JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

pubs.acs.org/jcim Review

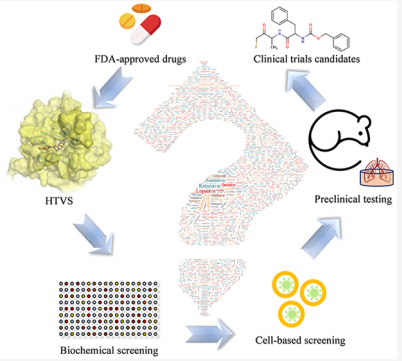
Comprehensive Consensus Analysis of SARS-CoV-2 Drug Repurposing Campaigns

Hazem Mslati, Francesco Gentile, Carl Perez, and Artem Cherkasov*

Cite This: https://doi.org/10.1021/acs.jcim.1c00384 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The current COVID-19 pandemic has elicited extensive repurposing efforts (both small and large scale) to rapidly identify COVID-19 treatments among approved drugs. Herein, we provide a literature review of large-scale SARS-CoV-2 antiviral drug repurposing efforts and highlight a marked lack of consistent potency reporting. This variability indicates the importance of standardizing best practices—including the use of relevant cell lines, viral isolates, and validated screening protocols. We further surveyed available biochemical and virtual screening studies against SARS-CoV-2 targets (Spike, ACE2, RdRp, PL^{pro}, and M^{pro}) and discuss repurposing candidates exhibiting consistent activity across diverse, triaging assays and predictive models. Moreover, we examine repurposed drugs and their efficacy against COVID-19 and the outcomes of representative repurposed drugs in clinical trials. Finally, we propose a drug repurposing pipeline to encourage the implementation of standard methods to fast-track the discovery of candidates and to ensure reproducible results.



KEYWORDS: *COVID-19, SARS-CoV-2, drug repurposing, chemical libraries, high-throughput screening, virtual screening, docking, main protease, spike protein*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA virus that causes many outcomes, including pulmonary infection and respiratory distress. COVID-19 was declared a pandemic by The World Health Organization in March 2020,[1] months after the original Wuhan outbreak occurred in 2019.[2] As of June of 2021, there were more than 170 million confirmed cases and 3.7 million deaths worldwide.[1] This novel betacoronavirus displays genomic and clinical features similar to the earlier severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) and is speculated to be of a zoonotic origin, with very few credible therapeutic options available to date.[3]

Traditionally, development of therapeutics requires greater than two billion dollars and may take up to 10−15 years.[4] Thus, the repurposing of FDA-approved drugs remains an attractive, rapid, and economic option to address SARS-CoV-2 infection. Consequently, an explosion in scientific publications and preprints describing a myriad of computational and experimental drug repurposing studies has emerged. Hundreds (if not thousands) of virtual screening campaigns have been reported, describing drugs that could bind to one of the six main therapeutic targets encoded by SARS-CoV-2 or the host's cell, including the viral receptor binding domain (RBD) of the spike glycoprotein (S protein), main protease (M^{pro}) and papain-like protease (PL^{pro}) enzymes, and RNA-dependent RNA polymerase (RdRp), as well as the host cell's angiotensin converting enzyme 2 (ACE2)—a human receptor serving as the viral entry point—and the transmembrane protease serine 2 (TMPRSS2).[5] Simultaneously, a large number of high-throughput screening (HTS) campaigns have been reported—identifying broadly acting (target unspecific) inhibitors for SARS-CoV-2 virus and/or its specific target proteins. These experimental and computational efforts generated valuable drug repurposing information—although frequently contradictive, thereby requiring rigorous benchmarking, standardization and postprocessing.

Computer-aided discovery of repurposed drugs helps avoid costly trial-and-error experiments involving cultured cells, biochemical screenings, and live systems.[6] As an example, baricitinib (a rheumatoid arthritis drug) was predicted using artificial intelligence as a repurposed drug[7,8] and was later granted an FDA-emergency approval for treatment of COVID-19 in combination with redemsivir.[9,10] However, most of the computational studies in the COVID-19 repositioning landscape were found to be lacking support from experimental results. In this review, we sought to reconcile *in vitro*, *in silico*,

Received: April 6, 2021

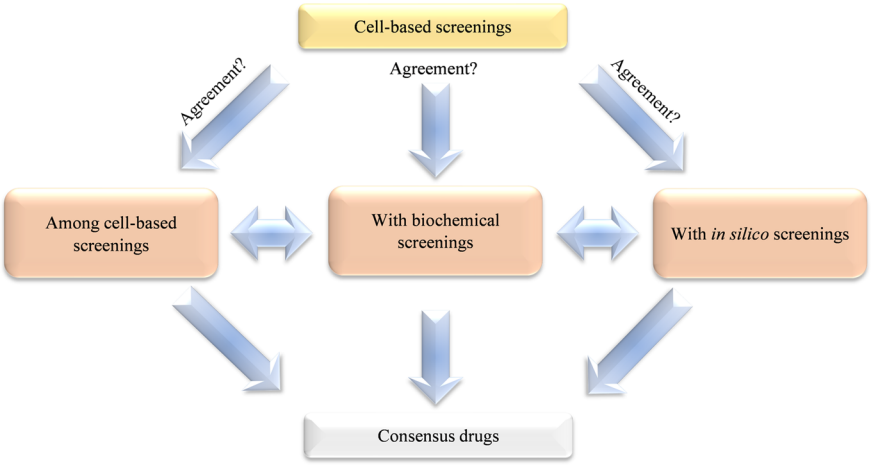


Figure 1. Proposed flowchart depicting how a promising COVID-19 drug could be identified across screening studies through consensus matching.

and biochemical repositioning studies to identify promising drugs. Prior to using empirical evidence to support *in silico* findings, we assessed the consensus drug activities among cell-based and biochemical screenings. Our strategy is summarized in the flowchart in Figure 1. We chose to use cell-culture repositioning studies to benchmark *in silico* and biochemical screening studies, as well as other cell-culture studies, benefiting from the large amount of cell-based experiments in the literature.

Several reviews reported progress on SARS-CoV-2 drug repositioning;[11−17] we present an extensive overview of the drug classes, the mode of action (MOA) in SARS-CoV-2 patients, the screening protocols that were used to identify them (accentuating interlab consensus findings), and the contradictory clinical trial outcomes.

CELL-BASED HIGH-THROUGHPUT SCREENS

We investigated half-maximal effective concentration (EC_{50}), half-maximal inhibitory concentration (IC_{50}), and half-maximal activity concentrationAC_{50}, as well as half-maximal cytotoxic concentration (CC_{50}) values, for the 19 experimental cell-based articles reviewed and compared overlapping hits identified from multiple independent studies (cross-validation).[18−37] Reported hits were reviewed in the National Center for Advancing Translational Sciences (NCATS) database.[38,39] Notably, the rich NCATS databases were trained in the computational model REDIAL-20—a user-friendly web program to retrieve activity against SARS-CoV-2 targets through DrugBank.[40] Cross-validation of hits between different HTS studies and NCATS results derived from the cytopathic or cytopathogenic effect (CPE) screening results are illustrated in Figure 2. While these studies utilized Vero E6 cells and similar viral MOIs, differing experimental conditions are probable sources of variability.

Active Compounds from Cell-Based HTS Repurposing Campaign Show Weak Consistency. Initially cell-based HTS experiments dominated *in vitro* COVID-19 drug repositioning research, involving a large number of assay variables, which in turn may have led to the low consistency in reported drug potency (Figure 2). However, unlike measurements of K_I, IC_{50} data are assay protocol specific.[41] The following subsections explore some of the cell-based experimental variables derived from SARS-CoV-2 screening campaigns.

Cell Lines. A number of cell-based HTS studies used the Vero 76 cell line or a lineage thereof such as Vero E6.[18−22,22−29,31−37,42,43] Vero E6 cells, originally cloned from the Vero 76 cell line,[44] are African green monkey kidney epithelial cells and are highly permissive to SARS-CoV-2 infection.[45] Vero E6 is broadly considered as the "gold standard" cell line for assaying SARS-CoV-2 viral-induced CPE.[27] Similarly, the ACE2 expression level is significantly elevated in Vero E6 cells.[46] Vero E6 cells are also interferon deficient which makes them more susceptible to viral infection.[47] Moreover, the engineered lineage, VeroE6/TMPRSS2 cells, displays 10-fold greater mRNA expression levels of cellular TMPRSS2, responsible for S protein cleavage,[48,49] compared to normal human lung tissue and other human cell lines, making them an attractive choice for use in SARS-CoV-2 repositioning screenings.[45]

Calu-3 cells (human lung epithelial cells) and Huh 7.5 cells, derived from parental cell line Huh-7 (human liver cells), are both infection-permissive human-derived cells.[20] However, Huh-7 cells were considered less desirable in some studies due to the low level expression of ACE2 and the lack of TMPRSS2 expression.[50,51] Caco-2 used in other repurposing studies[31,52] is an immortalized cell line derived from human colorectal adenocarcinoma cells, observed to differentiate into a mixture of intestinal-like cells with heterogeneous properties in cultures.[53] Both Caco-2 and Calu-3 cells (at a lower MOI) were shown to be more efficient in propagating SARS-CoV-2 infection—in contrast to Huh-7 cells and other human-derived cell lines.[54]

The differences in infection efficiencies and cell lines translate into variable CPE outcomes in drug screenings which in turn result in inconsistent reported drug activities. For instance, Dittmar et al.[20] evaluated a library (3000 drugs and drug-like molecules) via an HTS campaign using Vero E6, Huh-7.5, and Calu-3 cell lines (Figure 3). The authors identified six and 23 active compounds from Vero E6 and Huh-7.5 screens, respectively, with nine out of the Huh-7.5 active compounds displaying Calu-3 activity. Two drugs (Y-320 and salinomycin) demonstrated high potency in the three cell lines. In the same study, known antivirals, remdesivir and hydroxychloroquine (HCQ), displayed Huh-7.5 EC_{50} values more than 10-fold lower than those observed in Vero E6 cells. Additionally, HCQ, chloroquine, and structurally related

https://doi.org/10.1021/acs.jcim.1c00384
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

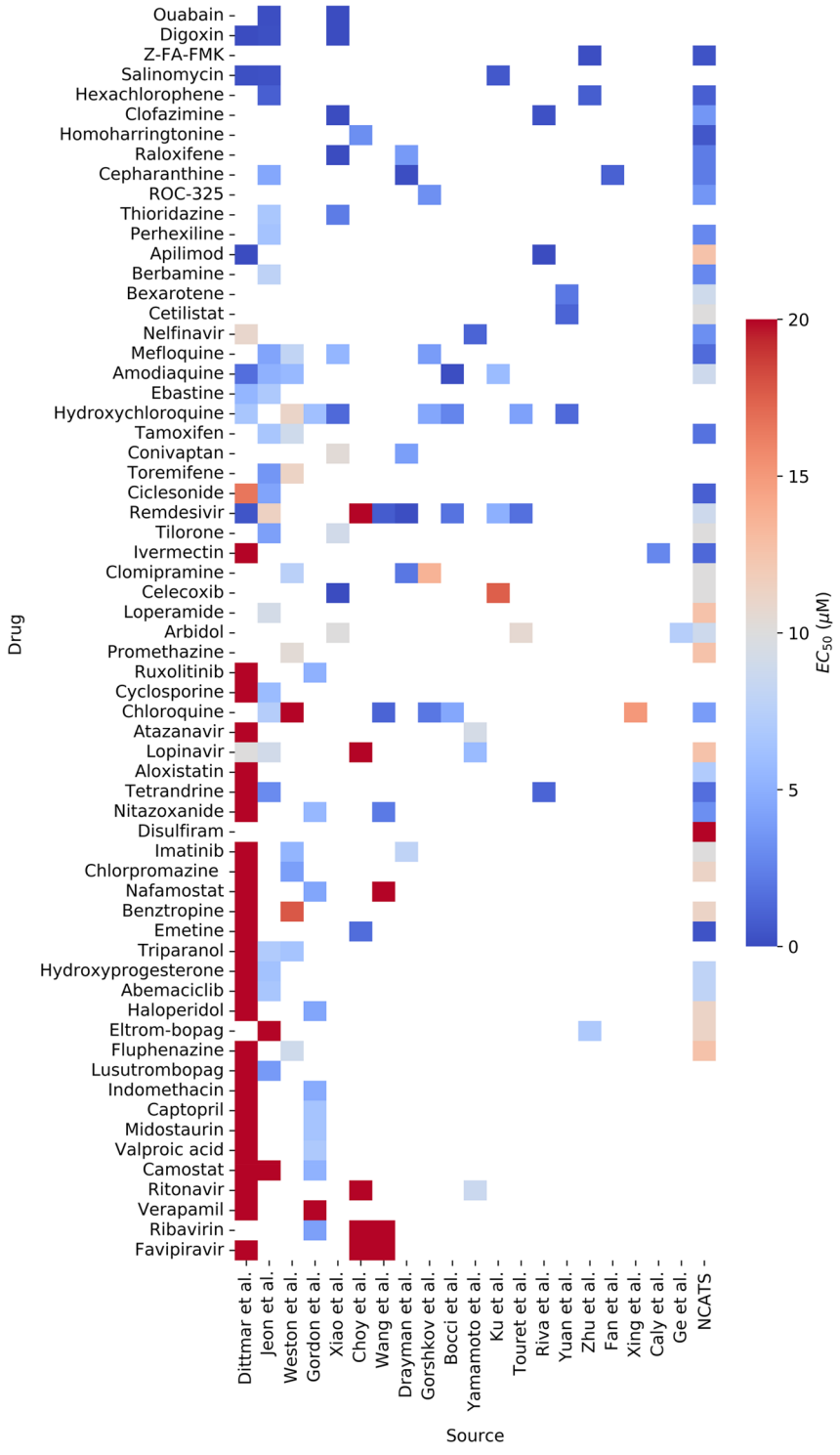


Figure 2. EC_{50} heatmap for SARS-CoV-2 active drugs in Vero E6 cells, identified in at least two independent studies. Values are compared with results from NCATS database (last column). Cells are colored in white where the drug activity or inactivity was not reported by the specific study.

compounds were demonstrated to have little to no activity in Calu-3 cells compared to Vero E6 and Huh-7.5 cell lines.[20]

Variability in potency employing different cell lines was reported in the study by Touret et al.,[31] who validated their drugs in Caco-2 cells and reported Arbidol to be less potent in the Vero E6 cells.[31] Viral infection efficiency appears to be cell line dependent and may require optimal endosomal acidification for entry into the host cell.[20,31] Not surprisingly, it was demonstrated that drug potency in Caco-2 cells was similar to other human cell lines (e.g., Calu-3 cells) compared to nonhuman cells (Vero E6 or BHK-21) and in particular for inhibitors associated with blocking virus entry into the host cell.[52]

Variations in Experimental Conditions Used to Determine EC_{50} Values. The phenotypic outcome associated with CPE measurements varies with culture conditions and with viral MOI.[22,55] Reported MOI values that were chosen in various SARS-CoV-2 cell-based repurposing studies ranged

https://doi.org/10.1021/acs.jcim.1c00384
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

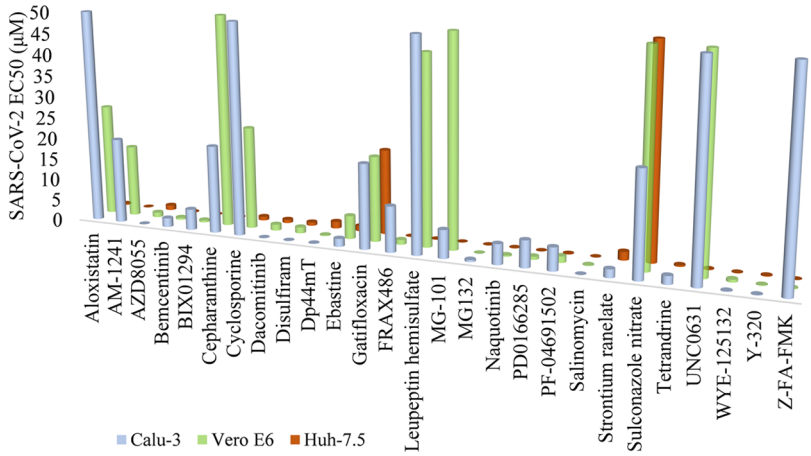


Figure 3. Cell-based SARS-CoV-2 actives determined in the HTS by Dittmar et al.[20] Drug hits with their corresponding EC_{50} in three different cell lines.

between 0.001[31] and 5.[22] Increasing MOI was shown to induce stochastic gene expression profiles which may hinder precise and reproducible readouts for EC_{50} values.[56] An MOI of 0.02 resulted in approximately 95% cell mortality and 72 h post infection (hpi) in one study,[22] while a MOI of 0.016 resulted in only 75% cell mortality within the same hpi time frame in another study.[29] In contrast, Weston et al. reported insignificant variation in the EC_{50} readouts as a function of MOI.[18]

Dose−response curves (DRC), from which EC_{50} values are extrapolated, are calculated using a variety of different viral indices—such as reverse transcription polymerase chain reaction (RT-PCR) to quantify viral RNA (vRNA).[18,20,23,25,26,31,33,43] In other studies, DRCs were calculated using CPE mixed analysis of cell morphology, fluorescence intensity of viral markers, position properties of cells, and cell confluence followed by fitting data with sigmoidal dose−response models.[21,22,32,52] Other works extrapolated EC_{50} values by measuring viral nucleoprotein levels from supernatants of drug-treated cells that were preinfected with SARS-CoV-2.[29] Importantly, EC_{50} values are also impacted by duration of viral infection.[57] While infection time was highly variable in drug screening assays, 72 h infection assessment was the most commonly reported.

Choice of Viral Isolate. Cell-based drug screening assays are generally conducted on the beta coronavirus HCoV-HKU1 or viral isolates obtained from COVID-19 patients of different origins.[18,20−23,25,27,29,31−33,43,52] Few exceptions were reported in the literature. Drayman et al. resorted to a different betacoronavirus predecessor, HCoV-OC43, which is a much less potent version and consequently a safer alternative as a viral isolate in screenings experiments.[30] A singular SARS-CoV isolate was used for the repositioning HTS by Fan et al., derived from a dead smuggled pangolin in 2017 (whose spike protein shares 92.2% amino acid identity with the spike protein of SARS-CoV-2).[28] Ultimately, different coronavirus lineages might have resulted in reported EC_{50} variable outcomes due to differences in ACE2-dependent cell entry RDBs affinities.[51]

Some Active Compounds from Cell-Based HTS Repurposing Campaign Show Promising Similarities. Despite the interlab variability in potency, some compounds were reported as active against SARS-CoV-2 at low concentration by multiple studies and are confirmed by NCATS experiments and are candidates for future COVID-19 treatments. The chemical structures of these candidate drugs, their speculated MOAs from experimental and/or computational studies involving molecular dynamics (MD), and stages of clinical evaluation are summarized in Table 1.

TARGET-BASED SARS-COV-2 REPOSITIONING SCREENINGS

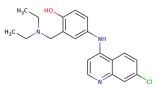
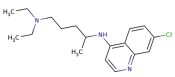
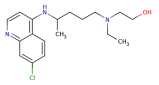
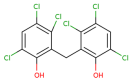
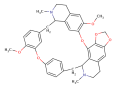
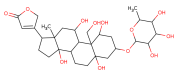
Compared to cell-based assays, biochemical assays and high-throughput virtual screenings (HTVS) provide more insights into the MOA. In contrast to M^{pro}-enzymatic and cell-based assays, there was little COVID-19 drug repositioning data for five SARS-CoV-2-encoded targets (Spike, ACE2, RdRp, PL^{pro}, and TMPRSS2). Docking studies, similarly, largely favored prioritizing the M^{pro} as the target in their screenings, although many drugs were demonstrated to have inhibitory effects against a different viral protein. Remdesivir, for example, which was cocrystallized with RdRp,[67] appeared in numerous M^{pro} computational docking campaigns as a predicted hit.[68−72] On the other hand, it is possible that identified drugs in a target-specific virtual repurposing campaign could act synergistically on more than one SARS-CoV-2 targe—as speculated for chloroquine inhibiting M^{pro} activity and interfering with the endosomal acidification process associated with SARS-CoV-2 viral entry.[73] The lack of sufficient biochemical data, in turn, may render it challenging to rule out off-target activity.

In the case of M^{pro}, only drugs that were predicted to be active by at least two different computational studies and displayed activity also in cell-based assays were retained (presented in Figure 4).

Repositioning Screenings against the Spike/ACE2 Interface. The glycosylated trimeric spike protein, encoded by SARS-CoV-2, is the ligand by which SARS-CoV-2 enters the host cell.[74] The larger binding interface and higher affinity of the S protein to host the ACE2 receptor likely contributes to its greater virulence compared to the S proteins expressed in SARS-CoV.[75] Additionally, the S protein, localized to the plasma membrane, can trigger receptor-dependent syncytia formation,[76] which is a process not addressed during vaccine development. The crystal structure of the S protein receptor-binding domain complexed with the ACE2 receptor (6M0J)[77] has been used in many virtual screening campaigns for identifying repurposed drugs.[78−80] Viral entry inhibition may be evaluated [under biosafety level 2 (BSL-2)] using pseudotyped virus particles coated with S glycoproteins that

https://doi.org/10.1021/acs.jcim.1c00384
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

Table 1. Consensus Drugs from Independent Cell-Based HTS Campaigns, External Evaluation of MOA, and Corresponding Current Clinical Trial Stage, If Applicable[a]

Drug name	Structure	Reported EC_{50} (μM)	MOA	Original indication	COVID-19 Clinical trial
Amodiaquine		1.16μM[20] and 0.13μM[58]	ND	Antimalarial	Phase II (NCT04532931)
Chloroquine		1.13μM[34] and 2μM[22]	Acts on S/ACE interface[59]	Antimalarial	Phase IV[1] (NCT04362332)
Hydroxychloroquine		2.7μM[19] and 1.33μM[35]	Acts on Spike/ACE 2 interface[59]	Antimalarial	Phase IV[1] (NCT04362333)
Mefloquine		4.3μM[21] and 3.9μM[22]	ND	Antimalarial	Phase III (NCT04347031)
Tetrandrine		1.1μM[27] and 3μM[21]	Disrupts endosomal signalling (TPC2)[60]	Calcium channel blocker	Phase IV[1] (NCT04308317)
Clofazimine		0.31μM[27] and 0.01μM[35]	Interferes with Spike-mediated cell fusion as well as viral helicase activity[61]	Treats leprosy	Phase II (NCT04465695)
Apilimod		0.01μM[20] and 0.02μM[27]	Interfers with entry through endosome PIKfyve kinase inhibition[27]	Antiviral and anticancer	Phase II (NCT04446377)
Hexachlorophene		0.9μM[21] and 0.79μM[24]	Inhibiting at viral entry level[62]	Antibacterial	NA
Cepharanthine		4.5μM[21] and 0.98μM[28]	Acts on Spike/ACE 2 interface[63]	Antiinflammatory and antineoplastic	NA
Raloxifene		3.8μM[30] and 0.02μM[35]	Prevents viral escape from the endolysozome and antagonizes IL-6 signaling in severe COVID-19 patients[64]	Treats osteoporosis	NA
Ouabain		0.097μM[21] and 0.02μM[35]	Inhibition of Src-mediated endocytosis in the entry step[62,65]	Cardiac glycoside	NA

https://doi.org/10.1021/acs.jcim.1c00384
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

Table 1. continued

Drug name	Structure	Reported EC_{50} (μM)	MOA	Original indication	COVID-19 Clinical trial
Digoxin		0.19μM[21], 0.07μM[20], and 0.04[35]	Viral RNA synthesis inhibition[65]	Cardiac glycoside	NA
Salinomycin		0.24μM[21] and 0.17μM[18]	Disrupts endosomal acidification (cell entry)[66]	Antibacterial	NA

[a]EC_{50} values are reported for Vero E6 cells. [†]No results were posted. ND: no data. NA: not applicable.

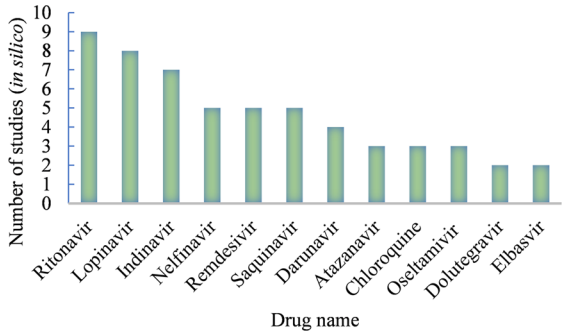


Figure 4. Histogram depicting drugs found to be in consensus among multiple *in silico* screenings directed against M^{pro} which were also found active in in cell-based screenings.

encapsulate a luciferase reporter RNA which, in turn, is used to monitor the rate of infection in ACE2-expressing cells.[81] Remdesivir (EC_{50} = 1.8 μM),[19] chloroquine (EC_{50} = 4.5 μM),[19] HCQ (EC_{50} = 2.7 μM),[19] favipiravir (EC_{50} > 40 μM),[20] darunavir (EC_{50} = 46.41 μM),[26] lopinavir (EC_{50} = 9.12 μM),[21] mefloquine (EC_{50} = 4.3 μM),[21] ribavirin (EC_{50} = 4.09 μM),[36] amodiaquine (EC_{50} = 0.13 μM),[19] and methylene blue (EC_{50} = 20 μM)[32] have been identified in *in silico* studies targeting Spike/ACE2,[78−80] in addition to having demonstrated activity in cell-based assays. NCATS drug screening data on drugs that could play a role in the S protein−ACE2 distraction revealed important intersections of the aforementioned drugs, which were *in silico* and cell-based consensused, with drugs emerging from biochemical assays: remdesivir (AC_{50} = 22.53 μM), lopinavir (AC_{50} = 4.22 μM), and methylene blue (AC_{50} = 7.52 μM).[39]

Repositioning Screenings against RdRp. The RNA-dependent RNA polymerase (RdRp) is the principal component of the multi-subunit complex facilitating viral replication.[82−84] During the proteolytic cleavage products of the 16 nonstructured proteins (NSPs), RdRp is generated from NSP 12 which requires the attachment of NSP 7 and two NSP 8 molecules to assemble a minimally functioning complex.[83] RdRp shares significant homology within the RNA virus *Coronaviridae* family and is a popular target for SARS-CoV-2 repositioning studies due to a given drug's prospect of high selectivity and low probability of associated cytotoxicity.[82,83] Many nucleoside analogues have been proposed due to low RdRp replication fidelity.[85] Due to the inhibitory potential of remdesivir for the RdRp in Ebola virus,[67,86] several virtual screening campaigns were conducted.[83−85,87] Despite the lack of consensus for hits identified among the virtual repurposing campaigns, two of the *in silico* shortlisted drugs were reported among the hits identified in cell-based repurposing studies, namely, digoxin (a cardiac glycoside; EC_{50} = 0.07 μM)[20] and ritonavir (an HIV protease inhibitor; AC_{50} = 22.53 μM).[21,23,26,88]

Repositioning Screenings against PL^{pro}. During SARS-CoV-2 replication, 16 NSPs are generated from two large overlapping polyproteins (PPs): PP1a and PPab.[89] Two types of cysteine proteases process these PPs, of which the N-terminal termini are proteolytically processed by the papain-like protease (PL^{pro}).[90] Moreover, SARS-CoV-2 PL^{pro} efficiently inhibits ISGylation of the central interferon (IFN) regulatory factor thereby diminishing IFN-mediated innate viral immunity.[91] Therefore, PL^{pro} inhibition has been the focus of many SARS-CoV-2 drug repositioning studies as it may impede viral replication and help restore innate viral immunity.[91,92]

The anti-inflammatory drug ebselen was reported as an effective PL^{pro} inhibitor[93] and a potent M^{pro} inhibitor.[94] Only two drugs, ribavirin (an antiviral) (EC_{50} = 4.09 μM)[36] and oxprenolol (a beta-blocker) (EC_{50} = 20.22 μM),[31] were identified *in silico* as potential PL^{pro} ligands and were effective in cell-based assays.[23,31,87]

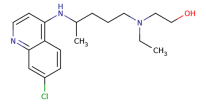
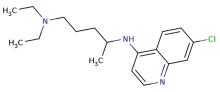
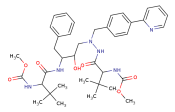
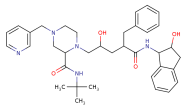
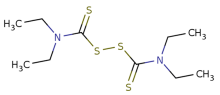
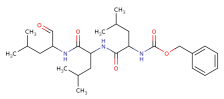
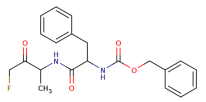
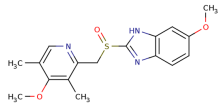
Targeting PL^{pro} may be challenging in translational development since host deubiquitinases and PL^{pro} recognize the same C-terminal human ubiquitin domain.[95,96]

Repositioning Screenings against M^{pro}. The C-terminal termini of PPs are proteolytically cleaved by a chymotrypsin-like cysteine protease [aka M^{pro}; 3C-like protease ($3CL^{pro}$)], hydrolyzing the Gln-Ser peptide bond in the Leu-Gln-Ser-Ala-Gly recognition sequence.[97]

Only one FDA-approved compound, boceprevir, was found to be active and in consensus among the M^{pro} biochemical repositioning screening studies.[24,96,98−101] Additionally, the large-scale X-ray crystallographic study led by Günther et al. and its lack of identifying similar compounds in M^{pro} screens suggests significant inconsistencies.[101] The authors conducted SARS-CoV-2 M^{pro} cocrystallization experiments using a 5935-drug library and identified 37 M^{pro} ligands binding at different pockets.[101] Of note, the crystallographic finding in one paper[30] documented masitinib (an antineoplastic drug) as an M^{pro} active site ligand and was not reproduced by Gunther et al.[30,101] This inconsistency might be explained by the inherent technical difference between crystal soaking and cocrystallization experiments.[102] However, drugs have been found to be active in both the M^{pro} target-directed biochemical and cell-based assays (Table 2).

https://doi.org/10.1021/acs.jcim.1c00384
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

Table 2. Common Hits in M^{pro}- and SARS-CoV-2-Infected Cell Line Screenings with Corresponding Current Stage of Clinical Trials, If Applicable[a]

Drug name	Structure	Reported IC_{50} and EC_{50} (μM)	Clinical trial
Hydroxychloroquine		IC_{50}: 2.9μM[73] and Vero E6 cell line EC_{50}: 1.3μM[35]	Phase IV[†] (NCT04362333)
Chloroquine		IC_{50}: 3.9μM[73] and Vero E6 cell line EC_{50}: 1.13μM[34]	Phase IV (NCT04362332)
Atazanavir		IC_{50}: 7.5μM[73] and Vero E6 cell line EC_{50}: 9.36μM[26]	Phase III (NCT04468087)
Indinavir		IC_{50}: 43.1μM[73] and Vero E6 cell line EC_{50}: 59.14μM	NA
Disulfiram		IC_{50}: 9.35nM[96] and Vero E6 cell line EC_{50}: 5.89μM[20]	NA
MG-132		IC_{50}: 3.9μM[99] and Vero E6 cell line EC_{50}: 0.01μM[20]	NA
Z-FA-FMK		IC_{50}: 11.39μM[24] and Vero E6 Cell line EC_{50}: 0.2μM[20]	NA
Omeprazole		IC_{50}: 21μM[73] and Caco-2 cell line EC_{50}: 17.06μM[22]	NA

[a]EC_{50} values are from studies reporting the most potent values. [†]No results were posted. NA: not applicable.

With *in silico* drug repositioning against M^{pro}, only a handful of molecules were found to be common in multiple studies. These molecules were active in cell-based repurposing screenings: dolutegravir, elbasvir, nelfinavir, atazanavir, lopinavir, ritonavir, darunavir, saquinavir, indinavir, oseltamivir, chloroquine, and remdesivir (Figure 4).[19,21,23,26,30,31,52,58,68,69,69−73,98,103−116]

Active compounds identified in *in silico* and cell-based assays were compared with biochemical assay—NCATS screening data.[39] Only the drug darunavir (AC_{50} = 39.8 μM) satisfied this triplex consensus.[39]

Repositioning Screenings against the TMPRSS2 Protease. TMPRSS2 is a type II serine protease and is primarily expressed in respiratory and gastrointestinal epithelial cells.[117] This serine protease cleaves a specific sequence from the S protein upon ACE2 interaction, thereby promoting cellular endocytosis of the virus and potential syncytia formation.[117] Recently, TMPRSS2 knockout mice demonstrated coronavirus-infection resistance,[118] suggesting this cellular host protein is a potential drug target.

Camostat mesylate was the only drug predicted by multiple *in silico* studies.[119,120] The drug is a trypsin-like serine protease inhibitor and blocked coronaviral cell entry via TMPRSS2 inhibition.[121] Recent biochemical HTS reported camostat mesylate activities of IC_{50} = 6.7[117] and 2.7 nM.[119] Similarly, biochemical HTS identified nafamostat, FOY 251, and gabaxate with low nanomolar potency ranges.[117,119] Five shortlisted drugs were identified by combining computational and cell-based screenings: nafamostat (EC_{50} = 0.04 μM), camostat mesylate (EC_{50} = 0.64 μM), lopinavir (EC_{50} = 5.73 μM), olaparib (EC_{50} = 10.34 μM), and midostaurin (EC_{50} = 6.47 μM).[25,26,36,52,84,119,120,122]

COVID-19 CLINICAL EFFECTIVENESS OF REPURPOSED DRUGS

The above-discussed *in vitro* SARS-CoV-2 active drugs include antivirals, antimalarials, anticancer therapeutics, immunomodulators, antibacterial agents, antipsychotics, and calcium channel blockers. Inevitably, repurposed drugs will act on their ontological targets and potentially exhibit synergistic complications with adverse side effects.[19] In the following

https://doi.org/10.1021/acs.jcim.1c00384
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

subsections, the possible direct and indirect actions of a given drug, or its class, and the results of any clinical trials on COVID-19 patients are discussed.

Direct-Acting Antivirals. COVID-19 treatment strategies include antiviral drugs that interfere with SARS-CoV-2 replication enzymes, i.e., proteases and RdRp. Remdesivir is proposed to treat COVID-19 by disrupting the SARS-CoV-2 RdRp machinery.[123] Briefly, remdesivir triphosphate competes with adenosine triphosphate for incorporation into the replicating viral RNA chain—resulting in early termination.[123,124] Remdesivir was used either as a reference drug[21,52] or a positive control[19] for many repositioning studies, yet, it was also reported as a hit by Choy et al.[23] and Touret et al.[31]

Clinical effectiveness appeared to be generally inconclusive for repurposed antivirals. For instance, remdesivir, favipiravir, ribavirin, a ritonavir−lopinavir combination, and Arbidol were reported to be effective in some clinical trials[125−128] but ineffective in others.[129−138] Emtricitabine−tenofovir, a prescription medicine for HIV, revealed reduced viral titers in infected ferrets after 8 days post infection (dpi) in comparison to the control; but after 10 dpi, both the control and the treated ferrets exhibited insignificant statistical outcomes.[50] Thus, SARS-CoV-2 efficacy of current antiviral drugs remains to be determined through further clinical investigations.

Antimalarial Drugs. The exact MOA for antimalarials for treating COVID-19 is still ambiguous. Notable antimalarials (like amodiaquine, which has been widely used for prophylaxis and treatment of malaria for over 60 years) were identified as lead hits by Bocci et al.[19] after they evaluated an FDA drug library based on the chemical Morgan Fingerprint similarity to HCQ. These drugs exhibit broad spectrum antiviral activity and inhibit infection by other SARS, influenza, and Ebola viruses.[50,139] The potency of other antimalarial drugs (e.g., chloroquine and HCQ) were attributed to interfering with the glycosylation pattern of the host's ACE2 extracellular receptors—thereby disrupting the SARS-CoV-2 spike-mediated entry.[59] Furthermore, HCQ increases endosomal/lysosomal pH, which in turn interferes with the viral replication process.[19]

Extensive antimalarial *in vivo* trials were conducted with variable and indeterminate outcomes; despite this, many antimalarial agents were deemed promising for clinical studies. For instance, amodiaquine was withdrawn from use in the United States due to rare occurrences of agranulocytosis and liver damage after high doses or prolonged treatment.[140] FDA also cautioned against the use of HCQ and chloroquine outside a hospital setting due to risks of arrhythmia.[141] While several studies advocated HCQ's and chloroquine's anti-SARS-CoV-2 potency,[34,142−148] Weston et al. and others reported ineffective outcomes for either drug during *in vivo* studies.[18,149−151]

Immunomodulators, Antineoplastic Therapeutics, and Antibacterial Drugs. Important severe COVID-19 infection manifestations are shared with neoplasia, inflammation, immune dysfunction, and coagulopathy.[152] Regulation of several cytokines is disordered in the peripheral blood of SARS patients evidenced by an increase in the levels of cytokines and chemokines and a decrease in the levels of anti-inflammatory cytokines such as IL-10.[153,154] Notably, the release of pro-inflammatory cytokines, especially interferon (IFN)-α and IFN-γ, was observed to correlate with lethal SARS.[155] The cytokines associated with increased levels in fatal SARS patients are IL-6, IL-1β, IFN, and CXCL10—which are mainly secreted by dendritic cells and macrophages, indicating that innate immunity may play a pivotal part in lethal SARS.[154] Therefore, anticancer and immunomodulatory drugs—NF-κB and STAT3 regulators—have been used to manage the "cytokine storm" that is often observed in SARS-CoV-2 patients. In addition, PARP-inhibiting cancer agents and IL-1β and Il-6 inhibiting immunomodulators could prevent caspase-8-mediated necroptosis, whose activation is one of the reported hallmarks of SARS-CoV-2 viral infection.[156]

Antibacterial azithromycin, identified by Touret et al.,[31] was reported to decrease viral entry into cells by upregulating type I and III IFN expressions (especially IFN-β and IFN-λ), as well as upregulating genes involved in virus recognition (e.g., MDA5 and RIG-I).[31,157] Another antibacterial, salinomycin, reported by Dittmar et al.[20] as an ionophore, may attenuate viral entry by disrupting endosome acidification.[20,158]

Disagreement in clinical studies include immunosuppressive drugs like tocilizumab and dexamethasone which were demonstrated to be effective in one study[138] but were rebuffed in other works.[159,160] It is still questionable if immunomodulatory corticosteroids are useful since they have been associated with increased mortality and delayed viral clearance in coronavirus infectious diseases.[161]

Antipsychotics. Several FDA-approved drugs with antipsychotic-acting ontology were reported as active against SARS-CoV-2. The MOA of chlorpromazine (CPZ), a lead drug identified by Weston et al.,[18] entails the inhibition of clathrin coating in cells, thereby disrupting infection by many viruses that require clathrin-mediated endocytosis (e.g., SARS-Cov-2).[162] It is still unclear whether other antipsychotic dopaminergic antagonists like spiperone, reported to exhibit inhibit human pathogenic polyomaviruses,[31,163] have a similar effect in SARS-CoV-2 infection. Indeed, clinical evaluations of the antipsychotic CPZ revealed ineffective outcomes *in vivo*.[18]

Calcium Channel Blockers. Several antiviral candidates belong to the calcium channel blockers (CCBs) drug class. Since CCBs block intracellular calcium influx, any anti-SARS-CoV-2 effect may reduce the intracellular calcium level.[164] Indeed, Vero E6 cells treated with serial concentrations of calcium chelators BAPTA-AM or 2APB3 and then infected with SARS-CoV-2 exhibited significant inhibition of virus replication in a concentration-dependent manner, confirming the dependent role of intracellular Ca^{2+} for SARS-CoV-2 replication.[165] Calcium chelator drugs were also shown to reduce SARS-COV-2 viral titers in infected Vero E6 cells in a dose-dependent manner while also reducing cell viability.[166] Multiple CCBs were evaluated by Touret et al.[31] and Ko et al.[167] for efficacy *in vitro* with Calu-3 cells and exhibited no activity. While some studies report efficacy of CCB in patients with pre-existing hypertension,[165] their efficacy *in vivo* remains to be clearly assessed.

EXPERIMENTAL VALIDATION OF SELECTED DRUGS AGAINST M^{PRO}

Since many repurposed drug MOAs were speculated to act on M^{pro} as a target, drugs that showed promising consensus between cell-based assays and biochemical or virtual screenings (Table 2) were evaluated in-house. A method was adapted from the SARS-CoV fluorescence-based cleavage assay previously described by Hamill et al.[168] with the substrate (Abz-AVLQSGFR-Y (3-NO2) G-NH_2; PL Laboratories Inc.) used for SARS-CoV-2 screening.

https://doi.org/10.1021/acs.jcim.1c00384
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

(a)

IC_{50}	17a analogue	GC-376	Ratio
High	18μM	0.084μM	0.006
Low	12μM	0.045μM	0.003
Overall	12.96μM	0.072μM	0.004

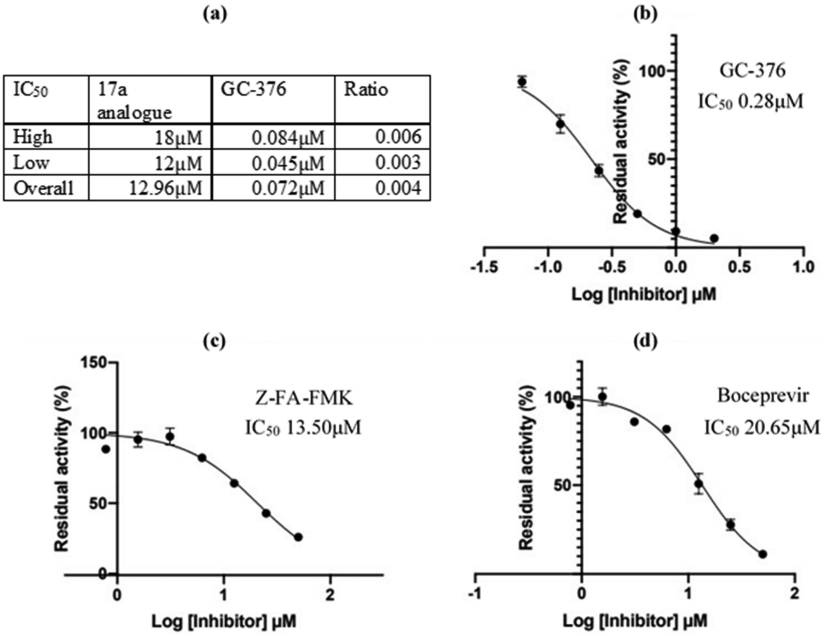


Figure 5. In-house assay validation of consensus drugs against the M^{pro} target in SARS-CoV-2. (a) Summary of IC_{50} runs on the secondary control (17a analogue) and the primary control (GC376) to derive MSR validation of the M^{pro} assay. IC_{50} curves for (b) primary control compound GC376, (c) Z-FA-FMK, and (d) boceprevir in the M^{pro} assay.

Prior to screening drugs, we validated the robustness of the M^{pro} assay using a two-compound approach[169,170] based on the primary control, GC-376,[171] and the secondary control, 17a[172] analogue (Figure 5a). The minimum standard ratio (MSR) derived was 2.55, indicating that the assay was robust and reproducible (<7.5).[170] Interestingly, only boceprevir and Z-FA-FMK out of the nine selected drugs (boceprevir, nelfinavir, MG-132, darunavir, elbasvir, indinavir, Z-FA-FMK, saquinavir, and disulfiram) displayed IC_{50} values within the low micromolar potent range in this M^{pro} biochemical assay (Figure 5c and d). Due to the minimal activity observed, a few takeaways were discussed. First, the vast majority of repurposed drugs possess undetermined MOAs and therefore are "moonshot candidates" for COVID-19 clinical trials. Second, the MOA remains to be evaluated rigorously via biochemical assays (Figure 5). Third, the in-house IC_{50} values for boceprevir and MG-132 were notably different from the values reported in literature, thereby reinforcing the notion of the implementation of standardized evaluation protocols in the research community.

LESSONS LEARNED

Throughout the landscape of drug repositioning research, a minority of proposed drugs had undergone a thorough triaging validation. There is a considerable need to implement best practices using a consensus rapid approach to exclude false positives before translational evaluation.

All SARS-CoV-2 antiviral entities must be evaluated in live virus cellular assays (2D cellular assays or 3D organoids) and potential animal models (ferrets, huACE-2 transgenic mice). However, screening thousands of compounds adhering to BSL-3/CL3 safety protocols is time consuming and very expensive.

Therefore, our workflow (Figure 6) encourages the use of rigorous computational docking analysis as the first step, thereby prioritizing the biochemical assays experiments for a subset of candidate drugs to evaluate their MOA hypothesis. Subsequent cell-based screenings could then be carried out

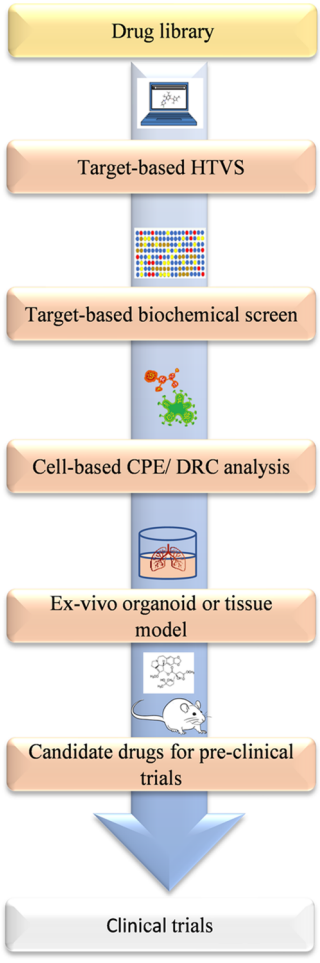


Figure 6. Proposed pipeline for triaging repurposed drugs in SARS-CoV-2 repositioning screenings.

https://doi.org/10.1021/acs.jcim.1c00384
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

using standardized protocols: EC_{50} determination using all three Huh-7, Caco-2 and Calu-3 cell lines; CC_{50} determination to evaluate cytotoxicity; and calculation of the therapeutic index (ratio CC_{50}:EC_{50}) to determine relevance for *in vivo* studies. Since SARS-CoV-2 was reported to have preferential tropism toward nasal epithelial cells, pneumocytes, and enterocytes in the bowel,[173] we recommend that all three cell lines—Huh-7, Caco-2 and Calu-3—be used to orthogonally validate drug potencies but not the Vero E6 cell line due to the factors discussed earlier (see Cell-Based High-Throughput Screens).

EC_{50} value determination may be standardized by (a) determining viral titers by RT-qPCR quantification[18,20,23,25,26,31,33,43] and (b) standardizing the MOI. The most common MOIs reported among the cell-based repositioning studies were 0.01 and 0.1; however, using MOI of 0.2 was effective in all three human cell lines with viral titers peaking at 48 hpi.[174,175] Finally, independent orthogonal validation assays such as the viral titers reduction assay may be performed to concretize results from cell culture experiments.[19]

Additionally, the SARS-CoV-2 clinical isolate and its genome must also be evaluated for its relevance before cell-based screenings take place.[176] For example, the D614G mutation affecting the S protein of SARS-CoV-2 strains had been experimentally reported to exhibit more cell infectivity than other known strains.[177,178] The D614G mutation is reportedly the most dominant variant to date[178] and thus might be the most currently relevant SARS-CoV-2 model to test repurposing drugs against. Due to the rapid emergence of the variants of concern (VOCs),[179] it is recommended that the investigator review the WHO and U.S. CDC updates and determine the VOCs most relevant for *in vivo* experiments and clinical development.

Using relevant primary tissue organoid or explant models to clarify pharmacological properties (kinetics, absorption, cytotoxicity, and dosage) was seen as a necessary integration in the workflow proposed by Si et al.[50] The authors suggested to test anti-SARS-CoV-2 compounds in an airway chip that contains highly differentiated human lung epithelium cells expressing high levels of serine proteases involved in viral entry.[50] The human organ chip model was claimed to have successfully predicted the inability of chloroquine, HCQ, and Arbidol to work in animals and human patients, thus validating recent reports.[180−182]

The penultimate "rung" in the flowchart is evaluating the repurposed drug in an appropriate COVID-19 animal model.[183] The K18-hACE2 mouse, in which transgenic human ACE2 expression is driven by the human K18 promoter in mouse epithelial cells, is a powerful model for SARS-COV-2 virus nasal administration. Post infection, the mice experiences severe respiratory illness and succumbs in 4 days. This model has been used to evaluate the antiviral efficacy of an inhibitor to TMPRSS2.[184]

CONCLUDING REMARKS

The route of identification of antiviral candidates through drug repositioning is convenient, saves preclinical development time, and has been deemed safe by regulatory agencies following clinical trials. However, few repositioning efforts have borne fruit since the concept was deployed.[185] Excluding serendipitous findings or drugs retailored based on rational MOA, the challenge remains to reposition drugs to the new target tissue. For COVID-19 treatment, the plethora of autonomous protocols to assess antiviral activity, such as sparse independent triaging, internal orthogonal validation and external data validation data, makes drug repurposing unreliable Therefore, the COVID-19 research community should implement a collective effort to standardize and coordinate screening protocols and deploy the proposed pipeline to identify drug candidates for clinical translation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jcim.1c00384.

SMILES and M^{pro} inhibition data of tested drugs and SMILES of drugs mentioned in the text (XLSX)

AUTHOR INFORMATION

Corresponding Author

Artem Cherkasov − *Vancouver Prostate Centre, University of British Columbia, Vancouver, BC V6H 3Z6, Canada;* orcid.org/0000-0002-1599-1439; Email: acherkasov@prostatecentre.com

Authors

Hazem Mslati − *Vancouver Prostate Centre, University of British Columbia, Vancouver, BC V6H 3Z6, Canada*

Francesco Gentile − *Vancouver Prostate Centre, University of British Columbia, Vancouver, BC V6H 3Z6, Canada;* orcid.org/0000-0001-8299-1976

Carl Perez − *Vancouver Prostate Centre, University of British Columbia, Vancouver, BC V6H 3Z6, Canada*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jcim.1c00384

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was funded by Canadian Institutes of Health Research (CIHR), Canadian 2019 Novel Coronavirus (2019-nCoV) Rapid Research grants (OV3-170631 and VR3-172639), and generous donations for COVID-19 research from TELUS, Teck Resources, 625 Powell Street Foundation, Tai Hung Fai Charitable Foundation, Vancouver General Hospital Foundation. F.G.'s work is supported by fellowships from the CIHR (MFE-171324), Michael Smith Foundation for Health Research/VCHRI & VGH UBC Hospital Foundation (RT-2020-0408), and Ermenegildo Zegna Foundation. The authors thank Dr. Francois Jean and his lab (University of British Columbia) for providing help to assess the compound activities. The authors thank Dr. Larry Goldenberg for his tireless support of research efforts on COVID-19 therapeutics development.

LIST OF ABBREVIATIONS

COVID-19 coronavirus disease 2019
SARS-CoV-2 severe acute respiratory syndrome coronavirus 2
SARS-CoV severe acute respiratory syndrome coronavirus
MERS-CoV Middle East respiratory syndrome coronavirus
RBD receptor binding domain
S protein spike glycoprotein

M^{pro} main protease
PL^{pro} papain-like protease
RdRp RNA-dependent RNA polymerase
ACE2 angiotensin converting enzyme 2
TMPRSS2 transmembrane protease serine 2
HTS high-throughput screening
MOA mode of action
EC_{50} half-maximal effective concentration
IC_{50} half-maximal inhibitory concentration
AC_{50} half-maximal activity concentration
CC_{50} half-maximal cytotoxic concentration
NCATS National Center for Advancing Translational Sciences
CPE cytopathic or cytopathogenic effects
MOI multiplicity of infection
HCQ hydroxychloroquine
Hpi hours post infection
DRC dose−response curves
RT-PCR reverse transcription polymerase chain reaction
vRNA viral RNA
MD molecular dynamics
HTVS high-throughput virtual screenings
NSP nonstructured proteins
PPs polyproteins
IFN interferon
CPZ chlorpromazine
CCBs calcium channel blockers

REFERENCES

(1) *WHO Coronavirus Disease (COVID-19) Dashboard.* https://covid19.who.int (accessed 2020-12-23).
(2) 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**, *395*, 497−506.
(3) Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; Niu, P.; Zhan, F.; Ma, X.; Wang, D.; Xu, W.; Wu, G.; Gao, G. F.; Tan, W. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N. Engl. J. Med.* **2020**, *382*, 727−733.
(4) Parvathaneni, V.; Kulkarni, N. S.; Muth, A.; Gupta, V. Drug Repurposing: A Promising Tool to Accelerate the Drug Discovery Process. *Drug Discovery Today* **2019**, *24*, 2076−2085.
(5) Wu, Y.; Chang, K. Y.; Lou, L.; Edwards, L. G.; Doma, B. K.; Xie, Z.-R. In Silico Identification of Drug Candidates against COVID-19. *Inform. Med. Unlocked* **2020**, *21*, 100461.
(6) Sarvagalla, S.; Syed, S. B.; Coumar, M. S. An Overview of Computational Methods, Tools, Servers, and Databases for Drug Repurposing. In *In Silico Drug Design*; Elsevier, 2019; pp 743−780. DOI: 10.1016/B978-0-12-816125-8.00025-0.
(7) Richardson, P.; Griffin, I.; Tucker, C.; Smith, D.; Oechsle, O.; Phelan, A.; Rawling, M.; Savory, E.; Stebbing, J. Baricitinib as Potential Treatment for 2019-NCoV Acute Respiratory Disease. *Lancet* **2020**, *395*, e30−e31.
(8) Stebbing, J.; Phelan, A.; Griffin, I.; Tucker, C.; Oechsle, O.; Smith, D.; Richardson, P. COVID-19: Combining Antiviral and Anti-Inflammatory Treatments. *Lancet Infect. Dis.* **2020**, *20*, 400−402.
(9) Kalil, A. C.; Patterson, T. F.; Mehta, A. K.; Tomashek, K. M.; Wolfe, C. R.; Ghazaryan, V.; Marconi, V. C.; Ruiz-Palacios, G. M.; Hsieh, L.; Kline, S.; Tapson, V.; Iovine, N. M.; Jain, M. K.; Sweeney, D. A.; El Sahly, H. M.; Branche, A. R.; Regalado Pineda, J.; Lye, D. C.; Sandkovsky, U.; Luetkemeyer, A. F.; Cohen, S. H.; Finberg, R. W.; Jackson, P. E. H.; Taiwo, B.; Paules, C. I.; Arguinchona, H.; Erdmann, N.; Ahuja, N.; Frank, M.; Oh, M.; Kim, E.-S.; Tan, S. Y.; Mularski, R. A.; Nielsen, H.; Ponce, P. O.; Taylor, B. S.; Larson, L.; Rouphael, N. G.; Saklawi, Y.; Cantos, V. D.; Ko, E. R.; Engemann, J. J.; Amin, A. N.; Watanabe, M.; Billings, J.; Elie, M.-C.; Davey, R. T.; Burgess, T. H.; Ferreira, J.; Green, M.; Makowski, M.; Cardoso, A.; de Bono, S.; Bonnett, T.; Proschan, M.; Deye, G. A.; Dempsey, W.; Nayak, S. U.; Dodd, L. E.; Beigel, J. H. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N. Engl. J. Med.* **2021**, *384*, 795−807.
(10) Coronavirus (COVID-19) Update: FDA Authorizes Drug Combination for Treatment of COVID-19. *U.S. Food and Drug Administration*. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-combination-treatment-covid-19 (accessed 2021-06-12).
(11) Altay, O.; Mohammadi, E.; Lam, S.; Turkez, H.; Boren, J.; Nielsen, J.; Uhlen, M.; Mardinoglu, A. Current Status of COVID-19 Therapies and Drug Repositioning Applications. *iScience* **2020**, *23*, 101303.
(12) Sultana, J.; Crisafulli, S.; Gabbay, F.; Lynn, E.; Shakir, S.; Trifirò, G. Challenges for Drug Repurposing in the COVID-19 Pandemic Era. *Front. Pharmacol.* **2020**, *11*, 588654.
(13) Savosina, P. I.; Druzhilovskii, D. S.; Poroikov, V. V. COVID-19: Analysis of Drug Repositioning Practice. *Pharm. Chem. J.* **2021**, *54*, 989−996.
(14) Won, J.-H.; Lee, H. The Current Status of Drug Repositioning and Vaccine Developments for the COVID-19 Pandemic. *Int. J. Mol. Sci.* **2020**, *21*, 9775.
(15) Gao, K.; Nguyen, D. D.; Chen, J.; Wang, R.; Wei, G.-W. Repositioning of 8565 Existing Drugs for COVID-19. *J. Phys. Chem. Lett.* **2020**, *11*, 5373−5382.
(16) Galindez, G.; Matschinske, J.; Rose, T. D.; Sadegh, S.; Salgado-Albarrán, M.; Späth, J.; Baumbach, J.; Pauling, J. K. Lessons from the COVID-19 Pandemic for Advancing Computational Drug Repurposing Strategies. *Nat. Comput. Sci.* **2021**, *1*, 33−41.
(17) Kuleshov, M. V.; Stein, D. J.; Clarke, D. J. B.; Kropiwnicki, E.; Jagodnik, K. M.; Bartal, A.; Evangelista, J. E.; Hom, J.; Cheng, M.; Bailey, A.; Zhou, A.; Ferguson, L. B.; Lachmann, A.; Ma'ayan, A. The COVID-19 Drug and Gene Set Library. *Patterns* **2020**, *1*, 100090.
(18) Weston, S.; Coleman, C. M.; Haupt, R.; Logue, J.; Matthews, K.; Frieman, M. B. Broad Anti-Coronaviral Activity of FDA Approved Drugs against SARS-CoV-2 in Vitro and SARS-CoV in Vivo. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.03.25.008482.
(19) Bocci, G.; Bradfute, S. B.; Ye, C.; Garcia, M. J.; Parvathareddy, J.; Reichard, W.; Surendranathan, S.; Bansal, S.; Bologa, C. G.; Perkins, D. J.; Jonsson, C. B.; Sklar, L. A.; Oprea, T. I. Virtual and *In Vitro* Antiviral Screening Revive Therapeutic Drugs for COVID-19. *ACS Pharmacol. Transl. Sci.* **2020**, *3*, 1278−1292.
(20) Dittmar, M.; Lee, J. S.; Whig, K.; Segrist, E.; Li, M.; Jurado, K.; Samby, K.; Ramage, H.; Schultz, D.; Cherry, S. Drug Repurposing Screens Reveal FDA Approved Drugs Active against SARS-Cov-2. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.06.19.161042.
(21) Jeon, S.; Ko, M.; Lee, J.; Choi, I.; Byun, S. Y.; Park, S.; Shum, D.; Kim, S. Identification of Antiviral Drug Candidates against SARS-CoV-2 from FDA-Approved Drugs. *Antimicrob. Agents Chemother.* **2020**, *64*, e00819−e00820.
(22) Gorshkov, K.; Chen, C. Z.; Bostwick, R.; Rasmussen, L.; Xu, M.; Pradhan, M.; Tran, B. N.; Zhu, W.; Shamim, K.; Huang, W.; Hu, X.; Shen, M.; Klumpp-Thomas, C.; Itkin, Z.; Shinn, P.; Simeonov, A.; Michael, S.; Hall, M. D.; Lo, D. C.; Zheng, W. The SARS-CoV-2 Cytopathic Effect Is Blocked with Autophagy Modulators. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.05.16.091520.
(23) Choy, K.-T.; Wong, A. Y.-L.; Kaewpreedee, P.; Sia, S. F.; Chen, D.; Hui, K. P. Y.; Chu, D. K. W.; Chan, M. C. W.; Cheung, P. P.-H.; Huang, X.; Peiris, M.; Yen, H.-L. Remdesivir, Lopinavir, Emetine, and Homoharringtonine Inhibit SARS-CoV-2 Replication in Vitro. *Antiviral Res.* **2020**, *178*, 104786.
(24) Zhu, W.; Xu, M.; Chen, C. Z.; Guo, H.; Shen, M.; Hu, X.; Shinn, P.; Klumpp-Thomas, C.; Michael, S. G.; Zheng, W. Identification of SARS-CoV-2 3CL Protease Inhibitors by a Quantitative High-Throughput Screening. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.07.17.207019.

(25) Ge, Y.; Tian, T.; Huang, S.; Wan, F.; Li, J.; Li, S.; Yang, H.; Hong, L.; Wu, N.; Yuan, E.; Cheng, L.; Lei, Y.; Shu, H.; Feng, X.; Jiang, Z.; Chi, Y.; Guo, X.; Cui, L.; Xiao, L.; Li, Z.; Yang, C.; Miao, Z.; Tang, H.; Chen, L.; Zeng, H.; Zhao, D.; Zhu, F.; Shen, X.; Zeng, J. A Data-Driven Drug Repositioning Framework Discovered a Potential Therapeutic Agent Targeting COVID-19. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.03.11.986836.

(26) Yamamoto, N.; Matsuyama, S.; Hoshino, T.; Yamamoto, N. Nelfinavir Inhibits Replication of Severe Acute Respiratory Syndrome Coronavirus 2 in Vitro. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.04.06.026476.

(27) Riva, L.; Yuan, S.; Yin, X.; Martin-Sancho, L.; Matsunaga, N.; Pache, L.; Burgstaller-Muehlbacher, S.; De Jesus, P. D.; Teriete, P.; Hull, M. V.; Chang, M. W.; Chan, J. F.-W.; Cao, J.; Poon, V. K.-M.; Herbert, K. M.; Cheng, K.; Nguyen, T.-T. H.; Rubanov, A.; Pu, Y.; Nguyen, C.; Choi, A.; Rathnasinghe, R.; Schotsaert, M.; Miorin, L.; Dejosez, M.; Zwaka, T. P.; Sit, K.-Y.; Martinez-Sobrido, L.; Liu, W.-C.; White, K. M.; Chapman, M. E.; Lendy, E. K.; Glynne, R. J.; Albrecht, R.; Ruppin, E.; Mesecar, A. D.; Johnson, J. R.; Benner, C.; Sun, R.; Schultz, P. G.; Su, A. I.; García-Sastre, A.; Chatterjee, A. K.; Yuen, K.-Y.; Chanda, S. K. Discovery of SARS-CoV-2 Antiviral Drugs through Large-Scale Compound Repurposing. *Nature* **2020**, *586*, 113−119.

(28) Fan, H.-H.; Wang, L.-Q.; Liu, W.-L.; An, X.-P.; Liu, Z.-D.; He, X.-Q.; Song, L.-H.; Tong, Y.-G. Repurposing of Clinically Approved Drugs for Treatment of Coronavirus Disease 2019 in a 2019-Novel Coronavirus-Related Coronavirus Model. *Chin. Med. J. (Engl.)* **2020**, *133*, 1051−1056.

(29) Yuan, S.; Chan, J. F. W.; Chik, K. K. H.; Chan, C. C. Y.; Tsang, J. O. L.; Liang, R.; Cao, J.; Tang, K.; Chen, L.-L.; Wen, K.; Cai, J.-P.; Ye, Z.-W.; Lu, G.; Chu, H.; Jin, D.-Y.; Yuen, K.-Y. Discovery of the FDA-Approved Drugs Bexarotene, Cetilistat, Diiodohydroxyquinoline, and Abiraterone as Potential COVID-19 Treatments with a Robust Two-Tier Screening System. *Pharmacol. Res.* **2020**, *159*, 104960.

(30) Drayman, N.; Jones, K. A.; Azizi, S.-A.; Froggatt, H. M.; Tan, K.; Maltseva, N. I.; Chen, S.; Nicolaescu, V.; Dvorkin, S.; Furlong, K.; Kathayat, R. S.; Firpo, M. R.; Mastrodomenico, V.; Bruce, E. A.; Schmidt, M. M.; Jedrzejczak, R.; Muñoz-Alía, M. Á.; Schuster, B.; Nair, V.; Botten, J. W.; Brooke, C. B.; Baker, S. C.; Mounce, B. C.; Heaton, N. S.; Dickinson, B. C.; Jaochimiak, A.; Randall, G.; Tay, S. Drug Repurposing Screen Identifies Masitinib as a 3CLpro Inhibitor That Blocks Replication of SARS-CoV-2 in Vitro. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.08.31.274639.

(31) Touret, F.; Gilles, M.; Barral, K.; Nougairède, A.; van Helden, J.; Decroly, E.; de Lamballerie, X.; Coutard, B. In Vitro Screening of a FDA Approved Chemical Library Reveals Potential Inhibitors of SARS-CoV-2 Replication. *Sci. Rep.* **2020**, *10*, 13093.

(32) Xing, J.; Shankar, R.; Drelich, A.; Paithankar, S.; Chekalin, E.; Dexheimer, T.; Chua, M.-S.; Rajasekaran, S.; Tseng, C.-T. K.; Chen, B. Analysis of Infected Host Gene Expression Reveals Repurposed Drug Candidates and Time-Dependent Host Response Dynamics for COVID-19. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.04.07.030734.

(33) Caly, L.; Druce, J. D.; Catton, M. G.; Jans, D. A.; Wagstaff, K. M. The FDA-Approved Drug Ivermectin Inhibits the Replication of SARS-CoV-2 in Vitro. *Antiviral Res.* **2020**, *178*, 104787.

(34) 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**, *30*, 269−271.

(35) Xiao, X.; Wang, C.; Chang, D.; Wang, Y.; Dong, X.; Jiao, T.; Zhao, Z.; Ren, L.; Dela Cruz, C. S.; Sharma, L.; Lei, X.; Wang, J. Identification of Potent and Safe Antiviral Therapeutic Candidates against SARS-CoV-2. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.07.06.188953.

(36) Gordon, D. E.; Jang, G. M.; Bouhaddou, M.; Xu, J.; Obernier, K.; White, K. M.; O'Meara, M. J.; Rezelj, V. V.; Guo, J. Z.; Swaney, D. L.; Tummino, T. A.; Hüttenhain, R.; Kaake, R. M.; Richards, A. L.; Tutuncuoglu, B.; Foussard, H.; Batra, J.; Haas, K.; Modak, M.; Kim, M.; Haas, P.; Polacco, B. J.; Braberg, H.; Fabius, J. M.; Eckhardt, M.; Soucheray, M.; Bennett, M. J.; Cakir, M.; McGregor, M. J.; Li, Q.; Meyer, B.; Roesch, F.; Vallet, T.; Mac Kain, A.; Miorin, L.; Moreno, E.; Naing, Z. Z. C.; Zhou, Y.; Peng, S.; Shi, Y.; Zhang, Z.; Shen, W.; Kirby, I. T.; Melnyk, J. E.; Chorba, J. S.; Lou, K.; Dai, S. A.; Barrio-Hernandez, I.; Memon, D.; Hernandez-Armenta, C.; Lyu, J.; Mathy, C. J. P.; Perica, T.; Pilla, K. B.; Ganesan, S. J.; Saltzberg, D. J.; Rakesh, R.; Liu, X.; Rosenthal, S. B.; Calviello, L.; Venkataramanan, S.; Liboy-Lugo, J.; Lin, Y.; Huang, X.-P.; Liu, Y.; Wankowicz, S. A.; Bohn, M.; Safari, M.; Ugur, F. S.; Koh, C.; Savar, N. S.; Tran, Q. D.; Shengjuler, D.; Fletcher, S. J.; O'Neal, M. C.; Cai, Y.; Chang, J. C. J.; Broadhurst, D. J.; Klippsten, S.; Sharp, P. P.; Wenzell, N. A.; Kuzuoglu-Ozturk, D.; Wang, H.-Y.; Trenker, R.; Young, J. M.; Cavero, D. A.; Hiatt, J.; Roth, T. L.; Rathore, U.; Subramanian, A.; Noack, J.; Hubert, M.; Stroud, R. M.; Frankel, A. D.; Rosenberg, O. S.; Verba, K. A.; Agard, D. A.; Ott, M.; Emerman, M.; Jura, N.; von Zastrow, M.; Verdin, E.; Ashworth, A.; Schwartz, O.; d'Enfert, C.; Mukherjee, S.; Jacobson, M.; Malik, H. S.; Fujimori, D. G.; Ideker, T.; Craik, C. S.; Floor, S. N.; Fraser, J. S.; Gross, J. D.; Sali, A.; Roth, B. L.; Ruggero, D.; Taunton, J.; Kortemme, T.; Beltrao, P.; Vignuzzi, M.; García-Sastre, A.; Shokat, K. M.; Shoichet, B. K.; Krogan, N. J. A SARS-CoV-2 Protein Interaction Map Reveals Targets for Drug Repurposing. *Nature* **2020**, *583*, 459−468.

(37) Ku, K. B.; Shin, H. J.; Kim, H. S.; Kim, B.-T.; Kim, S.-J.; Kim, C. Repurposing Screens of FDA-Approved Drugs Identify 29 Inhibitors of SARS-CoV-2. *J. Microbiol. Biotechnol.* **2020**, *30*, 1843−1853.

(38) Brimacombe, K. R.; Zhao, T.; Eastman, R. T.; Hu, X.; Wang, K.; Backus, M.; Baljinnyam, B.; Chen, C. Z.; Chen, L.; Eicher, T.; Ferrer, M.; Fu, Y.; Gorshkov, K.; Guo, H.; Hanson, Q. M.; Itkin, Z.; Kales, S. C.; Klumpp-Thomas, C.; Lee, E. M.; Michael, S.; Mierzwa, T.; Patt, A.; Pradhan, M.; Renn, A.; Shinn, P.; Shrimp, J. H.; Viraktamath, A.; Wilson, K. M.; Xu, M.; Zakharov, A. V.; Zhu, W.; Zheng, W.; Simeonov, A.; Mathé, E. A.; Lo, D. C.; Hall, M. D.; Shen, M. An OpenData Portal to Share COVID-19 Drug Repurposing Data in Real Time. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.06.04.135046.

(39) OpenData, COVID-19, 2020. *National Center for Advancing Translational Sciences (NCATS*. https://opendata.ncats.nih.gov/covid19/ (accessed 2020-12-26).

(40) KC, G. B.; Bocci, G.; Verma, S.; Hassan, M. M.; Holmes, J.; Yang, J. J.; Sirimulla, S.; Oprea, T. I. A Machine Learning Platform to Estimate Anti-SARS-CoV-2 Activities. *Nat. Mach. Intell.* **2021**, *3*, 527.

(41) Kalliokoski, T.; Kramer, C.; Vulpetti, A.; Gedeck, P. Comparability of Mixed IC50 Data − A Statistical Analysis. *PLoS One* **2013**, *8*, No. e61007.

(42) Ko, M.; Chang, S. Y.; Byun, S. Y.; Ianevski, A.; Choi, I.; d'Alexandry d'Orengiani, A.-L. P. H.; Kainov, D. E.; Shum, D.; Min, J.-Y.; Windisch, M. P. Screening of FDA-Approved Drugs Using a MERS-CoV Clinical Isolate from South Korea Identifies Potential Therapeutic Options for COVID-19. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.02.25.965582.

(43) Chen, C. Z.; Shinn, P.; Itkin, Z.; Eastman, R. T.; Bostwick, R.; Rasmussen, L.; Huang, R.; Shen, M.; Hu, X.; Wilson, K. M.; Brooks, B.; Guo, H.; Zhao, T.; Klump-Thomas, C.; Simeonov, A.; Michael, S. G.; Lo, D. C.; Hall, M. D.; Zheng, W. Drug Repurposing Screen for Compounds Inhibiting the Cytopathic Effect of SARS-CoV-2. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.08.18.255877.

(44) Osada, N.; Kohara, A.; Yamaji, T.; Hirayama, N.; Kasai, F.; Sekizuka, T.; Kuroda, M.; Hanada, K. The Genome Landscape of the African Green Monkey Kidney-Derived Vero Cell Line. *DNA Res.* **2014**, *21*, 673−683.

(45) Matsuyama, S.; Nao, N.; Shirato, K.; Kawase, M.; Saito, S.; Takayama, I.; Nagata, N.; Sekizuka, T.; Katoh, H.; Kato, F.; Sakata, M.; Tahara, M.; Kutsuna, S.; Ohmagari, N.; Kuroda, M.; Suzuki, T.; Kageyama, T.; Takeda, M. Enhanced Isolation of SARS-CoV-2 by TMPRSS2-Expressing Cells. *Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117*, 7001−7003.

https://doi.org/10.1021/acs.jcim.1c00384
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

(46) Ren, X.; Glende, J.; Al-Falah, M.; de Vries, V.; Schwegmann-Wessels, C.; Qu, X.; Tan, L.; Tschernig, T.; Deng, H.; Naim, H. Y.; Herrler, G. Analysis of ACE2 in Polarized Epithelial Cells: Surface Expression and Function as Receptor for Severe Acute Respiratory Syndrome-Associated Coronavirus. *J. Gen. Virol.* **2006**, *87*, 1691−1695.
(47) Desmyter, J.; Melnick, J. L.; Rawls, W. E. Defectiveness of Interferon Production and of Rubella Virus Interference in a Line of African Green Monkey Kidney Cells (Vero). *J. Virol.* **1968**, *2*, 955−961.
(48) Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T. S.; Herrler, G.; Wu, N.-H.; Nitsche, A.; Müller, M. A.; Drosten, C.; Pöhlmann, S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **2020**, *181*, 271−280.
(49) Sungnak, W.; Huang, N.; Bécavin, C.; Berg, M.; Queen, R.; Litvinukova, M.; Talavera-López, C.; Maatz, H.; Reichart, D.; Sampaziotis, F.; Worlock, K. B.; Yoshida, M.; Barnes, J. L. SARS-CoV-2 Entry Factors Are Highly Expressed in Nasal Epithelial Cells Together with Innate Immune Genes. *Nat. Med.* **2020**, *26*, 681−687.
(50) Si, L.; Bai, H.; Rodas, M.; Cao, W.; Oh, C. Y.; Jiang, A.; Möller, R.; Hoagland, D.; Oishi, K.; Horiuchi, S.; Uhl, S.; Blanco-Melo, D.; Albrecht, R. A.; Liu, W.-C.; Jordan, T.; Nilsson-Payant, B. E.; Logue, J.; Haupt, R.; McGrath, M.; Weston, S.; Nurani, A.; Kim, S. M.; Zhu, D. Y.; Benam, K. H.; Goyal, G.; Gilpin, S. E.; Prantil-Baun, R.; Powers, R. K.; Carlson, K.; Frieman, M.; tenOever, B. R.; Ingber, D. E. Human Organ Chip-Enabled Pipeline to Rapidly Repurpose Therapeutics during Viral Pandemics. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.04.13.039917.
(51) Letko, M.; Marzi, A.; Munster, V. Functional Assessment of Cell Entry and Receptor Usage for SARS-CoV-2 and Other Lineage B Betacoronaviruses. *Nat. Microbiol.* **2020**, *5*, 562−569.
(52) Ellinger, B.; Bojkova, D.; Zaliani, A.; Cinatl, J.; Claussen, C.; Westhaus, S.; Reinshagen, J.; Kuzikov, M.; Wolf, M.; Geisslinger, G.; Gribbon, P.; Ciesek, S. Identification of Inhibitors of SARS-CoV-2 in-Vitro Cellular Toxicity in Human (Caco-2) Cells Using a Large Scale Drug Repurposing Collection. preprint, 2020. DOI: 10.21203/rs.3.rs-23951/v1.
(53) Lea, T. Caco-2 Cell Line. In *The Impact of Food Bioactives on Health*; Verhoeckx, K., Cotter, P., López-Expósito, I., Kleiveland, C., Lea, T., Mackie, A., Requena, T., Swiatecka, D., Wichers, H., Eds.; Springer International Publishing: Cham, 2015; pp 103−111. DOI: 10.1007/978-3-319-16104-4_10.
(54) Chu, H.; Chan, J. F.-W.; Yuen, T. T.-T.; Shuai, H.; Yuan, S.; Wang, Y.; Hu, B.; Yip, C. C.-Y.; Tsang, J. O.-L.; Huang, X.; Chai, Y.; Yang, D.; Hou, Y.; Chik, K. K.-H.; Zhang, X.; Fung, A. Y.-F.; Tsoi, H.-W.; Cai, J.-P.; Chan, W.-M.; Ip, J. D.; Chu, A. W.-H.; Zhou, J.; Lung, D. C.; Kok, K.-H.; To, K. K.-W.; Tsang, O. T.-Y.; Chan, K.-H.; Yuen, K.-Y. Comparative Tropism, Replication Kinetics, and Cell Damage Profiling of SARS-CoV-2 and SARS-CoV with Implications for Clinical Manifestations, Transmissibility, and Laboratory Studies of COVID-19: An Observational Study. *Lancet Microbe* **2020**, *1*, e14−e23.
(55) Yao, H.; Lu, X.; Chen, Q.; Xu, K.; Chen, Y.; Cheng, L.; Liu, F.; Wu, Z.; Wu, H.; Jin, C.; Zheng, M.; Wu, N.; Jiang, C.; Li, L. Patient-Derived Mutations Impact Pathogenicity of SARS-CoV-2; *medRxiv* preprint, 2020. DOI: 10.1101/2020.04.14.20060160.
(56) Luk, K.-C.; Mark, K.-K. Effect of Multiplicity of Infection on Transcription in Escherichia Coli Cells Infected by Bacteriophage Lambda. *J. Gen. Virol.* **1983**, *64*, 183−189.
(57) Postnikova, E.; Cong, Y.; DeWald, L. E.; Dyall, J.; Yu, S.; Hart, B. J.; Zhou, H.; Gross, R.; Logue, J.; Cai, Y.; Deiuliis, N.; Michelotti, J.; Honko, A. N.; Bennett, R. S.; Holbrook, M. R.; Olinger, G. G.; Hensley, L. E.; Jahrling, P. B. Testing Therapeutics in Cell-Based Assays: Factors That Influence the Apparent Potency of Drugs. *PLoS One* **2018**, *13*, No. e0194880.
(58) Wang, J. Fast Identification of Possible Drug Treatment of Coronavirus Disease-19 (COVID-19) through Computational Drug Repurposing Study. *J. Chem. Inf. Model.* **2020**, *60*, 3277−3286.
(59) Satarker, S.; Ahuja, T.; Banerjee, M.; E, V. B.; Dogra, S.; Agarwal, T.; Nampoothiri, M. Hydroxychloroquine in COVID-19: Potential Mechanism of Action Against SARS-CoV-2. *Curr. Pharmacol. Rep.* **2020**, *6*, 203−211.
(60) Zhang, Y.; Kutateladze, T. G. Molecular Structure Analyses Suggest Strategies to Therapeutically Target SARS-CoV-2. *Nat. Commun.* **2020**, *11*, 2920.
(61) Yuan, S.; Yin, X.; Meng, X.; Chan, J. F.-W.; Ye, Z.-W.; Riva, L.; Pache, L.; Chan, C. C.-Y.; Lai, P.-M.; Chan, C. C.-S.; Poon, V. K.-M.; Lee, A. C.-Y.; Matsunaga, N.; Pu, Y.; Yuen, C.-K.; Cao, J.; Liang, R.; Tang, K.; Sheng, L.; Du, Y.; Xu, W.; Lau, C.-Y.; Sit, K.-Y.; Au, W.-K.; Wang, R.; Zhang, Y.-Y.; Tang, Y.-D.; Clausen, T. M.; Pihl, J.; Oh, J.; Sze, K.-H.; Zhang, A. J.; Chu, H.; Kok, K.-H.; Wang, D.; Cai, X.-H.; Esko, J. D.; Hung, I. F.-N.; Li, R. A.; Chen, H.; Sun, H.; Jin, D.-Y.; Sun, R.; Chanda, S. K.; Yuen, K.-Y. Clofazimine Broadly Inhibits Coronaviruses Including SARS-CoV-2. *Nature* **2021**, *593*, 418−423.
(62) Liu, Y.; Hur, J.; Chan, W. K. B.; Wang, Z.; Xie, J.; Sun, D.; Handelman, S.; Sexton, J.; Yu, H.; He, Y. Ontological Modeling and Analysis of Experimentally or Clinically Verified Drugs against Coronavirus Infection. *Sci. Data* **2021**, *8*, 16.
(63) Rogosnitzky, M.; Okediji, P.; Koman, I. Cepharanthine: A Review of the Antiviral Potential of a Japanese-Approved Alopecia Drug in COVID-19. *Pharmacol. Rep.* **2020**, *72*, 1509−1516.
(64) Hong, S.; Chang, J.; Jeong, K.; Lee, W. Raloxifene as a Treatment Option for Viral Infections. *J. Microbiol.* **2021**, *59*, 124−131.
(65) Cho, J.; Lee, Y. J.; Kim, J.-H.; Kim, S.; Kim, S. S.; Choi, B.-S.; Choi, J.-H. Antiviral Activity of Digoxin and Ouabain against SARS-CoV-2 Infection and Its Implication for COVID-19. preprint, 2020. DOI: 10.21203/rs.3.rs-34731/v1.
(66) Pindiprolu, S. K. S.S.; Kumar, C. S. P.; Kumar Golla, V. S.; P., L.; K., S. C.; S.K., E. B.; R.K., R. Pulmonary Delivery of Nanostructured Lipid Carriers for Effective Repurposing of Salinomycin as an Antiviral Agent. *Med. Hypotheses* **2020**, *143*, 109858.
(67) Yin, W.; Mao, C.; Luan, X.; Shen, D.-D.; Shen, Q.; Su, H.; Wang, X.; Zhou, F.; Zhao, W.; Gao, M.; Chang, S.; Xie, Y.-C.; Tian, G.; Jiang, H.-W.; Tao, S.-C.; Shen, J.; Jiang, Y.; Jiang, H.; Xu, Y.; Zhang, S.; Zhang, Y.; Xu, H. E. Structural Basis for Inhibition of the RNA-Dependent RNA Polymerase from SARS-CoV-2 by Remdesivir. *Science* **2020**, *368*, 1499−1504.
(68) Piplani, S.; Singh, P.; Petrovsky, N.; Winkler, D. A. Computational Screening of Repurposed Drugs and Natural Products against SARS-Cov-2 Main Protease (Mpro) as Potential COVID-19 Therapies. *arXiv:2009.00744v1* preprint, 2020.
(69) Al-Khafaji, K.; Al-Duhaidahawi, D.; Taskin Tok, T. Using Integrated Computational Approaches to Identify Safe and Rapid Treatment for SARS-CoV-2. *J. Biomol. Struct. Dyn.* **2020**, 1−9.
(70) Shah, B.; Modi, P.; Sagar, S. R. In Silico Studies on Therapeutic Agents for COVID-19: Drug Repurposing Approach. *Life Sci.* **2020**, *252*, 117652.
(71) Hall, D. C.; Ji, H.-F. A Search for Medications to Treat COVID-19 via in Silico Molecular Docking Models of the SARS-CoV-2 Spike Glycoprotein and 3CL Protease. *Travel Med. Infect. Dis.* **2020**, *35*, 101646.
(72) Sachdeva, C.; Wadhwa, A.; Kumari, A.; Hussain, F.; Jha, P.; Kaushik, N. K. *In Silico* Potential of Approved Antimalarial Drugs for Repurposing Against COVID-19. *OMICS J. Integr. Biol.* **2020**, *24*, 568−580.
(73) Li, Z.; Li, X.; Huang, Y.-Y.; Wu, Y.; Liu, R.; Zhou, L.; Lin, Y.; Wu, D.; Zhang, L.; Liu, H.; Xu, X.; Yu, K.; Zhang, Y.; Cui, J.; Zhan, C.-G.; Wang, X.; Luo, H.-B. Identify Potent SARS-CoV-2 Main Protease Inhibitors via Accelerated Free Energy Perturbation-Based Virtual Screening of Existing Drugs. *Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117*, 27381−27387.
(74) Walls, A. C.; Park, Y.-J.; Tortorici, M. A.; Wall, A.; McGuire, A. T.; Veesler, D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell* **2020**, *181*, 281−292.

https://doi.org/10.1021/acs.jcim.1c00384
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

(75) Watashi, K. Identifying and Repurposing Antiviral Drugs against Severe Acute Respiratory Syndrome Coronavirus 2 with in Silico and in Vitro Approaches. *Biochem. Biophys. Res. Commun.* **2021**, *538*, 137.
(76) Buchrieser, J.; Dufloo, J.; Hubert, M.; Monel, B.; Planas, D.; Rajah, M. M.; Planchais, C.; Porrot, F.; Guivel-Benhassine, F.; Van der Werf, S.; Casartelli, N.; Mouquet, H.; Bruel, T.; Schwartz, O. Syncytia Formation by SARS-CoV-2-infected Cells. *EMBO J.* **2020**, *39*, na.
(77) Lan, J.; Ge, J.; Yu, J.; Shan, S.; Zhou, H.; Fan, S.; Zhang, Q.; Shi, X.; Wang, Q.; Zhang, L.; Wang, X. Structure of the SARS-CoV-2 Spike Receptor-Binding Domain Bound to the ACE2 Receptor. *Nature* **2020**, *581*, 215−220.
(78) Kalamatianos, K. Drug Repurposing for Coronavirus (COVID-19): In Silico Screening of Known Drugs Against the SARS-CoV-2 Spike Protein Bound to Angiotensin Converting Enzyme 2 (ACE2) (6M0J). *medRxiv* preprint, 2020. DOI: 10.26434/chemrxiv.12857678.v1.
(79) Hussien, M. A.; Abdelaziz, A. E. M. Molecular Docking Suggests Repurposing of Brincidofovir as a Potential Drug Targeting SARS-CoV-2 ACE2 Receptor and Main Protease. *Netw. Model. Anal. Health Inform. Bioinforma.* **2020**, *9*, 56.
(80) Choudhary, S.; Malik, Y. S.; Tomar, S. Identification of SARS-CoV-2 Cell Entry Inhibitors by Drug Repurposing Using in Silico Structure-Based Virtual Screening Approach. *Front. Immunol.* **2020**, *11*, 1664.
(81) Chen, C. Z.; Xu, M.; Pradhan, M.; Gorshkov, K.; Petersen, J. D.; Straus, M. R.; Zhu, W.; Shinn, P.; Guo, H.; Shen, M.; Klumpp-Thomas, C.; Michael, S. G.; Zimmerberg, J.; Zheng, W.; Whittaker, G. R. Identifying SARS-CoV-2 Entry Inhibitors through Drug Repurposing Screens of SARS-S and MERS-S Pseudotyped Particles. *ACS Pharmacol. Transl. Sci.* **2020**, *3*, 1165−1175.
(82) Chu, C. K.; Gadthula, S.; Chen, X.; Choo, H.; Olgen, S.; Barnard, D. L.; Sidwell, R. W. Antiviral Activity of Nucleoside Analogues against SARS-Coronavirus (SARS-CoV). *Antivir. Chem. Chemother.* **2006**, *17*, 285−289.
(83) Ahmad, J.; Ikram, S.; Ahmad, F.; Rehman, I. U.; Mushtaq, M. SARS-CoV-2 RNA Dependent RNA Polymerase (RdRp) − A Drug Repurposing Study. *Heliyon* **2020**, *6*, No. e04502.
(84) Baby, K.; Maity, S.; Mehta, C. H.; Suresh, A.; Nayak, U. Y.; Nayak, Y. Targeting SARS-CoV-2 RNA-Dependent RNA Polymerase: An in Silico Drug Repurposing for COVID-19. *F1000Research* **2020**, *9*, 1166.
(85) Zhu, W.; Chen, C. Z.; Gorshkov, K.; Xu, M.; Lo, D. C.; Zheng, W. RNA-Dependent RNA Polymerase as a Target for COVID-19 Drug Discovery. *SLAS Discovery Adv. Sci. Drug Discovery* **2020**, *25*, 1141−1151.
(86) Wang, J.; Reiss, K.; Shi, Y.; Lolis, E.; Lisi, G. P.; Batista, V. S. Mechanism of Inhibition of the Reproduction of SARS-CoV-2 and Ebola Viruses by Remdesivir. *Biochemistry* **2021**, *60*, 1869−1875.
(87) Wu, C.; Liu, Y.; Yang, Y.; Zhang, P.; Zhong, W.; Wang, Y.; Wang, Q.; Xu, Y.; Li, M.; Li, X.; Zheng, M.; Chen, L.; Li, H. Analysis of Therapeutic Targets for SARS-CoV-2 and Discovery of Potential Drugs by Computational Methods. *Acta Pharm. Sin. B* **2020**, *10*, 766−788.
(88) Kandeel, M.; Kitade, Y.; Almubarak, A. Repurposing FDA-Approved Phytomedicines, Natural Products, Antivirals and Cell Protectives against SARS-CoV-2 (COVID-19) RNA-Dependent RNA Polymerase. *PeerJ* **2020**, *8*, No. e10480.
(89) Lindner, H. A.; Fotouhi-Ardakani, N.; Lytvyn, V.; Lachance, P.; Sulea, T.; Ménard, R. The Papain-Like Protease from the Severe Acute Respiratory Syndrome Coronavirus Is a Deubiquitinating Enzyme. *J. Virol.* **2005**, *79*, 15199−15208.
(90) Prajapat, M.; Sarma, P.; Shekhar, N.; Avti, P.; Sinha, S.; Kaur, H.; Kumar, S.; Bhattacharyya, A.; Kumar, H.; Bansal, S.; Medhi, B. Drug for Corona Virus: A Systematic Review. *Indian J. Pharmacol.* **2020**, *52*, 56.
(91) Shin, D.; Mukherjee, R.; Grewe, D.; Bojkova, D.; Baek, K.; Bhattacharya, A.; Schulz, L.; Widera, M.; Mehdipour, A. R.; Tascher, G.; Geurink, P. P.; Wilhelm, A.; van der Heden van Noort, G. J.; Ovaa, H.; Müller, S.; Knobeloch, K.-P.; Rajalingam, K.; Schulman, B. A.; Cinatl, J.; Hummer, G.; Ciesek, S.; Dikic, I. Papain-like Protease Regulates SARS-CoV-2 Viral Spread and Innate Immunity. *Nature* **2020**, *587*, 657−662.
(92) McClain, C. B.; Vabret, N. SARS-CoV-2: The Many Pros of Targeting PLpro. *Signal Transduct. Target. Ther.* **2020**, *5*, 223.
(93) Węglarz-Tomczak, E.; Tomczak, J. M.; Talma, M.; Brul, S. Ebselen as a Highly Active Inhibitor of PL ^{Pro} CoV2. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.05.17.100768.
(94) Ma, C.; Hu, Y.; Townsend, J. A.; Lagarias, P. I.; Marty, M. T.; Kolocouris, A.; Wang, J. Ebselen, Disulfiram, Carmofur, PX-12, Tideglusib, and Shikonin Are Nonspecific Promiscuous SARS-CoV-2 Main Protease Inhibitors. *ACS Pharmacol. Transl. Sci.* **2020**, *3*, 1265−1277.
(95) Ullrich, S.; Nitsche, C. The SARS-CoV-2 Main Protease as Drug Target. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 127377.
(96) Jin, Z.; Du, X.; Xu, Y.; Deng, Y.; Liu, M.; Zhao, Y.; Zhang, B.; Li, X.; Zhang, L.; Peng, C.; Duan, Y.; Yu, J.; Wang, L.; Yang, K.; Liu, F.; Jiang, R.; Yang, X.; You, T.; Liu, X.; Yang, X.; Bai, F.; Liu, H.; Liu, X.; Guddat, L. W.; Xu, W.; Xiao, G.; Qin, C.; Shi, Z.; Jiang, H.; Rao, Z.; Yang, H. Structure of Mpro from SARS-CoV-2 and Discovery of Its Inhibitors. *Nature* **2020**, *582*, 289−293.
(97) Gioia, M.; Ciaccio, C.; Calligari, P.; De Simone, G.; Sbardella, D.; Tundo, G.; Fasciglione, G. F.; Di Masi, A.; Di Pierro, D.; Bocedi, A.; Ascenzi, P.; Coletta, M. Role of Proteolytic Enzymes in the COVID-19 Infection and Promising Therapeutic Approaches. *Biochem. Pharmacol.* **2020**, *182*, 114225.
(98) Ghahremanpour, M. M.; Tirado-Rives, J.; Deshmukh, M.; Ippolito, J. A.; Zhang, C.-H.; de Vaca, I. C.; Liosi, M.-E.; Anderson, K. S.; Jorgensen, W. L. Identification of 14 Known Drugs as Inhibitors of the Main Protease of SARS-CoV-2. *bioRxiv* preprint, **2020**. DOI: 10.1101/2020.08.28.271957.
(99) Ma, C.; Sacco, M. D.; Hurst, B.; Townsend, J. A.; Hu, Y.; Szeto, T.; Zhang, X.; Tarbet, B.; Marty, M. T.; Chen, Y.; Wang, J. Boceprevir, GC-376, and Calpain Inhibitors II, XII Inhibit SARS-CoV-2 Viral Replication by Targeting the Viral Main Protease. *Cell Res.* **2020**, *30*, 678−692.
(100) Fu, L.; Ye, F.; Feng, Y.; Yu, F.; Wang, Q.; Wu, Y.; Zhao, C.; Sun, H.; Huang, B.; Niu, P.; Song, H.; Shi, Y.; Li, X.; Tan, W.; Qi, J.; Gao, G. F. Both Boceprevir and GC376 Efficaciously Inhibit SARS-CoV-2 by Targeting Its Main Protease. *Nat. Commun.* **2020**, *11*, 4417.
(101) Günther, S.; Reinke, P. Y. A.; Fernández-García, Y.; Lieske, J.; Lane, T. J.; Ginn, H. M.; Koua, F. H. M.; Ehrt, C.; Ewert, W.; Oberthuer, D.; Yefanov, O.; Meier, S.; Lorenzen, K.; Krichel, B.; Kopicki, J.-D.; Gelisio, L.; Brehm, W.; Dunkel, I.; Seychell, B.; Gieseler, H.; Norton-Baker, B.; Escudero-Pérez, B.; Domaracky, M.; Saouane, S.; Tolstikova, A.; White, T. A.; Hänle, A.; Groessler, M.; Fleckenstein, H.; Trost, F.; Galchenkova, M.; Gevorkov, Y.; Li, C.; Awel, S.; Peck, A.; Barthelmess, M.; Schlünzen, F.; Xavier, P. L.; Werner, N.; Andaleeb, H.; Ullah, N.; Falke, S.; Srinivasan, V.; Franca, B. A.; Schwinzer, M.; Brognaro, H.; Rogers, C.; Melo, D.; Zaitsev-Doyle, J. J.; Knoska, J.; Peña Murillo, G. E.; Mashhour, A. R.; Guicking, F.; Hennicke, V.; Fischer, P.; Hakanpää, J.; Meyer, J.; Gribbon, P.; Ellinger, B.; Kuzikov, M.; Wolf, M.; Beccari, A. R.; Bourenkov, G.; Stetten, D. von; Pompidor, G.; Bento, I.; Panneerselvam, S.; Karpics, I.; Schneider, T. R.; Garcia Alai, M. M.; Niebling, S.; Günther, C.; Schmidt, C.; Schubert, R.; Han, H.; Boger, J.; Monteiro, D. C. F.; Zhang, L.; Sun, X.; Pletzer-Zelgert, J.; Wollenhaupt, J.; Feiler, C. G.; Weiss, M. S.; Schulz, E.-C.; Mehrabi, P.; Karničar, K.; Usenik, A.; Loboda, J.; Tidow, H.; Chari, A.; Hilgenfeld, R.; Uetrecht, C.; Cox, R.; Zaliani, A.; Beck, T.; Rarey, M.; Günther, S.; Turk, D.; Hinrichs, W.; Chapman, H. N.; Pearson, A. R.; Betzel, C.; Meents, A. Inhibition of SARS-CoV-2 Main Protease by Allosteric Drug-Binding. *bioRxiv* preprint, **2020**. DOI: 10.1101/2020.11.12.378422.
(102) Ehrmann, F. R.; Stojko, J.; Metz, A.; Debaene, F.; Barandun, L. J.; Heine, A.; Diederich, F.; Cianférani, S.; Reuter, K.; Klebe, G. Soaking Suggests "Alternative Facts": Only Co-Crystallization

Discloses Major Ligand-Induced Interface Rearrangements of a Homodimeric TRNA-Binding Protein Indicating a Novel Mode-of-Inhibition. *PLoS One* **2017**, *12*, No. e0175723.
(103) Beck, B. R.; Shin, B.; Choi, Y.; Park, S.; Kang, K. Predicting Commercially Available Antiviral Drugs That May Act on the Novel Coronavirus (SARS-CoV-2) through a Drug-Target Interaction Deep Learning Model. *Comput. Struct. Biotechnol. J.* **2020**, *18*, 784−790.
(104) Maffucci, I.; Contini, A. In Silico Drug Repurposing for SARS-CoV-2 Main Proteinase and Spike Proteins. *J. Proteome Res.* **2020**, *19*, 4637−4648.
(105) Alexpandi, R.; De Mesquita, J. F.; Pandian, S. K.; Ravi, A. V. Quinolines-Based SARS-CoV-2 3CLpro and RdRp Inhibitors and Spike-RBD-ACE2 Inhibitor for Drug-Repurposing Against COVID-19: An in Silico Analysis. *Front. Microbiol.* **2020**, *11*, 1796.
(106) Pant, S.; Singh, M.; Ravichandiran, V.; Murty, U. S. N.; Srivastava, H. K. Peptide-like and Small-Molecule Inhibitors against Covid-19. *J. Biomol. Struct. Dyn.* **2021**, *39*, 2904−2913.
(107) Das, S.; Sarmah, S.; Lyndem, S.; Singha Roy, A. An Investigation into the Identification of Potential Inhibitors of SARS-CoV-2 Main Protease Using Molecular Docking Study. *J. Biomol. Struct. Dyn.* **2020**, 1−11.
(108) Kumar, Y.; Singh, H.; Patel, C. N. In Silico Prediction of Potential Inhibitors for the Main Protease of SARS-CoV-2 Using Molecular Docking and Dynamics Simulation Based Drug-Repurposing. *J. Infect. Public Health* **2020**, *13*, 1210−1223.
(109) Sencanski, M.; Perovic, V.; Pajovic, S. B.; Adzic, M.; Paessler, S.; Glisic, S. Drug Repurposing for Candidate SARS-CoV-2 Main Protease Inhibitors by a Novel In Silico Method. *Molecules* **2020**, *25*, 3830.
(110) Mamidala, E.; Davella, R.; Gurrapu, S.; Shivakrishna, P. In Silico Identification of Clinically Approved Medicines against the Main Protease of SARS-CoV-2, Causative Agent of Covid-19. *arXiv:2004.12055v1* preprint, 2020.
(111) Cavasotto, C. N.; Di Filippo, J. I. *In Silico* Drug Repurposing for COVID-19: Targeting SARS-CoV-2 Proteins through Docking and Consensus Ranking. *Mol. Inf.* **2021**, *40*, 2000115.
(112) Pinzi, L.; Tinivella, A.; Caporuscio, F.; Rastelli, G. Drug Repurposing and Polypharmacology to Fight SARS-CoV-2 through the Inhibition of the Main Protease. preprint, 2020. DOI: 10.21203/rs.3.rs-27222/v1.
(113) Farag, A.; Wang, P.; Boys, I. N.; L. Eitson, J.; Ohlson, M. B.; Fan, W.; McDougal, M. B.; Ahmed, M.; W. Schoggins, J.; Sadek, H. Identification of Atovaquone, Ouabain and Mebendazole as FDA Approved Drugs Tar-Geting SARS-CoV-2 (Version 4). *ChemRxiv* preprint, 2020. DOI: 10.26434/chemrxiv.12003930.
(114) Sharma, S.; Deep, S. *In-Silico Drug Repurposing for Targeting SARS-CoV-2 Mpro*. *ChemRxiv* preprint, 2020. DOI: 10.26434/chemrxiv.12210845.v1.
(115) Mittal, L.; Kumari, A.; Srivastava, M.; Singh, M.; Asthana, S. Identification of Potential Molecules against COVID-19 Main Protease through Structure-Guided Virtual Screening Approach. *J. Biomol. Struct. Dyn.* **2021**, *39*, 3662−3680.
(116) Huynh, T.; Wang, H.; Luan, B. *In Silico* Exploration of the Molecular Mechanism of Clinically Oriented Drugs for Possibly Inhibiting SARS-CoV-2's Main Protease. *J. Phys. Chem. Lett.* **2020**, *11*, 4413−4420.
(117) Shrimp, J. H.; Kales, S. C.; Sanderson, P. E.; Simeonov, A.; Shen, M.; Hall, M. D. An Enzymatic TMPRSS2 Assay for Assessment of Clinical Candidates and Discovery of Inhibitors as Potential Treatment of COVID-19. *ACS Pharmacol. Transl. Sci.* **2020**, *3*, 997−1007.
(118) Hoffmann, M.; Hofmann-Winkler, H.; Smith, J. C.; Krüger, N.; Sørensen, L. K.; Søgaard, O. S.; Hasselstrøm, J. B.; Winkler, M.; Hempel, T.; Raich, L.; Olsson, S.; Yamazoe, T.; Yamatsuta, K.; Mizuno, H.; Ludwig, S.; Noé, F.; Sheltzer, J. M.; Kjolby, M.; Pöhlmann, S. Camostat Mesylate Inhibits SARS-CoV-2 Activation by TMPRSS2-Related Proteases and Its Metabolite GBPA Exerts Antiviral Activity. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.08.05.237651.
(119) Peiffer, A. L.; Garlick, J. M.; Wu, Y.; Soellner, M. B.; Brooks, C. L.; Mapp, A. K. TMPRSS2 Inhibitor Discovery Facilitated through an in Silico and Biochemical Screening Platform. *bioRxiv* preprint, 2021. DOI: 10.1101/2021.03.22.436465.
(120) Singh, R.; Gautam, A.; Chandel, S.; Sharma, V.; Ghosh, A.; Dey, D.; Roy, S.; Ravichandiran, V.; Ghosh, D. Computational Screening of FDA Approved Drugs of Fungal Origin That May Interfere with SARS-CoV-2 Spike Protein Activation, Viral RNA Replication, and Post-translational Modification: A Multiple Target Approach. *Silico Pharmacol.* **2021**, *9*, 27.
(121) Kawase, M.; Shirato, K.; van der Hoek, L.; Taguchi, F.; Matsuyama, S. Simultaneous Treatment of Human Bronchial Epithelial Cells with Serine and Cysteine Protease Inhibitors Prevents Severe Acute Respiratory Syndrome Coronavirus Entry. *J. Virol.* **2012**, *86*, 6537−6545.
(122) Trezza, A.; Iovinelli, D.; Santucci, A.; Prischi, F.; Spiga, O. An Integrated Drug Repurposing Strategy for the Rapid Identification of Potential SARS-CoV-2 Viral Inhibitors. *Sci. Rep.* **2020**, *10*, 13866.
(123) Wang, X.; Guan, Y. COVID-19 Drug Repurposing: A Review of Computational Screening Methods, Clinical Trials, and Protein Interaction Assays. *Med. Res. Rev.* **2021**, *41*, 5−28.
(124) Saha, A.; Sharma, A. R.; Bhattacharya, M.; Sharma, G.; Lee, S.-S.; Chakraborty, C. Probable Molecular Mechanism of Remdesivir for the Treatment of COVID-19: Need to Know More. *Arch. Med. Res.* **2020**, *51*, 585−586.
(125) Grein, J.; Ohmagari, N.; Shin, D.; Diaz, G.; Asperges, E.; Castagna, A.; Feldt, T.; Green, G.; Green, M. L.; Lescure, F.-X.; Nicastri, E.; Oda, R.; Yo, K.; Quiros-Roldan, E.; Studemeister, A.; Redinski, J.; Ahmed, S.; Bernett, J.; Chelliah, D.; Chen, D.; Chihara, S.; Cohen, S. H.; Cunningham, J.; D'Arminio Monforte, A.; Ismail, S.; Kato, H.; Lapadula, G.; L'Her, E.; Maeno, T.; Majumder, S.; Massari, M.; Mora-Rillo, M.; Mutoh, Y.; Nguyen, D.; Verweij, E.; Zoufaly, A.; Osinusi, A. O.; DeZure, A.; Zhao, Y.; Zhong, L.; Chokkalingam, A.; Elboudwarej, E.; Telep, L.; Timbs, L.; Henne, I.; Sellers, S.; Cao, H.; Tan, S. K.; Winterbourne, L.; Desai, P.; Mera, R.; Gaggar, A.; Myers, R. P.; Brainard, D. M.; Childs, R.; Flanigan, T. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *N. Engl. J. Med.* **2020**, *382*, 2327−2336.
(126) Beigel, J. H.; Tomashek, K. M.; Dodd, L. E.; Mehta, A. K.; Zingman, B. S.; Kalil, A. C.; Hohmann, E.; Chu, H. Y.; Luetkemeyer, A.; Kline, S.; Lopez de Castilla, D.; Finberg, R. W.; Dierberg, K.; Tapson, V.; Hsieh, L.; Patterson, T. F.; Paredes, R.; Sweeney, D. A.; Short, W. R.; Touloumi, G.; Lye, D. C.; Ohmagari, N.; Oh, M.; Ruiz-Palacios, G. M.; Benfield, T.; Fätkenheuer, G.; Kortepeter, M. G.; Atmar, R. L.; Creech, C. B.; Lundgren, J.; Babiker, A. G.; Pett, S.; Neaton, J. D.; Burgess, T. H.; Bonnett, T.; Green, M.; Makowski, M.; Osinusi, A.; Nayak, S.; Lane, H. C. Remdesivir for the Treatment of Covid-19 — Final Report. *N. Engl. J. Med.* **2020**, *383*, 1813−1826.
(127) Cai, Q.; Yang, M.; Liu, D.; Chen, J.; Shu, D.; Xia, J.; Liao, X.; Gu, Y.; Cai, Q.; Yang, Y.; Shen, C.; Li, X.; Peng, L.; Huang, D.; Zhang, J.; Zhang, S.; Wang, F.; Liu, J.; Chen, L.; Chen, S.; Wang, Z.; Zhang, Z.; Cao, R.; Zhong, W.; Liu, Y.; Liu, L. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. *Engineering* **2020**, *6*, 1192−1198.
(128) Deng, L.; Li, C.; Zeng, Q.; Liu, X.; Li, X.; Zhang, H.; Hong, Z.; Xia, J. Arbidol Combined with LPV/r versus LPV/r Alone against Corona Virus Disease 2019: A Retrospective Cohort Study. *J. Infect.* **2020**, *81*, e1−e5.
(129) Wang, Y.; Zhang, D.; Du, G.; Du, R.; Zhao, J.; Jin, Y.; Fu, S.; Gao, L.; Cheng, Z.; Lu, Q.; Hu, Y.; Luo, G.; Wang, K.; Lu, Y.; Li, H.; Wang, S.; Ruan, S.; Yang, C.; Mei, C.; Wang, Y.; Ding, D.; Wu, F.; Tang, X.; Ye, X.; Ye, Y.; Liu, B.; Yang, J.; Yin, W.; Wang, A.; Fan, G.; Zhou, F.; Liu, Z.; Gu, X.; Xu, J.; Shang, L.; Zhang, Y.; Cao, L.; Guo, T.; Wan, Y.; Qin, H.; Jiang, Y.; Jaki, T.; Hayden, F. G.; Horby, P. W.; Cao, B.; Wang, C. Remdesivir in Adults with Severe COVID-19: A Randomised, Double-Blind, Placebo-Controlled, Multicentre Trial. *Lancet* **2020**, *395*, 1569−1578.
(130) Antinori, S.; Cossu, M. V.; Ridolfo, A. L.; Rech, R.; Bonazzetti, C.; Pagani, G.; Gubertini, G.; Coen, M.; Magni, C.; Castelli, A.;

https://doi.org/10.1021/acs.jcim.1c00384
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

Borghi, B.; Colombo, R.; Giorgi, R.; Angeli, E.; Mileto, D.; Milazzo, L.; Vimercati, S.; Pellicciotta, M.; Corbellino, M.; Torre, A.; Rusconi, S.; Oreni, L.; Gismondo, M. R.; Giacomelli, A.; Meroni, L.; Rizzardini, G.; Galli, M. Compassionate Remdesivir Treatment of Severe Covid-19 Pneumonia in Intensive Care Unit (ICU) and Non-ICU Patients: Clinical Outcome and Differences in Post-Treatment Hospitalisation Status. *Pharmacol. Res.* **2020**, *158*, 104899.

(131) Chen, C.; Zhang, Y.; Huang, J.; Yin, P.; Cheng, Z.; Wu, J.; Chen, S.; Zhang, Y.; Chen, B.; Lu, M.; Luo, Y.; Ju, L.; Zhang, J.; Wang, X. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. *medRxiv* preprint, 2020. DOI: 10.1101/2020.03.17.20037432.

(132) Yuan, J.; Zou, R.; Zeng, L.; Kou, S.; Lan, J.; Li, X.; Liang, Y.; Ding, X.; Tan, G.; Tang, S.; Liu, L.; Liu, Y.; Pan, Y.; Wang, Z. The Correlation between Viral Clearance and Biochemical Outcomes of 94 COVID-19 Infected Discharged Patients. *Inflammation Res.* **2020**, *69*, 599−606.

(133) Yan, D.; Liu, X.-Y.; Zhu, Y.; Huang, L.; Dan, B.; Zhang, G.; Gao, Y. Factors Associated with Prolonged Viral Shedding and Impact of Lopinavir/Ritonavir Treatment in Hospitalised Non-Critically Ill Patients with SARS-CoV-2 Infection. *Eur. Respir. J.* **2020**, *56*, 2000799.

(134) Cao, B.; Wang, Y.; Wen, D.; Liu, W.; Wang, J.; Fan, G.; Ruan, L.; Song, B.; Cai, Y.; Wei, M.; Li, X.; Xia, J.; Chen, N.; Xiang, J.; Yu, T.; Bai, T.; Xie, X.; Zhang, L.; Li, C.; Yuan, Y.; Chen, H.; Li, H.; Huang, H.; Tu, S.; Gong, F.; Liu, Y.; Wei, Y.; Dong, C.; Zhou, F.; Gu, X.; Xu, J.; Liu, Z.; Zhang, Y.; Li, H.; Shang, L.; Wang, K.; Li, K.; Zhou, X.; Dong, X.; Qu, Z.; Lu, S.; Hu, X.; Ruan, S.; Luo, S.; Wu, J.; Peng, L.; Cheng, F.; Pan, L.; Zou, J.; Jia, C.; Wang, J.; Liu, X.; Wang, S.; Wu, X.; Ge, Q.; He, J.; Zhan, H.; Qiu, F.; Guo, L.; Huang, C.; Jaki, T.; Hayden, F. G.; Horby, P. W.; Zhang, D.; Wang, C. A Trial of Lopinavir−Ritonavir in Adults Hospitalized with Severe Covid-19. *N. Engl. J. Med.* **2020**, *382*, 1787−1799.

(135) Wen, C. Y.; Xie, Z. W.; Li, Y. P.; Deng, X. L.; Chen, X. T.; Cao, Y.; Ou, X.; Lin, W. Y.; Li, F.; Cai, W. P.; Li, L. H. Real-World Efficacy and Safety of Lopinavir/Ritonavir and Arbidol in Treating with COVID-19: An Observational Cohort Study. *Zhonghua Nei Ke Za Zhi* **2020**, *59*, E012.

(136) Ye, X.-T.; Luo, Y.-L.; Xia, S.-C.; Sun, Q.-F.; Ding, J.-G.; Zhou, Y.; Chen, W.; Wang, X.-F.; Zhang, W.-W.; Du, W.-J.; Ruan, Z.-W.; Hong, L. Clinical Efficacy of Lopinavir/Ritonavir in the Treatment of Coronavirus Disease 2019. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 3390−3396.

(137) Zhu, Z.; Lu, Z.; Xu, T.; Chen, C.; Yang, G.; Zha, T.; Lu, J.; Xue, Y. Arbidol Monotherapy Is Superior to Lopinavir/Ritonavir in Treating COVID-19. *J. Infect.* **2020**, *81*, e21−e23.

(138) Xu, P.; Huang, J.; Fan, Z.; Huang, W.; Qi, M.; Lin, X.; Song, W.; Yi, L. Arbidol/IFN-A2b Therapy for Patients with Corona Virus Disease 2019: A Retrospective Multicenter Cohort Study. *Microbes Infect.* **2020**, *22*, 200−205.

(139) Johansen, L. M.; DeWald, L. E.; Shoemaker, C. J.; Hoffstrom, B. G.; Lear-Rooney, C. M.; Stossel, A.; Nelson, E.; Delos, S. E.; Simmons, J. A.; Grenier, J. M.; Pierce, L. T.; Pajouhesh, H.; Lehár, J.; Hensley, L. E.; Glass, P. J.; White, J. M.; Olinger, G. G. A Screen of Approved Drugs and Molecular Probes Identifies Therapeutics with Anti−Ebola Virus Activity. *Sci. Transl. Med.* **2015**, *7*, 290ra89−290ra89.

(140) International Notes Agranulocytosis Associated with the Use of Amodiaquine for Malaria Prophylaxis. *Centers for Disease Control and Prevention*. https://www.cdc.gov/mmwr/preview/mmwrhtml/00000702.htm (accessed 2020-12-26).

(141) FDA Cautions against Use of Hydroxychloroquine or Chloroquine for COVID-19 Outside of the Hospital Setting or a Clinical Trial Due to Risk of Heart Rhythm Problems, 2020. *U.S. Food and Drug Administration*. https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or (accessed 2020).

(142) Meyerowitz, E. A.; Vannier, A. G. L.; Friesen, M. G. N.; Schoenfeld, S.; Gelfand, J. A.; Callahan, M. V.; Kim, A. Y.; Reeves, P. M.; Poznansky, M. C. Rethinking the Role of Hydroxychloroquine in the Treatment of COVID-19. *FASEB J.* **2020**, *34*, 6027−6037.

(143) Liu, J.; Cao, R.; Xu, M.; Wang, X.; Zhang, H.; Hu, H.; Li, Y.; Hu, Z.; Zhong, W.; Wang, M. Hydroxychloroquine, a Less Toxic Derivative of Chloroquine, Is Effective in Inhibiting SARS-CoV-2 Infection in Vitro. *Cell Discovery* **2020**, *6*, 16.

(144) Yao, X.; Ye, F.; Zhang, M.; Cui, C.; Huang, B.; Niu, P.; Liu, X.; Zhao, L.; Dong, E.; Song, C.; Zhan, S.; Lu, R.; Li, H.; Tan, W.; Liu, D. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin. Infect. Dis.* **2020**, *71*, 732−739.

(145) 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**, *14*, 72−73.

(146) Huang, M.; Tang, T.; Pang, P.; Li, M.; Ma, R.; Lu, J.; Shu, J.; You, Y.; Chen, B.; Liang, J.; Hong, Z.; Chen, H.; Kong, L.; Qin, D.; Pei, D.; Xia, J.; Jiang, S.; Shan, H. Treating COVID-19 with Chloroquine. *J. Mol. Cell Biol.* **2020**, *12*, 322−325.

(147) Chen, Z.; Hu, J.; Zhang, Z.; Jiang, S.; Han, S.; Yan, D.; Zhuang, R.; Hu, B.; Zhang, Z. Efficacy of Hydroxychloroquine in Patients with COVID-19: Results of a Randomized Clinical Trial. *medRxiv* preprint, 2020. DOI: 10.1101/2020.03.22.20040758.

(148) Gautret, P.; Lagier, J.-C.; Parola, P.; Hoang, V. T.; Meddeb, L.; Sevestre, J.; Mailhe, M.; Doudier, B.; Aubry, C.; Amrane, S.; Seng, P.; Hocquart, M.; Eldin, C.; Finance, J.; Vieira, V. E.; Tissot-Dupont, H. T.; Honoré, S.; Stein, A.; Million, M.; Colson, P.; La Scola, B.; Veit, V.; Jacquier, A.; Deharo, J.-C.; Drancourt, M.; Fournier, P. E.; Rolain, J.-M.; Brouqui, P.; Raoult, D. Clinical and Microbiological Effect of a Combination of Hydroxychloroquine and Azithromycin in 80 COVID-19 Patients with at Least a Six-Day Follow up: A Pilot Observational Study. *Travel Med. Infect. Dis.* **2020**, *34*, 101663.

(149) Molina, J. M.; Delaugerre, C.; Le Goff, J.; Mela-Lima, B.; Ponscarme, D.; Goldwirt, L.; de Castro, N. No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection. *Médecine Mal. Infect.* **2020**, *50*, 384.

(150) Tang, W.; Cao, Z.; Han, M.; Wang, Z.; Chen, J.; Sun, W.; Wu, Y.; Xiao, W.; Liu, S.; Chen, E.; Chen, W.; Wang, X.; Yang, J.; Lin, J.; Zhao, Q.; Yan, Y.; Xie, Z.; Li, D.; Yang, Y.; Liu, L.; Qu, J.; Ning, G.; Shi, G.; Xie, Q. Hydroxychloroquine in Patients with Mainly Mild to Moderate Coronavirus Disease 2019: Open Label, Randomised Controlled Trial. *BMJ.* **2020**, No. m1849.

(151) Mahévas, M.; Tran, V.-T.; Roumier, M.; Chabrol, A.; Paule, R.; Guillaud, C.; Fois, E.; Lepeule, R.; Szwebel, T.-A.; Lescure, F.-X.; Schlemmer, F.; Matignon, M.; Khellaf, M.; Crickx, E.; Terrier, B.; Morbieu, C.; Legendre, P.; Dang, J.; Schoindre, Y.; Pawlotsky, J.-M.; Michel, M.; Perrodeau, E.; Carlier, N.; Roche, N.; de Lastours, V.; Ourghanlian, C.; Kerneis, S.; Ménager, P.; Mouthon, L.; Audureau, E.; Ravaud, P.; Godeau, B.; Gallien, S.; Costedoat-Chalumeau, N. Clinical Efficacy of Hydroxychloroquine in Patients with Covid-19 Pneumonia Who Require Oxygen: Observational Comparative Study Using Routine Care Data. *BMJ.* **2020**, No. m1844.

(152) Saini, K. S.; Lanza, C.; Romano, M.; de Azambuja, E.; Cortes, J.; de las Heras, B.; de Castro, J.; Lamba Saini, M.; Loibl, S.; Curigliano, G.; Twelves, C.; Leone, M.; Patnaik, M. M. Repurposing Anticancer Drugs for COVID-19-Induced Inflammation, Immune Dysfunction, and Coagulopathy. *Br. J. Cancer* **2020**, *123*, 694−697.

(153) Chen, J.; Subbarao, K. The Immunobiology of SARS. *Annu. Rev. Immunol.* **2007**, *25*, 443−472.

(154) Tang, Y.; Liu, J.; Zhang, D.; Xu, Z.; Ji, J.; Wen, C. Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. *Front. Immunol.* **2020**, *11*, 1708.

(155) Cameron, M. J.; Ran, L.; Xu, L.; Danesh, A.; Bermejo-Martin, J. F.; Cameron, C. M.; Muller, M. P.; Gold, W. L.; Richardson, S. E.; Poutanen, S. M.; Willey, B. M.; DeVries, M. E.; Fang, Y.; Seneviratne, C.; Bosinger, S. E.; Persad, D.; Wilkinson, P.; Greller, L. D.; Somogyi, R.; Humar, A.; Keshavjee, S.; Louie, M.; Loeb, M. B.; Brunton, J.;

https://doi.org/10.1021/acs.jcim.1c00384
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

McGeer, A. J.; Kelvin, D. J. Interferon-Mediated Immunopathological Events Are Associated with Atypical Innate and Adaptive Immune Responses in Patients with Severe Acute Respiratory Syndrome. *J. Virol.* **2007**, *81*, 8692−8706.
(156) Li, S.; Zhang, Y.; Guan, Z.; Li, H.; Ye, M.; Chen, X.; Shen, J.; Zhou, Y.; Shi, Z.-L.; Zhou, P.; Peng, K. SARS-CoV-2 Triggers Inflammatory Responses and Cell Death through Caspase-8 Activation. *Signal Transduct. Target. Ther.* **2020**, *5*, 235.
(157) Bleyzac, N.; Goutelle, S.; Bourguignon, L.; Tod, M. Azithromycin for COVID-19: More Than Just an Antimicrobial? *Clin. Drug Invest.* **2020**, *40*, 683−686.
(158) Jang, Y.; Shin, J. S.; Yoon, Y.-S.; Go, Y. Y.; Lee, H. W.; Kwon, O. S.; Park, S.; Park, M.-S.; Kim, M. Salinomycin Inhibits Influenza Virus Infection by Disrupting Endosomal Acidification and Viral Matrix Protein 2 Function. *J. Virol.* **2018**, *92*, No. e01441-18.
(159) Luo, P.; Liu, Y.; Qiu, L.; Liu, X.; Liu, D.; Li, J. Tocilizumab Treatment in COVID-19: A Single Center Experience. *J. Med. Virol.* **2020**, *92*, 814−818.
(160) Horby, P.; Lim, W. S.; Emberson, J.; Mafham, M.; Bell, J.; Linsell, L.; Staplin, N.; Brightling, C.; Ustianowski, A.; Elmahi, E.; Prudon, B.; Green, C.; Felton, T.; Chadwick, D.; Rege, K.; Fegan, C.; Chappell, L. C.; Faust, S. N.; Jaki, T.; Jeffery, K.; Montgomery, A.; Rowan, K.; Juszczak, E.; Baillie, J. K.; Haynes, R.; Landray, M. J., RECOVERY Collaborative Group Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. *medRxiv* preprint, 2020. DOI: 10.1101/2020.06.22.20137273.
(161) Auyeung, T.; Lee, J.; Lai, W.; Choi, C.; Lee, H.; Lee, J.; Li, P.; Lok, K.; Ng, Y.; Wong, W. The Use of Corticosteroid as Treatment in SARS Was Associated with Adverse Outcomes: A Retrospective Cohort Study. *J. Infect.* **2005**, *51*, 98−102.
(162) Wang, L. H.; Rothberg, K. G.; Anderson, R. G. Mis-Assembly of Clathrin Lattices on Endosomes Reveals a Regulatory Switch for Coated Pit Formation. *J. Cell Biol.* **1993**, *123*, 1107−1117.
(163) Goodwin, E. C.; Atwood, W. J.; DiMaio, D. High-Throughput Cell-Based Screen for Chemicals That Inhibit Infection by Simian Virus 40 and Human Polyomaviruses. *J. Virol.* **2009**, *83*, 5630−5639.
(164) Missiaen, L.; Callewaert, G.; De Smedt, H.; Parys, J. B. 2-Aminoethoxydiphenyl Borate Affects the Inositol 1,4,5-Trisphosphate Receptor, the Intracellular Ca2+pump and the Non-Specific Ca2+leak from the Non-Mitochondrial Ca2+stores in Permeabilized A7r5 Cells. *Cell Calcium* **2001**, *29*, 111−116.
(165) Zhang, L.-K.; Sun, Y.; Zeng, H.; Peng, Y.; Jiang, X.; Shang, W.-J.; Wu, Y.; Li, S.; Zhang, Y.-L.; Yang, L.; Chen, H.; Jin, R; Liu, W.; Li, H.; Peng, K.; Xiao, G. Calcium Channel Blocker Amlodipine Besylate Is Associated with Reduced Case Fatality Rate of COVID-19 Patients with Hypertension. *medRxiv* preprint3, 2020. DOI: 10.1101/2020.04.08.20047134.
(166) Straus, M. R.; Bidon, M.; Tang, T.; Whittaker, G. R.; Daniel, S. FDA Approved Calcium Channel Blockers Inhibit SARS-CoV-2 Infectivity in Epithelial Lung Cells. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.07.21.214577.
(167) Ko, M.; Jeon, S.; Ryu, W.-S.; Kim, S. Comparative Analysis of Antiviral Efficacy of FDA-Approved Drugs against SARS-CoV-2 in Human Lung Cells: Nafamostat Is the Most Potent Antiviral Drug Candidate. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.05.12.090035.
(168) Hamill, P.; Hudson, D.; Kao, R. Y.; Chow, P.; Raj, M.; Xu, H.; Richer, M. J.; Jean, F. Development of a Red-Shifted Fluorescence-Based Assay for SARS-Coronavirus 3CL Protease: Identification of a Novel Class of Anti-SARS Agents from the Tropical Marine Sponge Axinella Corrugata. *Biol. Chem.* **2006**, *387*, 1063−1074.
(169) Haas, J. V.; Eastwood, B. J.; Iversen, P. W.; Devanarayan, V.; Weidner, J. R. Minimum Significant Ratio − A Statistic to Assess Assay Variability. In *Assay Guidance Manual*; Markossian, S., Sittampalam, G. S., Grossman, A., Brimacombe, K., Arkin, M., Auld, D., Austin, C. P., Baell, J., Caaveiro, J. M. M., Chung, T. D. Y., Coussens, N. P., Dahlin, J. L., Devanaryan, V., Foley, T. L., Glicksman, M., Hall, M. D., Haas, J. V., Hoare, S. R. J., Inglese, J., Iversen, P. W., Kahl, S. D., Kales, S. C., Kirshner, S., Lal-Nag, M., Li, Z., McGee, J., McManus, O., Riss, T., Saradjian, P., Trask, O. J., Weidner, J. R., Wildey, M. J., Xia, M., Xu, X., Eds.; Eli Lilly & Company, National Center for Advancing Translational Sciences: Bethesda, MD, 2004.
(170) Beck, B.; Chen, Y.-F.; Dere, W.; Devanarayan, V.; Eastwood, B. J.; Farmen, M. W.; Iturria, S. J.; Iversen, P. W.; Kahl, S. D.; Moore, R. A.; Sawyer, B. D.; Weidner, J. Assay Operations for SAR Support. In *Assay Guidance Manual*; Markossian, S., Sittampalam, G. S., Grossman, A., Brimacombe, K., Arkin, M., Auld, D., Austin, C. P., Baell, J., Caaveiro, J. M. M., Chung, T. D. Y., Coussens, N. P., Dahlin, J. L., Devanaryan, V., Foley, T. L., Glicksman, M., Hall, M. D., Haas, J. V., Hoare, S. R. J., Inglese, J., Iversen, P. W., Kahl, S. D., Kales, S. C., Kirshner, S., Lal-Nag, M., Li, Z., McGee, J., McManus, O., Riss, T., Saradjian, P., Trask, O. J., Weidner, J. R., Wildey, M. J., Xia, M., Xu, X., Eds.; Eli Lilly & Company, National Center for Advancing Translational Sciences: Bethesda, MD, 2004.
(171) Kim, Y.; Lovell, S.; Tiew, K.-C.; Mandadapu, S. R.; Alliston, K. R.; Battaile, K. P.; Groutas, W. C.; Chang, K.-O. Broad-Spectrum Antivirals against 3C or 3C-Like Proteases of Picornaviruses, Noroviruses, and Coronaviruses. *J. Virol.* **2012**, *86*, 11754−11762.
(172) Turlington, M.; Chun, A.; Tomar, S.; Eggler, A.; Grum-Tokars, V.; Jacobs, J.; Daniels, J. S.; Dawson, E.; Saldanha, A.; Chase, P.; Baez-Santos, Y. M.; Lindsley, C. W.; Hodder, P.; Mesecar, A. D.; Stauffer, S. R. Discovery of N-(Benzo[1,2,3]Triazol-1-Yl)-N-(Benzyl)-Acetamido)Phenyl) Carboxamides as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) 3CLpro Inhibitors: Identification of ML300 and Noncovalent Nanomolar Inhibitors with an Induced-Fit Binding. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6172−6177.
(173) Eastman, R. T.; Roth, J. S.; Brimacombe, K. R.; Simeonov, A.; Shen, M.; Patnaik, S.; Hall, M. D. Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. *ACS Cent. Sci.* **2020**, *6*, 672−683.
(174) Shuai, H.; Chu, H.; Hou, Y.; Yang, D.; Wang, Y.; Hu, B.; Huang, X.; Zhang, X.; Chai, Y.; Cai, J.-P.; Chan, J. F.-W.; Yuen, K.-Y. Differential Immune Activation Profile of SARS-CoV-2 and SARS-CoV Infection in Human Lung and Intestinal Cells: Implications for Treatment with IFN-β and IFN Inducer. *J. Infect.* **2020**, *81*, e1−e10.
(175) Mirabelli, C.; Wotring, J. W.; Zhang, C. J.; McCarty, S. M.; Fursmidt, R.; Frum, T.; Kadambi, N. S.; Amin, A. T.; O'Meara, T. R.; Pretto, C. D.; Spence, J. R.; Huang, J.; Alysandratos, K. D.; Kotton, D. N.; Handelman, S. K.; Wobus, C. E.; Weatherwax, K. J.; Mashour, G. A.; O'Meara, M. J.; Sexton, J. Z. *Morphological Cell Profiling of SARS-CoV-2 Infection Identifies Drug Repurposing Candidates for COVID-19*. *bioRxiv* preprint, 2020. DOI: 10.1101/2020.05.27.117184.
(176) Song, S.; Ma, L.; Zou, D.; Tian, D.; Li, C.; Zhu, J.; Chen, M.; Wang, A.; Ma, Y.; Li, M.; Teng, X.; Cui, Y.; Duan, G.; Zhang, M.; Jin, T.; Shi, C.; Du, Z.; Zhang, Y.; Liu, C.; Li, R.; Zeng, J.; Hao, L.; Jiang, S.; Chen, H.; Han, D.; Xiao, J.; Zhang, Z.; Zhao, W.; Xue, Y.; Bao, Y. The Global Landscape of SARS-CoV-2 Genomes, Variants, and Haplotypes in 2019nCoVR. *Genomics Proteomics Bioinformatics* **2020**, S1672022920301315.
(177) Korber, B.; Fischer, W. M.; Gnanakaran, S.; Yoon, H.; Theiler, J.; Abfalterer, W.; Hengartner, N.; Giorgi, E. E.; Bhattacharya, T.; Foley, B.; Hastie, K. M.; Parker, M. D.; Partridge, D. G.; Evans, C. M.; Freeman, T. M.; de Silva, T. I.; McDanal, C.; Perez, L. G.; Tang, H.; Moon-Walker, A.; Whelan, S. P.; LaBranche, C. C.; Saphire, E. O.; Montefiori, D. C.; Angyal, A.; Brown, R. L.; Carrilero, L.; Green, L. R.; Groves, D. C.; Johnson, K. J.; Keeley, A. J.; Lindsey, B. B.; Parsons, P. J.; Raza, M.; Rowland-Jones, S.; Smith, N.; Tucker, R. M.; Wang, D.; Wyles, M. D. Tracking Changes in SARS-CoV-2 Spike: Evidence That D614G Increases Infectivity of the COVID-19 Virus. *Cell* **2020**, *182*, 812−827.
(178) Baric, R. S. Emergence of a Highly Fit SARS-CoV-2 Variant. *N. Engl. J. Med.* **2020**, *383*, 2684−2686.
(179) Coronavirus Disease 2019 (COVID-19). *Centers for Disease Control and Prevention*. https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html (accessed 2021-06-27).
(180) Li, Y.; Xie, Z.; Lin, W.; Cai, W.; Wen, C.; Guan, Y.; Mo, X.; Wang, J.; Wang, Y.; Peng, P.; Chen, X.; Hong, W.; Xiao, G.; Liu, J.;

Zhang, L.; Hu, F.; Li, F.; Zhang, F.; Deng, X.; Li, L. Efficacy and Safety of Lopinavir/Ritonavir or Arbidol in Adult Patients with Mild/Moderate COVID-19: An Exploratory Randomized Controlled Trial. *Med.* **2020**, *1*, 105−113.

(181) Boulware, D. R.; Pullen, M. F.; Bangdiwala, A. S.; Pastick, K. A.; Lofgren, S. M.; Okafor, E. C.; Skipper, C. P.; Nascene, A. A.; Nicol, M. R.; Abassi, M.; Engen, N. W.; Cheng, M. P.; LaBar, D.; Lother, S. A.; MacKenzie, L. J.; Drobot, G.; Marten, N.; Zarychanski, R.; Kelly, L. E.; Schwartz, I. S.; McDonald, E. G.; Rajasingham, R.; Lee, T. C.; Hullsiek, K. H. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. *N. Engl. J. Med.* **2020**, *383*, 517−525.

(182) Borba, M. G. S.; Val, F. F. A.; Sampaio, V. S.; Alexandre, M. A. A.; Melo, G. C.; Brito, M.; Mourão, M. P. G.; Brito-Sousa, J. D.; Baía-da-Silva, D.; Guerra, M. V. F.; Hajjar, L. A.; Pinto, R. C.; Balieiro, A. A. S.; Pacheco, A. G. F.; Santos, J. D. O.; Naveca, F. G.; Xavier, M. S.; Siqueira, A. M.; Schwarzbold, A.; Croda, J.; Nogueira, M. L.; Romero, G. A. S.; Bassat, Q.; Fontes, C. J.; Albuquerque, B. C.; Daniel-Ribeiro, C.-T.; Monteiro, W. M.; Lacerda, M. V. G. for the CloroCovid-19 Team. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. *JAMA Netw. Open* **2020**, *3*, No. e208857.

(183) Cleary, S. J.; Pitchford, S. C.; Amison, R. T.; Carrington, R.; Robaina Cabrera, C. L.; Magnen, M.; Looney, M. R.; Gray, E.; Page, C. P. Animal Models of Mechanisms of SARS-COV-2 Infection and COVID-19 Pathology. *Br. J. Pharmacol.* **2020**, *177*, 4851−4865.

(184) Shapira, T.; Monreal, I. A.; Dion, S. P.; Jager, M.; Désilets, A.; Olmstead, A. D.; Vandal, T.; Buchholz, D. W.; Imbiakha, B.; Gao, G.; Chin, A.; Rees, W. D.; Steiner, T.; Nabi, I. R.; Marsault, E.; Sahler, J.; August, A.; Van de Walle, G.; Whittaker, G. R.; Boudreault, P.-L.; Aguilar, H. C.; Leduc, R.; Jean, F. A Novel Highly Potent Inhibitor of TMPRSS2-like Proteases Blocks SARS-CoV-2 Variants of Concern and Is Broadly Protective against Infection and Mortality in Mice. *bioRxiv* preprint, 2021. DOI: 10.1101/2021.05.03.442520.

(185) Edwards, A. What Are the Odds of Finding a COVID-19 Drug from a Lab Repurposing Screen? *J. Chem. Inf. Model.* **2020**, *60*, 5727.

https://doi.org/10.1021/acs.jcim.1c00384
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX