

1 **Updated approaches against SARS-CoV-2**

2 Haiou Li<sup>1,2</sup>, Yunjiao Zhou<sup>1,2</sup>, Meng Zhang<sup>1,2</sup>, Haizhou Wang<sup>1,2</sup>, Qiu Zhao<sup>1,2</sup>, Jing  
3 Liu<sup>1,2#</sup>

4 1. Department of Gastroenterology, Zhongnan Hospital of Wuhan University, Wuhan

5 430071, China

6 2. Hubei Clinical Center & Key Lab of Intestinal & Colorectal Diseases, Wuhan

7 430071, China

8 #Correspondence to:

9 Jing Liu, M.D., Ph.D.

10 Department of Gastroenterology, Zhongnan Hospital of Wuhan University, No. 169,

11 Donghu Road, Wuchang District, Wuhan 430071, Hubei Province, China.

12 Email: [liujing\\_GI@whu.edu.cn](mailto:liujing_GI@whu.edu.cn)

13 **ORCID :** Jing Liu <https://orcid.org/0000-0003-3467-9392>

14

15

16 **Abstract**

17 The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)  
18 lies behind the ongoing outbreak of coronavirus disease 2019 (COVID-19). There is a  
19 growing understanding of SARS-CoV-2 in the virology, epidemiology and clinical  
20 management strategies. However, no anti-SARS-CoV-2 drug or vaccine has been  
21 officially approved due to the absence of adequate evidence. Scientists are racing  
22 towards the development of treatment for COVID-19. Recent studies have revealed  
23 many attractive therapeutic options, even if some of them remain to be further confirmed  
24 in rigorous preclinical models and clinical trials. In this minireview, we aim to  
25 summarize the updated potential approaches against SARS-CoV-2. We emphasize  
26 that further efforts are warranted to develop the safest and most effective approach.

27

28 **Keywords:** SARS-CoV-2; COVID-19; treatment; anti-viral drugs; vaccines

29

30 **1. Introduction**

31 Since December 2019, coronavirus disease 2019 (COVID-19) has been spreading  
32 around the world with over 130,000 confirmed cases (as time of March 13, 2020) (1,  
33 2). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel  
34 betacoronavirus, is the causative agent of this global health threat (3). Like other  
35 coronavirus, SARS-CoV-2 is characterized by a spherical morphology with spike  
36 projections on the surface. It was demonstrated that SARS-CoV-2 shared high  
37 sequence identity with that of SARS-CoV and bat SARS-like coronavirus (SL-CoV)  
38 (4). Notably, SARS-CoV-2 has lower pathogenicity but higher transmissibility from  
39 human to human compared with SARS-CoV (5). Cell entry is the first step of  
40 cross-species transmission. SARS-CoV-2 is more likely to infect lung type II alveolar  
41 cells, which may explain the severe alveolar damage after infection (6).

42 The rapid spread of COVID-19 raises an urgently requirement for effective  
43 therapeutic strategies against SARS-CoV-2. Initially, without licensed vaccines or  
44 approved anti-viral drugs, COVID-19 treatment was mainly based on the experience  
45 of clinicians. The newest guideline published by National Health Commission (NHC)

46 recommends IFN- $\alpha$ , lopinavir/ritonavir, ribavirin, chloroquine phosphate and arbidol  
47 as anti-viral therapy (7). To date, many potential approaches have been revealed  
48 based on the research progress of SARS-CoV-2, including the inhibition of  
49 SARS-CoV-2 fusion/entry, disruption of SARS-CoV-2 replication, suppression of  
50 excessive inflammatory response, convalescent plasma treatment, vaccines as well as  
51 the combination of Traditional Chinese and Western medicine (as summarized in  
52 figure 1). Additionally, a number of clinical trials are in progress to test the safety and  
53 effectiveness of candidate drugs. In this review, we summarize the current knowledge  
54 on the potential treatment against SARS-CoV-2 based on the emerging basic and  
55 clinical data.

56

## 57 **2. Updated attractive approaches against SARS-CoV-2**

### 58 **2.1 Inhibition of SARS-CoV-2 fusion/entry**

59 Similar to SARS-CoV, SARS-CoV-2 uses spike (S) protein to gain entry into host  
60 cells (8). It was shown that the spike (S) protein on the surface of SARS-CoV-2 cell  
61 bound the entry receptor angiotensin-converting enzyme 2 (ACE2) on infected cells

62 (9). SARS-CoV-2 was predicted to recognize human ACE2 more efficiently than  
63 SARS-CoV (10). Thus, targeting the interactions between ACE2 and S protein may  
64 be a potential approach. Specifically, receptor binding domain (RBD) within the S  
65 protein is the critical target for neutralizing antibodies. Since SARS-CoV-2 S protein  
66 displayed high homology toward that of SARS-CoV, the available neutralizing  
67 antibody of SARS-CoV CR3022 was found to bind potently with SARS-CoV-2 RBD  
68 (4). Nevertheless, Zheng et al. recently reported that more than 85% of the RBD  
69 antibody epitopes in SARS-CoV-2 implied remarkable alterations when compared  
70 with SARS-CoV, indicating the necessity to develop new monoclonal antibodies for  
71 SARS-CoV-2 (11). In addition, the rationale for ACE2 receptor as a specific target  
72 has been reviewed elsewhere (12, 13). Notably, an open label, randomized, controlled,  
73 pilot clinical trial is in progress, further investigating the effect of recombinant human  
74 ACE2 (rhACE2; GSK2586881) in patients with severe COVID-19 (NCT04287686).  
75 It was suggested that S protein-derived cell entry depended on not only ACE2 but  
76 also the host cellular serine protease TMPRSS2 (14). Camostat mesylate, a clinically  
77 proven inhibitor of TMPRSS2, significantly reduced lung cell line infection with

78 SARS-CoV-2 and could be considered for COVID-19 treatment (14). In addition, the  
79 heptad repeat 1 (HR1) and heptad repeat 2 (HR2) on SARS-CoV-2 involved viral and  
80 cell membrane fusion (15). Xia et al. reported that HR2-derived peptides (HR2P) and  
81 EK1 (a modified OC43-HR2P peptide) exhibited effective fusion inhibitory activity  
82 towards SARS-CoV-2, which would act as fusion/entry inhibitors to treat  
83 SARS-CoV-2 infection. Further studies are warranted to substantiate these concepts.

84 Moreover, it was suggested that coronavirus entry also involved pH- and  
85 receptor-dependent endocytosis (16, 17). Targeting endocytosis may be another  
86 option for fighting SARS-CoV-2. AP-2-associated protein kinase 1 (AAK1) is a host  
87 kinase that regulates clathrin-mediated endocytosis (18). A group of approved drugs  
88 targeting AAK1 were searched out based on artificial intelligence (AI) technology  
89 (19). Among them, the janus kinase inhibitor baricitinib, an AAK1-binding drug, was  
90 supposed as a suitable candidate drug for COVID-19 because the standard treatment  
91 doses of baricitinib was sufficient to inhibit AAK1 (19).

92 Arbidol and chloroquine phosphate have been added into the NHC guideline of  
93 COVID-19 treatment (7). Arbidol was shown to inhibit multiple enveloped viruses by

94 inhibiting virus entry/fusion of viral membranes with cellular membranes (20).  
95 Chloroquine, a traditional antimalarial drug, was shown to be effective against  
96 SRAS-CoV-2 infection in vitro (21). Several clinical trials are in progress to test the  
97 efficacy and safety of chloroquine phosphate against COVID-19 (22). More than 100  
98 patients provided the first evidence that chloroquine phosphate was more effective in  
99 inhibiting the exacerbation of pneumonia compared with control treatment (22).  
100 Additionally, Yao et al. found that hydroxychloroquine ( $EC_{50}=0.72 \mu\text{M}$ ) was more  
101 potent to inhibit SARS-CoV-2 than chloroquine ( $EC_{50}=5.47 \mu\text{M}$ ) in vitro (23). Most  
102 importantly, the molecular mechanism of chloroquine phosphate in the treatment of  
103 COVID-19 remains elusive. It was reported that chloroquine could impair the  
104 endosome-mediated viral entry or the late stages of viral replication (24). More efforts  
105 are needed to pin down the exact mechanism.

106

## 107 **2.2 Disruption of SARS-CoV-2 replication**

108 A lot of anti-viral agents have been developed against viral proteases, polymerases,  
109 MTases, and entry proteins. A number of clinical trials of antiviral drugs are currently

110 in progress, such as remdesivir (NCT04252664, NCT04257656), favipiravir  
111 (ChiCTR2000029600, ChiCTR2000029544), ASC09 (ChiCTR2000029603),  
112 lopinavir/ritonavir (ChiCTR2000029387, ChiCTR2000029468, ChiCTR2000029539),  
113 arbidol (ChiCTR2000029621). Martinez reported that the most promising antiviral for  
114 fighting SARS-CoV-2 was remdesivir (25). Remdesivir is a monophosphoramidate  
115 prodrug of an adenosine analog. Its active form can incorporate into nascent viral  
116 RNA by RNA-dependent RNA polymerases (RdRps), which then causes RNA  
117 synthesis arrest (26). Wang et al. demonstrated that remdesivir effectively inhibited  
118 SARS-CoV-2 in vitro (21). The clinical condition of the first case of COVID-19  
119 confirmed in the United States improved following intravenous remdesivir  
120 administration (27). Similarly, favipiravir and ribavirin are monophosphoramidate  
121 prodrugs of guanine analogues and have been approved for some other viruses  
122 treatment (28). However, their antiviral effect in patients with COVID-19 needs  
123 rigorous data to support. Lopinavir and ritonavir are protease inhibitors targeting the  
124 coronavirus main proteinase (3C-like protease; 3CLpro). 3CLpro is responsible for  
125 processing the polypeptide translation product from the genomic RNA into the protein



126 components (29). High-throughput screening was also used to screen small molecular  
127 drugs targeting the viral main protease in clinical drug libraries (30). Four molecules  
128 were showed reasonable binding conformations with the viral main protease,  
129 including prulifloxacin, tegobuvir, bicittegravir and nelfinavir (30).

130 Targeting the RNA genome of SARS-CoV-2 may be another way. Nguyen et al.  
131 showed the application of the novel CRISPR/Cas13 RNA knockdown system in  
132 cleaving the SARS-CoV-2 RNA genome (31). This CRISPR/Cas13d system was  
133 composed of a Cas13d protein and guide RNAs-containing spacer sequences  
134 specifically complementary to the virus RNA genome. It was supposed that the  
135 Cas13d effector could be delivered by adeno-associated virus (AAV) to the lung  
136 infected with SARS-CoV-2 (31).

137

### 138 **2.3 Suppression of excessive inflammatory response**

139 A coordinated cytokine response is essential for the host immune response. However,  
140 a dysregulated response leads to a hyperinflammatory condition in some patients  
141 infected with SARS-CoV-2. It was reported that the patients in intensive care unit

142 (ICU) had higher concentration of cytokines in plasma compared with non-ICU  
143 patients with COVID-19, suggesting that the cytokine storm was associated with  
144 disease severity (32). Besides, higher percentage of GM-CSF<sup>+</sup> and IL-6<sup>+</sup>CD4<sup>+</sup> T cells  
145 was found from ICU patients infected with SARS-CoV-2 compared with non-ICU  
146 patients (33). In view of this, inhibition of excessive inflammatory response may be  
147 an adjunct for treating COVID-19. Nevertheless, the therapeutic use of corticosteroids  
148 that has excellent pharmacological effects to suppress exuberant and dysfunctional  
149 systematic inflammation is still controversy (25, 32). The current NHC guideline  
150 emphasizes that the routine use of systematic corticosteroids is not recommended  
151 unless indicated for another reason. In line, there was no available data showing that  
152 the patients benefited from corticosteroid treatment in SRAS-CoV or MERS infection,  
153 which might be attributed to the suppression of immune response against virus (34).  
154 Notably, a recent retrospective study showed the potential benefits from low-dose  
155 corticosteroids treatment in a subset of critically ill patients with SRAS-CoV-2 (35).  
156 More studies are needed to find out how and when to use corticosteroids properly.

157 At the cellular level, Zhou et al. demonstrated that the CD4<sup>+</sup>T cells were rapidly  
158 activated to produce GM-CSF and other inflammatory cytokines after SARS-CoV-2  
159 infection, which further induced CD14<sup>+</sup>CD16<sup>+</sup> monocytes activation with high  
160 expression of interleukin 6 (IL-6) (33). Thus, blocking GM-CSF or IL-6 receptor  
161 would potentially reduce immunopathology caused by SARS-CoV-2. In line, a  
162 multicenter, randomized, controlled clinical trial is under way to examine the efficacy  
163 and safety of tocilizumab (an IL-6 receptor-specific antibody) in patients with  
164 COVID-19 (ChiCTR2000029765). Moreover, Fu et al. mentioned the possible  
165 mechanisms of SARS-CoV-2-mediated inflammatory responses, in which the  
166 neutralizing antibodies triggered Fc receptors (FcR)-mediated inflammatory responses  
167 and acute lung injury (36). Various options to block FcR activation might reduce  
168 SARS-CoV-2-induced inflammatory responses (36).

169

#### 170 **2.4 Convalescent plasma treatment**

171 With infections wherein there is no specific therapy available, the therapy with  
172 convalescent plasma (CP) has been proposed as principal treatment (37). The CP is  
173 obtained from a donor who has recovered from infection by developing humoral  
174 immunity against the SARS-CoV-2 (38). The protective and therapeutic benefit of CP  
175 was attributed to the possible source of specific antibodies of human origin (39).  
176 However, the efficacy of CP treatment is still difficult to be evaluated because of the  
177 lack of high-quality randomized clinical trials and precise action mechanism of  
178 plasma therapy. According to the NHC guideline, the CP of recovered patients is  
179 mainly used for patients in rapid disease progression, severe or critical condition (40).  
180 Several clinical trials investigating the efficacy and safety of convalescent plasma  
181 transfusion in patients with COVID-19 are in progress (ChiCTR2000030010,  
182 ChiCTR2000030179, ChiCTR2000030381).

183

## 184 **2.5 Vaccines**

185 With the global spread of SARS-CoV-2, vaccination must be the most efficient and  
186 cost-effective mean to prevent and control COVID-19 (41). The robust researches are  
187 currently under way to facilitate the development of vaccines against SARS-CoV-2.  
188 Specifically, the S protein of SARS-CoV-2 remains a key target for vaccine  
189 development. Recently, Daniel et al. reported and shared the cryo-EM structure of  
190 SARS-CoV-2 S trimer, which allowed for additional protein engineering efforts and  
191 speeded up the process of vaccine development (42). Besides, Lucchese et al.  
192 searched the pentapeptides unique to SARS-CoV-2 by comparing the viral and the  
193 human proteomes and found that 107 human-foreign pentapeptides were embedded in  
194 S protein (43). Further, these S protein pentapeptides yielded 66 candidate epitopes  
195 for vaccine development (43). Moreover, since there were few available  
196 immunological studies related to SARS-CoV-2, Ahmed et al. screened the SARS-  
197 CoV-derived epitopes due to its high genetic similarity with SARS-CoV-2 (44). A  
198 screened set of SARS-CoV-derived B cell and T cell epitopes that mapped identically  
199 to SARS-CoV-2 proteins were identified, which would help the initial phase of  
200 vaccine development (44).

201 More than 15 potential vaccine candidates of COVID-19 are being developed  
202 around the world, including inactivated vaccine, recombinant subunits vaccine,  
203 nucleic acid-based vaccine, adenoviral vector vaccine, recombinant influenza viral  
204 vector vaccine, etc (45). On 23 January 2020, the Coalition for Epidemic  
205 Preparedness Innovations (CEPI) announced the finding to DNA, mRNA, and  
206 “molecular clamp” vaccine platforms (46). There was no existing literature search on  
207 SARS-CoV-2 vaccine trials as time of March 13, 2020. The safety of vaccine remains  
208 a top priority for vaccine development.

209

## 210 **2.6 Combination of Traditional Chinese and Western medicine**

211 It was reported that the Chinese medicine products that were used to treat respiratory  
212 tract infectious diseases might be helpful for SARS-CoV-2 treatment (47, 48). Among  
213 these products, Lianhuaqingwen capsules and ShuFeng JieDu capsules were shown to  
214 exert independent anti-viral effect and synergistic antiviral effect with western  
215 medicine products on influenza viruses, respectively (49, 50). The latest treatment

216 guideline in China added Traditional Chinese Medicine (TCM) as one of the treatment  
217 options for COVID-19. Wang et al. reported four cases with COVID-19 which gained  
218 improvement after taking combined Chinese and western medicine treatment (51).  
219 However, there are rarely published studies on Chinese medicine products in the  
220 treatment of COVID-19, especially the dearth of high-quality research. More  
221 prospective, rigorous population studies are urgently required to confirm the  
222 therapeutic effect of TCM. The mechanism of their antiviral action needs to be further  
223 illuminated.

224

### 225 **3 Conclusions**

226 The potential therapeutic strategies mentioned above are based on the updated  
227 research data for SARS-CoV-2. Among these options, we suppose the therapeutic  
228 drugs that directly target SARS-CoV-2 will be most effective. Besides, vaccines are  
229 critical for the prevention and limitation of COVID-19 transmission. Notably, the  
230 encouraging advances in deciphering SRAS-Cov-2 will lead to additional potential

231 therapeutic targets. Further, strong pre-clinical and clinical studies are needed to  
232 determine the safe and effective treatment for COVID-19.



233 **Conflict of interest**

234 All authors have no conflict of interest.

235 **Funding**

236 The work was supported by National Natural Science Foundation of China (J.L., No.

237 81472735); National Basic Research Program of China (973 program, J.L., Grant

238 #2015CB932600).

239

240 **References**

- 241 1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL,  
242 Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen  
243 PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH,  
244 Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ,  
245 Zhu SY, Zhong NS, China Medical Treatment Expert Group for C. 2020.  
246 Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*  
247 doi:10.1056/NEJMoa2002032.
- 248 2. World Health Organization.  
249 [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200313-sitrep-53-covid-19.pdf?sfvrsn=adb3f72_2)  
250 [313-sitrep-53-covid-19.pdf?sfvrsn=adb3f72\\_2](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200313-sitrep-53-covid-19.pdf?sfvrsn=adb3f72_2) (accessed March 13, 2020).
- 251 3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W,  
252 Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W, China  
253 Novel Coronavirus I, Research T. 2020. A Novel Coronavirus from Patients  
254 with Pneumonia in China, 2019. *N Engl J Med* 382:727-733.
- 255 4. Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, Lu L, Jiang S, Yang Z, Wu Y,  
256 Ying T. 2020. Potent binding of 2019 novel coronavirus spike protein by a  
257 SARS coronavirus-specific human monoclonal antibody. *Emerg Microbes*  
258 *Infect* 9:382-385.
- 259 5. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau  
260 EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J,  
261 Li M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y,  
262 Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G,  
263 Lam TTY, Wu JTK, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. 2020.  
264 Early Transmission Dynamics in Wuhan, China, of Novel  
265 Coronavirus-Infected Pneumonia. *N Engl J Med*  
266 doi:10.1056/NEJMoa2001316.
- 267 6. Zhao Y ZZ, Wang Y, Zhou Y, Ma Y, Zuo W. 2020. Single-cell RNA  
268 expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov.  
269 *BioRxiv* doi:<https://doi.org/10.1101/2020.01.26.919985>.
- 270 7. National Health Commission of the People's Republic of China. Notice on  
271 printing and distributing the diagnosis and treatment plan of pneumonia with

- 272 new coronavirus infection (trial version 7). [http://www.nhc.gov.cn/yzygj/](http://www.nhc.gov.cn/yzygj/s7653p/202001/f492c9153ea9437bb587ce2ffcbee1fa.shtml)  
273 [s7653p/202001/f492c9153ea9437bb587ce2ffcbee1fa.shtml](http://www.nhc.gov.cn/yzygj/s7653p/202001/f492c9153ea9437bb587ce2ffcbee1fa.shtml) (accessed March  
274 4, 2020).
- 275 8. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. 2020.  
276 Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein.  
277 *Cell* doi:10.1016/j.cell.2020.02.058.
- 278 9. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B,  
279 Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y,  
280 Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B,  
281 Zhan FX, Wang YY, Xiao GF, Shi ZL. 2020. A pneumonia outbreak  
282 associated with a new coronavirus of probable bat origin. *Nature*  
283 doi:10.1038/s41586-020-2012-7.
- 284 10. Wan Y, Shang J, Graham R, Baric RS, Li F. 2020. Receptor recognition by  
285 novel coronavirus from Wuhan: An analysis based on decade-long structural  
286 studies of SARS. *J Virol* doi:10.1128/JVI.00127-20.
- 287 11. Zheng M, Song L. 2020. Novel antibody epitopes dominate the antigenicity of  
288 spike glycoprotein in SARS-CoV-2 compared to SARS-CoV. *Cell Mol*  
289 *Immunol* doi:10.1038/s41423-020-0385-z.
- 290 12. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. 2020.  
291 Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor:  
292 molecular mechanisms and potential therapeutic target. *Intensive Care Med*  
293 doi:10.1007/s00134-020-05985-9.
- 294 13. Kruse RL. 2020. Therapeutic strategies in an outbreak scenario to treat the  
295 novel coronavirus originating in Wuhan, China. *F1000Res* 9:72.
- 296 14. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S,  
297 Schiergens TS, Herrler G, Wu NH, Nitsche A, Muller MA, Drosten C,  
298 Pohlmann S. 2020. SARS-CoV-2 Cell Entry Depends on ACE2 and  
299 TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*  
300 doi:10.1016/j.cell.2020.02.052.
- 301 15. Xia S, Zhu Y, Liu M, Lan Q, Xu W, Wu Y, Ying T, Liu S, Shi Z, Jiang S, Lu  
302 L. 2020. Fusion mechanism of 2019-nCoV and fusion inhibitors targeting  
303 HR1 domain in spike protein. *Cell Mol Immunol*  
304 doi:10.1038/s41423-020-0374-2.

- 305 16. Inoue Y, Tanaka N, Tanaka Y, Inoue S, Morita K, Zhuang M, Hattori T,  
306 Sugamura K. 2007. Clathrin-dependent entry of severe acute respiratory  
307 syndrome coronavirus into target cells expressing ACE2 with the cytoplasmic  
308 tail deleted. *J Virol* 81:8722-9.
- 309 17. Wang H, Yang P, Liu K, Guo F, Zhang Y, Zhang G, Jiang C. 2008. SARS  
310 coronavirus entry into host cells through a novel clathrin- and  
311 caveolae-independent endocytic pathway. *Cell Res* 18:290-301.
- 312 18. Neveu G, Ziv-Av A, Barouch-Bentov R, Berkerman E, Mulholland J, Einav S.  
313 2015. AP-2-associated protein kinase 1 and cyclin G-associated kinase  
314 regulate hepatitis C virus entry and are potential drug targets. *J Virol*  
315 89:4387-404.
- 316 19. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, Stebbing J.  
317 2020. Baricitinib as potential treatment for 2019-nCoV acute respiratory  
318 disease. *Lancet* 395:e30-e31.
- 319 20. Blaising J, Polyak SJ, Pecheur EI. 2014. Arbidol as a broad-spectrum antiviral:  
320 an update. *Antiviral Res* 107:84-94.
- 321 21. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao  
322 G. 2020. Remdesivir and chloroquine effectively inhibit the recently emerged  
323 novel coronavirus (2019-nCoV) in vitro. *Cell Res* 30:269-271.
- 324 22. Gao J, Tian Z, Yang X. 2020. Breakthrough: Chloroquine phosphate has  
325 shown apparent efficacy in treatment of COVID-19 associated pneumonia in  
326 clinical studies. *Biosci Trends* doi:10.5582/bst.2020.01047.
- 327 23. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song  
328 C, Zhan S, Lu R, Li H, Tan W, Liu D. 2020. In Vitro Antiviral Activity and  
329 Projection of Optimized Dosing Design of Hydroxychloroquine for the  
330 Treatment of Severe Acute Respiratory Syndrome Coronavirus 2  
331 (SARS-CoV-2). *Clin Infect Dis* doi:10.1093/cid/ciaa237.
- 332 24. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. 2003. Effects of  
333 chloroquine on viral infections: an old drug against today's diseases? *Lancet*  
334 *Infect Dis* 3:722-7.
- 335 25. Martinez MA. 2020. Compounds with therapeutic potential against novel  
336 respiratory 2019 coronavirus. *Antimicrob Agents Chemother*  
337 doi:10.1128/AAC.00399-20.

- 338 26. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. 2020. The antiviral  
339 compound remdesivir potently inhibits RNA-dependent RNA polymerase  
340 from Middle East respiratory syndrome coronavirus. *J Biol Chem*  
341 doi:10.1074/jbc.AC120.013056.
- 342 27. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters  
343 C, Ericson K, Wilkerson S, Tural A, Diaz G, Cohn A, Fox L, Patel A, Gerber  
344 SI, Kim L, Tong S, Lu X, Lindstrom S, Pallansch MA, Weldon WC, Biggs  
345 HM, Uyeki TM, Pillai SK, Washington State -nCoV VCIT. 2020. First Case of  
346 2019 Novel Coronavirus in the United States. *N Engl J Med* 382:929-936.
- 347 28. Li G, De Clercq E. 2020. Therapeutic options for the 2019 novel coronavirus  
348 (2019-nCoV). *Nat Rev Drug Discov* 19:149-150.
- 349 29. Morse JS, Lalonde T, Xu S, Liu WR. 2020. Learning from the Past: Possible  
350 Urgent Prevention and Treatment Options for Severe Acute Respiratory  
351 Infections Caused by 2019-nCoV. *Chembiochem* 21:730-738.
- 352 30. Li Y ZJ, Wang N, Li H, Shi Y, Guo G, Liu K, Zeng H, Zou Q. 2020.  
353 Therapeutic Drugs Targeting 2019-nCoV Main Protease by High-Throughput  
354 Screening. *BioRxiv* doi:10.1101/2020.01.28.922922.
- 355 31. Nguyen TM, Zhang Y, Pandolfi PP. 2020. Virus against virus: a potential  
356 treatment for 2019-nCoV (SARS-CoV-2) and other RNA viruses. *Cell Res*  
357 30:189-190.
- 358 32. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X,  
359 Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y,  
360 Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. 2020.  
361 Clinical features of patients infected with 2019 novel coronavirus in Wuhan,  
362 China. *Lancet* 395:497-506.
- 363 33. Zhou Y FB, Zheng X, Wang D, Zhao, C, Qi Y, Sun R, Tian Z, Xu X, Wei H.  
364 2020. Aberrant pathogenic GM-CSF+ T cells and inflammatory  
365 CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new  
366 coronavirus. *BioRxiv* doi:https://doi.org/10.1101/2020.02.12.945576.
- 367 34. Russell CD, Millar JE, Baillie JK. 2020. Clinical evidence does not support  
368 corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 395:473-475.

- 369 35. Zhou W, Liu Y, Tian D, Wang C, Wang S, Cheng J, Hu M, Fang M, Gao Y.  
370 2020. Potential benefits of precise corticosteroids therapy for severe  
371 2019-nCoV pneumonia. *Signal Transduct Target Ther* 5:18.
- 372 36. Fu Y, Cheng Y, Wu Y. 2020. Understanding SARS-CoV-2-Mediated  
373 Inflammatory Responses: From Mechanisms to Potential Therapeutic Tools.  
374 *Virol Sin* doi:10.1007/s12250-020-00207-4.
- 375 37. Chen L, Xiong J, Bao L, Shi Y. 2020. Convalescent plasma as a potential  
376 therapy for COVID-19. *Lancet Infect Dis*  
377 doi:10.1016/S1473-3099(20)30141-9.
- 378 38. Garraud O, Heshmati F, Pozzetto B, Lefrere F, Girot R, Saillol A, Laperche S.  
379 2016. Plasma therapy against infectious pathogens, as of yesterday, today and  
380 tomorrow. *Transfus Clin Biol* 23:39-44.
- 381 39. Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liunbruno GM,  
382 Grazzini G. 2016. Convalescent plasma: new evidence for an old therapeutic  
383 tool? *Blood Transfus* 14:152-7.
- 384 40. National Health Commission of the People's Republic of China. Notice on  
385 printing and distributing the convalescent plasma treatment for novel  
386 coronavirus pneumonia (trial version 2).  
387 [http://www.nhc.gov.cn/zyygj/s7658/202003/61d608a7e8bf49fca418a6074c2bf](http://www.nhc.gov.cn/zyygj/s7658/202003/61d608a7e8bf49fca418a6074c2bf5a2.shtml)  
388 [5a2.shtml](http://www.nhc.gov.cn/zyygj/s7658/202003/61d608a7e8bf49fca418a6074c2bf5a2.shtml) (accessed March 4, 2020).
- 389 41. Lu S. 2020. Timely development of vaccines against SARS-CoV-2. *Emerg*  
390 *Microbes Infect* 9:542-544.
- 391 42. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham  
392 BS, McLellan JS. 2020. Cryo-EM structure of the 2019-nCoV spike in the  
393 prefusion conformation. *Science* doi:10.1126/science.abb2507.
- 394 43. Lucchese G. 2020. Epitopes for a 2019-nCoV vaccine. *Cell Mol Immunol*  
395 doi:10.1038/s41423-020-0377-z.
- 396 44. Ahmed SF, Quadeer AA, McKay MR. 2020. Preliminary Identification of  
397 Potential Vaccine Targets for the COVID-19 Coronavirus (SARS-CoV-2)  
398 Based on SARS-CoV Immunological Studies. *Viruses* 12.
- 399 45. Pang J, Wang MX, Ang IYH, Tan SHX, Lewis RF, Chen JI, Gutierrez RA,  
400 Gwee SXW, Chua PEY, Yang Q, Ng XY, Yap RK, Tan HY, Teo YY, Tan CC,  
401 Cook AR, Yap JC, Hsu LY. 2020. Potential Rapid Diagnostics, Vaccine and

- 402 Therapeutics for 2019 Novel Coronavirus (2019-nCoV): A Systematic Review.  
403 J Clin Med 9.
- 404 46. CEPI. CEPI to fund three programmes to develop vaccines against the novel  
405 coronavirus, ncov-2019. Available online:  
406 [https://cepi.net/news\\_cepi/cepi-to-fund-three-programmes-to-develop-vaccine](https://cepi.net/news_cepi/cepi-to-fund-three-programmes-to-develop-vaccines-against-the-novel-coronavirus-ncov-2019/)  
407 [s-against-the-novel-coronavirus-ncov-2019/](https://cepi.net/news_cepi/cepi-to-fund-three-programmes-to-develop-vaccines-against-the-novel-coronavirus-ncov-2019/) (accessed on 29 January 2020).
- 408 47. Lu H. 2020. Drug treatment options for the 2019-new coronavirus  
409 (2019-nCoV). Biosci Trends doi:10.5582/bst.2020.01020.
- 410 48. Ren JL, Zhang AH, Wang XJ. 2020. Traditional Chinese medicine for  
411 COVID-19 treatment. Pharmacol Res 155:104743.
- 412 49. Ding Y, Zeng L, Li R, Chen Q, Zhou B, Chen Q, Cheng PL, Yutao W, Zheng  
413 J, Yang Z, Zhang F. 2017. The Chinese prescription lianhuaqingwen capsule  
414 exerts anti-influenza activity through the inhibition of viral propagation and  
415 impacts immune function. BMC Complement Altern Med 17:130.
- 416 50. Ji S, Bai Q, Wu X, Zhang DW, Wang S, Shen JL, Fei GH. 2020. Unique  
417 synergistic antiviral effects of Shufeng Jiedu Capsule and oseltamivir in  
418 influenza A viral-induced acute exacerbation of chronic obstructive  
419 pulmonary disease. Biomed Pharmacother 121:109652.
- 420 51. Wang Z, Chen X, Lu Y, Chen F, Zhang W. 2020. Clinical characteristics and  
421 therapeutic procedure for four cases with 2019 novel coronavirus pneumonia  
422 receiving combined Chinese and Western medicine treatment. Biosci Trends  
423 doi:10.5582/bst.2020.01030.

424

425

426 Figure legend

427 Figure1: The updated potential approach against SARS-CoV-2. (A) Dampening of  
428 SARS-CoV-2 fusion/entry; Disruption of SARS-CoV-2 replication; Inhibition of  
429 excessive inflammatory response. (B) Convalescent plasma treatment. (C) Vaccines.  
430 (D) Combination of Chinese traditional and Western medicine. ACE2;  
431 angiotensin-converting enzyme 2; rhACE2, recombinant human ACE2; HR2P, heptad  
432 repeat 2-derived peptides; EK1, a modified OC43-HR2P peptide; 3CLpro; 3C-like  
433 protease; RdRps, RNA-dependent RNA polymerases; AAV, adeno-associated virus;  
434 IL-6, interleukin-6; TCM, Traditional Chinese Medicine.  
435



