-2-pyrimidin-3-y1 acetamides (ML188) as potent noncovalent small molecule inhibitors of the severe acute respiratory syndrome coronavirus (SARS-CoV) 3CL protease. J. Med. Chem. 56, 534–546.

14. Berry, M., Fielding, B.C., and Gamieldien, J. (2015). Potential broad spectrum inhibitors of the coronavirus 3CLpro: A virtual screening and structure-based drug design study. Viruses 7, e6642–6660.

15. Moreno, A.J., Romero, A.R., Neocortosis, C., Groves, M., Velaquez, M.V., and Domling, A. (2020). Glititin repurposing for COVID-19. ChemRxiv. https://doi.org/10.26434/chemrxiv.12110760.v1.

16. Liu, X., and Wang, X.J. (2020). Potential inhibitors for 2019-nCoV coronavirus M protease from clinically approved medicines. bioRxiv. 2020.01.29.924100.

17. Jo, S., Kim, H., Kim, S., Shin, D.H., and Kim, M.S. (2019). Characteristics of flavonoids as potent MERS-CoV 3CL-like protease inhibitors. Chem. Biol. Drug Des. 94, 2023–2030.

18. Jo, S., Kim, S., Shin, D.H., and Kim, M.S. (2020). Inhibition of SARS-CoV 3CL protease by flavonoids. J. Enzyme Inhib. Med. Chem. 35, 145–151.

19. Chu, C.M., Cheng, V.C., Hung, I.F., Wong, M.M., Chan, K.H., Chan, K.S., Kao, R.Y., Poon, L.L., Wong, C.L., Guan, Y., et al. (2004). Role of lopinavir/ritonavir in the treatment of SARS. initial virological and clinical findings. Thorax 59, 252–256.

20. Chan, K.S., Lai, S.T., Chu, C.M., Tsui, E., Tam, C.Y., Wong, M.M., Tse, M.W., Que, T.L., Pairs, J.S., Sung, J., et al. (2003). Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med J. 9, 399–406.

21. Stockman, L.J., Bellamy, R., and Garner, P. (2004). SARS: systematic review of treatment effects. PLoS Med. 3, e435.

22. Lin, S., Shen, R., He, J., Li, X., and Guo, X. (2020). Molecular modeling evaluation of the binding effect of ritonavir, lopinavir and Darunavir to severe acute respiratory syndrome coronavirus 2 proteases. bioRxiv. https://doi.org/10.1101/2020.03.11.929695.

23. Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., et al. (2020). A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N. Engl. J. Med. 382, 1787–1799.

24. Rabi, F.A., Al Zoubi, M.S., Kasasbeh, G.A., Salameh, D.M., and Al-Nasser, A.D. (2020). SARS-CoV-2 and coronavirus disease 2019: what we know so far. Pathogens 9, 231.

25. Báez-Santos, Y.M., St John, S.E., and Mesecar, A.D. (2015). The SARS-coronavirus papain-like protease: structure, function and inhibition by designed antiviral compounds. Antiviral Res. 115, 21–38.

26. Lin, M.H., Moses, D.C., Hsieh, C.H., Cheng, S.C., Chen, Y.H., Sun, C.Y., and Chou, C.Y. (2018). Disulfiram can inhibit MERS and SARS coronavirus papain-like proteases via different modes. Antiviral Res. 150, 155–163.

27. Ratia, K., Pegan, S., Takayama, J., Sleeman, K., Couglin, S., Baliji, S., Chaudhuri, R., Wu, P., Prabakhar, B.S., Johnson, M.E., et al. (2008). A noncovalent class of papain-like protease–deubiquitination inhibitors blocks SARS virus replication. Proc. Natl. Acad. Sci. U.S.A. 105, 16119–16124.

28. Báez-Santos, Y.M., Barraza, S.J., Wilson, M.W., Agus, M.P., Mielech, A.M., Davis, N.M., Baker, S.C., Larsen, S.D., and Mesecar, A.D. (2014). X-ray structural and biological evaluation of a series of potent and highly selective inhibitors of human coronavirus papain-like proteases. J. Med. Chem. 57, 2393–2412.

29. Ghosh, A.K., Takayama, J., Rao, K.V., Ratia, K., Chaudhuri, R., Mulhearn, D.C., Lee, H., Nicholls, D.B., Balij, S., Baker, S.C., et al. (2010). Severe acute respiratory syndrome coronavirus papain-like protease inhibitors: design, synthesis, protein-ligand X-ray structure and biological evaluation. J. Med. Chem. 53, 4968–4979.

30. Wrapp, D., Wang, N., Corbett, K.S., Goldsmith, J.A., Hsieh, C.-L., Abiona, O., Graham, B.S., and McLellan, J.S. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 367, 1260–1263.

31. Hoffmann, M., Klein-Weber, H., Krüger, N., Müller, M., Drosten, C., and Pühlmann, S. (2020). The novel coronavirus 2019-nCoV uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. bioRxiv. https://doi.org/10.1101/2020.01.31.929042.

32. Wan, Y., Shang, J., Graham, R., Baric, R.S., and Li, P. (2021). Receptor utilization by the novel coronavirus from Wuhan: an analysis based on decacle-long structural studies of SARS Coronavirus. J. Virol. 94, e00127–20.

33. Zheng, Y.Y., Ma, Y.T., Zhang, J.Y., and Xie, X. (2020). COVID-19 and the cardiovascular system. Nat. Rev. Cardiol. 17, 259–260.

34. Grubauha, N.D., Petrone, M.E., and Holmes. (2020). Nucleosides for the treatment of respiratory RNA virus infections. Antivir. Chem. Chemother. 26, 2040206618764483.

35. Jordan, P.C., Stevens, S.K., and Deval, J. (2018). Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet 395, e30–e31.

36. Zumla, A., Chan, J.F., Azhar, E.I., and Yuen, K.Y. (2016). Coronaviruses — drug development and therapeutic options. Nat. Rev. Drug Discov. 15, 327–347.