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Advances in the computational landscape for repurposed drugs against COVID-19

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The COVID-19 pandemic has caused millions of deaths and massive societal distress worldwide. Therapeutic solutions are urgently needed, but *de novo* drug development remains a lengthy process. One promising alternative is computational drug repurposing, which enables the prioritization of existing compounds through fast *in silico* analyses. Recent efforts based on molecular docking, machine learning, and network analysis have produced actionable predictions. Some predicted drugs, targeting viral proteins and pathological host pathways are undergoing clinical trials. Here, we review this work, highlight drugs with high predicted efficacy and classify their mechanisms of action. We discuss the strengths and limitations of the published methodologies and outline possible future directions. Finally, we curate a list of COVID-19 data portals and other repositories that could be used to accelerate future research.

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Introduction

The emergence of the novel coronavirus, known as SARS-CoV-2, became a defining event for 2019. The virus was first discovered in Wuhan, China. Transmitted via respiratory secretions, it quickly spread to neighboring countries and the rest of the world, causing COVID-19 (Coronavirus Disease 2019). To date, the COVID-19 pandemic has resulted in over four million deaths. The relatively high mortality, alongside the massive societal distress caused by the virus, stimulated intensive research on its biology, associated disease, and the development of vaccines and therapeutics.

SARS-CoV-2 is an enveloped, non-segmented, positive-sense RNA virus. It is part of the Coronaviridae family of viruses, which are known to cause respiratory infections in human hosts. SARS-CoV-2 is a beta coronavirus most closely related to SARS-CoV-1, with which it shares 79% genetic similarity, and more distally related to MERS-CoV, with which it shares approximately 50% of its genomic sequence.[1,2] Several proteins encoded by the SARS-CoV-2 viral genome have been implicated in its pathogenesis. The spike protein, responsible for viral entry, binds to the angiotensin converting enzyme 2 (ACE2) receptor, which is broadly expressed in human tissues.[3,4] Other viral proteins have key roles in the viral transcriptase–replicase complex (RdRp, Mpro/3CL, PLPro, helicase).[5–7]

The defining features of COVID-19 are a high rate of asymptomatic spread and high incidence of life-threatening complications.[1,8–11] Owing to these complications and the lack of immunity in the population, the scientific and medical communities launched a large-scale research response that led to the development of multiple vaccines.[12] Despite the proven efficacy of these vaccines, there is an urgent need for COVID-19 therapeutics due to vaccine distribution delays, failed immunity, vaccine hesitancy, and the possible emergence of resistant strains.[13,14]

De novo development of therapeutics is a lengthy process, and is not a practical way to address the current pandemic.[15] Drug repurposing is an emerging strategy in which existing therapeutics, that have already tested safe in humans, are repositioned to treat other diseases.[16,17] For example, clinical trials showed that remdesivir, an antiviral known for its effectiveness against the Ebola virus, was superior to placebo in shortening the time to recovery in COVID-19 patients.[17,18] Nevertheless, a systematic experimental screening of the potentially very large pool of drugs to be considered for repurposing is not feasible, due to both lengthy time-scales and prohibitive cost. To overcome this limitation, one promising alternative is computational drug repurposing.

Computational drug repurposing, broadly speaking, uses algorithms and massive database information to prioritize drugs for repositioning.[19–25] One major advantage of computational approaches is the potential for fast large-scale screenings. Another major advantage is the potential to identify previously unknown benefits of existing drugs in disease contexts that are radically different from the original intended target conditions. By contrast, experimental drug repurposing is typically restricted to closely related disease contexts.

Multiple reviews in the area of computational repurposing of drugs have focused on drugs and mechanisms of action with potential for use against COVID-19, regardless of the specific computational methods used for prediction.[26–29] Other works have reviewed progress and perspectives relating to artificial intelligence-based methods.[30,31] Additional, more comprehensive, reviews have extended the methodological classes further to include network-, structure-, and signature-based drug repurposing methods.[32–34]

Our review, like that of Galindez *et al.*,[33] is positioned to include both a careful curation of the many published methods and the identification of the most promising drug predictions. While Galindez *et al.*[33] focused on generalized workflows in each method class, we provide a more in-depth review of selected works, aiming to illustrate the details of drug repurposing strategies that have resulted in experimentally validated drug predictions. In addition, a novel aspect of our review is the introduction of early progress in the category of text mining for COVID-19 drug repurposing.

The objectives of this review are: (1) the identification of published works that produce drug predictions that have been validated either *in vitro* or *in vivo*; (2) classification of the corresponding computational techniques, with a detailed presentation of selected works; (3) summarization of drug candidates and the mechanisms of pathogenesis that would be modulated; and (4) curation of the main data sources and COVID-19-specific portals. Finally, this review aims to guide future work in the field.

Classification of computational approaches for the repurposing of drugs against COVID-19

For a global view of efforts on computational drug repurposing, we conducted a manual curation of the literature and analyzed the COVID-19 Drug and Gene Set Library.[35] This resource includes both computationally predicted and experimentally validated drug candidates along with the associated publications. The COVID-19 Drug and Gene Set Library is one of the most comprehensive crowdsourcing initiatives to integrate drug and gene sets related to COVID-19 research.

We defined selection criteria for inclusion in this review to identify the most methodologically sound manuscripts that have undergone rigorous peer review, sufficient methodological diversity and the most promising drug candidate predictions (Fig. 1A). First, we applied two selection criteria to the COVID-19 Drug and Gene Set Library: the presence of a computational prediction for at least one experimentally validated compound; and publication of the associated paper in a peer-reviewed journal (excluding preprints, technical reports or other resources). Second, we manually curated relevant published works that are not yet in the COVID-19 Drug and Gene Set Library to increase coverage of the different methodological areas and to incorporate other major publications. In all, we include 44 peer-reviewed manuscripts (Fig. 1A). Consistent with previous reviews in the field of computational drug repurposing,[19–25] we group the selected works into the following categories: molecular docking, molecular docking with follow-up molecular dynamics simulations,
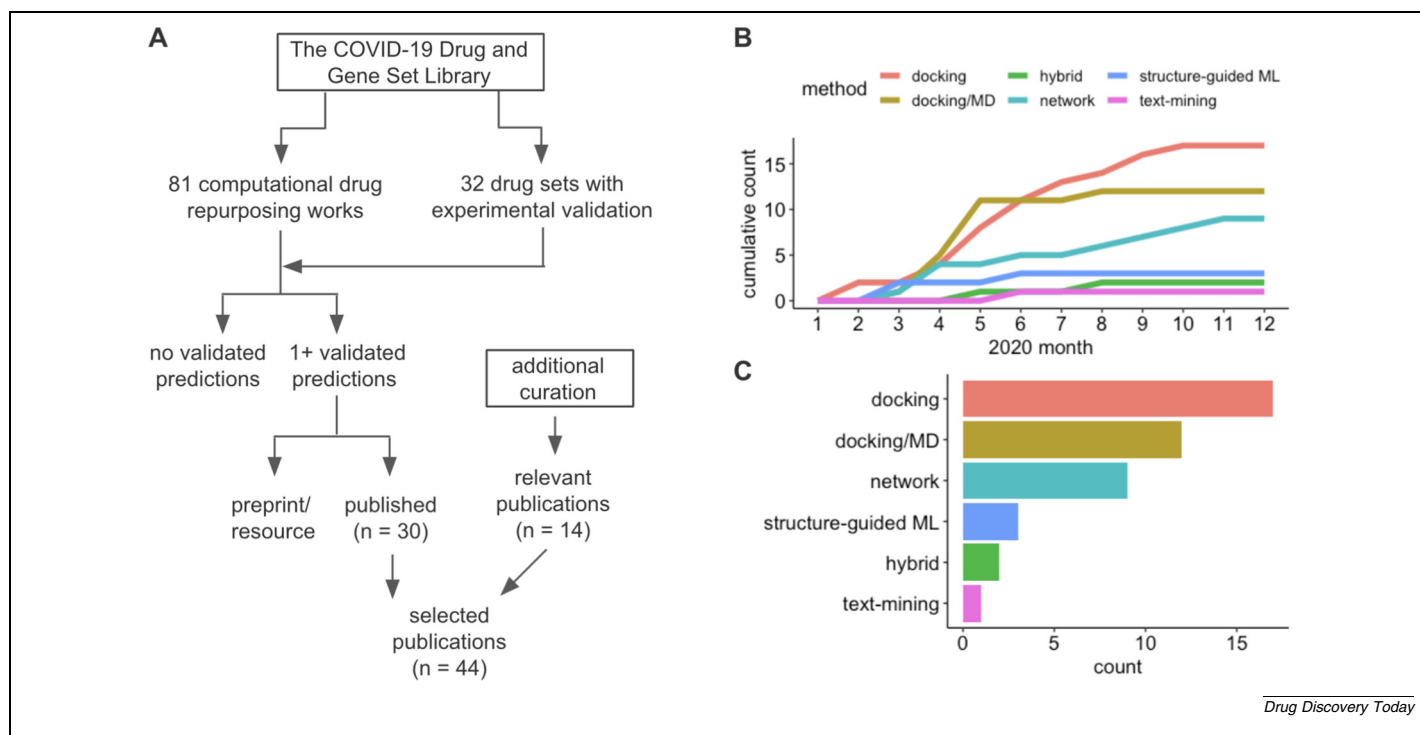
FIGURE 1

Selection and classification of works on computational drug repurposing for COVID-19. A. To identify the most effective computational drug repurposing works, we used the COVID-19 Drug and Gene Set Library,[35] complemented by manual curation of the literature. The selection criteria aimed to identify methods that resulted in at least one predicted compound that was validated with further experiments. B. We classified the selected works into six groups: docking, docking/MD (molecular dynamics), network, structure-guided machine-learning (ML), hybrid and text mining. The publication trends for these groups in 2020 are shown. C. The final numbers of publications in each category included in our review.

structure-guided machine learning, network-based methods, hybrid methods, and text mining.

Our review of the literature required the manual curation of manuscripts and drug predictions that, given the urgency of the pandemic, are being published at an exceptionally rapid rate. Thus, we restricted our curation to a time frame between the onset of the pandemic and January 2021. Analysis of publication trends during this time showed a very early production of works on molecular docking, with and without molecular dynamics simulations, followed by the publication of works on network-based approaches, structure-guided machine learning, and hybrid methods (Fig. 1B). Currently, the majority of the published works are in the docking category (39%), docking with follow-up molecular dynamics simulations (27%), network-based approaches (20%), structure-guided machine learning (7%), and hybrid methods (5%) (Fig. 1C). To date, the text-mining category has received relatively little attention, with only one published manuscript.[36] Text-mining approaches may be underrepresented in the context of COVID-19 because they look for previously unrecognized connections between drug targets and diseases, but the genes involved in COVID-19 pathogenesis are still largely unknown.

Molecular docking

In the context of drug repurposing for the development of therapeutics against viral infections, docking techniques assess the fitness of an interaction between small molecules and viral proteins with a known 3D structure.[22] The fitness (or binding affinity) is commonly computed as a potential energy, which is a function of force fields acting on the interacting molecular particles. Lower potential energy values (higher binding affinity) correspond to more stable conformations for complexes involving the small molecule and the viral protein, and are more likely to be associated with neutralization of the viral protein function by the ligand. Thus, small molecules that have high binding affinity for viral proteins are prioritized as potentially repurposable drugs. The well-established methods and software packages for docking approaches include GLIDE,[37] AutoDock Vina,[38] and SwissDock.[39] The packages differ from one another in terms of the employed algorithms, scoring methods, docking type (flexible or rigid), and docking elements (for example, protein–protein, protein–ligand, protein–peptide). Parks and Smith[40] provided a recent perspective on the potential advantages of molecular docking for quick repurposing of drugs for use against SARS-CoV-2.

The earliest studies faced the challenge of the lack of a solved structure for SARS-CoV-2 viral proteins. One way to circumvent this problem is to rely on the conservation of sequence and assume 3D structure conservation between SARS-CoV-2 and other coronaviruses, particularly SARS-CoV-1. For example, some early works predicted drug candidates targeting SARS-CoV-2 Mpro/3CL by leveraging the sequence and structure conserva-

tion of key protein residues in SARS-CoV-1 and SARS-CoV-2 inhibitor-binding pockets.[41]

A more principled way to overcome the challenge of unsolved viral protein structure is homology modelling.[42] Homology modeling refers to the construction of an atomic-resolution model of the protein of interest (e.g. SARS-CoV-2 Mpro/3CL) based on its amino acid sequence and an experimental three-dimensional structure of a homologous protein (e.g. SARS-CoV-1 Mpro/3CL).[43] For example, Wu et al.[44] systematically applied homology modeling to all of the proteins encoded by SARS-CoV-2 genes, predicting 19 structures. The authors then used these predicted structures to perform molecular docking against compound libraries such as the ZINC drug database[45] and a database of natural products. The study identified 78 commonly used antiviral drugs, including those currently on the market and undergoing clinical trials, as potential targets for SARS-CoV-2 Mpro/3CL (almitrine, carvedilol, telmisartan, conivaptan), RdRp (idarubicin), and PLpro (ribavirin). Additional studies have followed a similar strategy, leveraging homology modeling of the SARS-CoV-2 proteins RdRp,[46,47] Mpro/3CL,[48] Plpro,[49] helicase,[50] and the spike protein,[51] as well as the human protein TMPRSS2[52,53] in their docking studies. After the crystal structures of SARS-CoV-2 viral proteins were resolved, a second wave of papers applied docking methods directly to these solved structures to predict additional drug targets.[54–60] Interestingly, the predictions made by docking methods that used solved structures largely differed from those made using methods that leveraged homology modeling, with ribavirin being the most notable prediction made by methods in both categories.

Next, we illustrate how homology modeling, molecular docking and experimental techniques can be successfully combined by looking in depth at the study by Jin et al.[61] In an effort to develop drugs against human coronaviruses, an earlier study by Yang et al.[62] had found an MPro/3CL substrate recognition pocket that is highly conserved in the genus Coronavirus.[62] On the basis of this finding, Yang et al.[62] designed a wide-spectrum inhibitor of Mpro/3CL, named N3, that showed antiviral activity against SARS-CoV-1 and MERS. Jin et al.[61] started by constructing a homology model for SARS-CoV-2 Mpro/3CL, and used molecular docking to ascertain that N3 can target the modeled Mpro/3CL. Next, Jin et al.[61] experimentally assessed the efficacy of N3 for SARS-CoV-2 Mpro/3CL through analysis of binding kinetics, showing potent inhibition. In addition, the study determined the crystal structure of SARS-CoV-2 Mpro/3CL in complex with N3. The determined structure helped reveal a substrate-binding pocket highly conserved among Mpro/3CL in all coronaviruses. This served as a model for in silico screening of candidate inhibitors to target SARS-CoV-2 Mpro/3CL. Using the GLIDE docking software package, the analysis identified cinanserin, a well-characterized serotonin antagonist previously shown to inhibit SARS-CoV-1 Mpro/3CL,[63] as a potential inhibitor of SARS-CoV-2 Mpro/3CL. To discover other potential Mpro/3CL inhibitors, Jin et al.[61] used a fluorescence resonance energy transfer assay to screen a library of about 10,000 compounds consisting of approved drugs, clinical-trial drug candidates and natural products. The primary candidates included the approved drug disulfiram, as well as the clinical-trial drug candidate ebselen, which had shown efficacy against other

viruses.[64–66] Further in vitro experiments measuring viral replication in cell-based assays confirmed strong antiviral activity for N3 and ebselen.

Although docking methods can assess the fitness of an interaction between a drug and its intended target, they typically predict a large number of potential drug candidates. An effective way to restrict this pool of candidates is provided by Molecular Dynamics (MD) simulations. Docking methods are based on a static description of the interactions between drugs and targets, whereas MD gives a view of their dynamic interactions by analyzing the motion of atoms and molecules over time. Because molecular systems typically consist of a vast number of particles, the computational cost of MD simulations can be considerable. Therefore, it is computationally prohibitive to employ MD simulations to screen systematically against large drug databases, and MD simulations are typically applied to the most promising targets preselected through docking. MD and docking methods complement each other, leading to more reliable predictions and to less follow-up experimental work. Multiple software packages for MD simulations are available, including GROMACS,[67] and AMBER.[68] MD simulations, in combination with molecular docking, have been used to identify drug candidates against SARS-CoV-2 Mpro/3CL,[53,69–74] RdRp,[75] nsp16 and nsp10,[76] against the human protein ACE2,[77] and against the complex between the SARS-CoV-2 spike protein and ACE2.[51,78]

Structure-guided machine-learning approaches

The recent rapid growth of drug-related data sets, as well as of open data initiatives, has led to new developments in machine-learning methods, especially in deep-learning techniques. Docking methods compute binding affinity using the detailed molecular structures of drugs and their targets, whereas machine-learning models use simplified vector representations of these structures. In the simplest case, for example, the so-called 'fingerprint' representation of a molecule is a vector of the structural fragments in the molecule. Machine-learning models require a training set that pairs up input features, that is molecular descriptors of drugs and their targets (such as their molecular fingerprints), and outputs such as binding affinities. Like docking methods, trained machine-learning models produce a prediction that is an estimate of the binding affinity between a drug candidate and its target proteins, either viral or host. When compared to docking, machine-learning models have additional advantages in that (1) they can be applied in the absence of a solved 3D protein structure, which was the case for some early papers using this approach and (2) the calculation of the binding affinity is more computationally efficient.

Focusing on the SARS-CoV-2 Mpro/3CL, Gao et al.[79] proposed a machine-learning-based approach in which they compiled a carefully selected training set of 314 SARS-CoV-1 or SARS-CoV-2 Mpro/3CL protease inhibitors and their binding affinities collected from single protein experiments. The input variables for each inhibitor were constructed by encoding its high-dimensional biomolecular interactions with Mpro/3CL in a low-dimensional representation. A gradient boosting decision tree model showed good performance (Pearson correlation between predicted and true binding affinities of 0.79). Gao et al.[79]

then used the model to predict the binding affinities between the SARS-CoV-2 Mpro/3CL protease and 1553 US Food and Drug Administration (FDA)-approved drugs as well as 7012 investigational or off-market drugs. Among the FDA-approved drugs with predicted high-affinity scores were chloroxine (an antibacterial drug that belongs to the same family as chloroquine, but with a different predicted mechanism of action), demexiptiline (a tricyclic antidepressant) and fluorouracil (an antineoplastic). Among investigational compounds, the top result was debio-1347 (a fibroblast growth factor receptor (FGFR) inhibitor under investigation for the treatment of solid tumors). Interestingly, the predicted binding affinity of debio-1347 for SARS-CoV-2 Mpro/3CL was higher than that of any of the FDA-approved drugs, indicating the potential of debio-1347 for COVID-19 repurposing.

Batra et al.[80] trained a structure-based machine-learning model to repurpose drug candidates against the spike protein and the spike–human ACE2 interface complex. The model used as input a set of structural and physicochemical features that capture the interactions between the drug molecule and the target proteins at various spatial scales. As output, the model predicted the corresponding AutoDock Vina score. Predictions were based on a random forest model trained on docking-generated binding affinities. Top-scoring ligands, including FDA-approved antivirals (such as valaciclovir) and antibacterials (such as sulfamethoxazole), were further validated in silico by all-atom docking studies.

Studies by Beck et al.[81] and by Ton et al.[82] employed deep-learning-based models, called Molecule Transformer–Drug Target Interaction (MT–DTI) and Deep Docking, respectively, to predict drug–target interactions. MT-DTI was trained with a database of approximately a billion compounds combining data from the BindingDB database[83] and the Drug Target Common database,[84] and was used to predict the binding affinity between SARS-CoV-2 proteins and 3411 FDA-approved drugs. Interestingly, the predictions included drug candidates that are able to target multiple viral proteins simultaneously. For example, atazanavir was predicted to bind SARS-CoV-2 Mpro/3CL, RdRp, and helicase. Similarly, ganciclovir was predicted to bind to three subunits of the replication complex. Deep Docking, a recently developed deep-learning platform shown to provide accurate and fast approximations of docking outcomes, enabled a virtual screening of the entire ZINC library of over 10^9 compounds against Mpro/3CL.[45] Analysis of the top 1000 candidate inhibitors showed good chemical diversity and superior docking scores relative to those of known Mpro/3CL inhibitors. This method demonstrates the plausibility of performing exhaustive virtual screening, although the large number of predictions make it difficult to evaluate the success rate and the overall clinical applicability.

Network-based approaches

During the viral life cycle, the virus interacts with multiple components of the host cell. Previously described approaches have aimed to identify inhibitory molecules that directly target viral proteins. An alternative therapeutic option is to target the host or the virus–host interactome, typically using techniques from network pharmacology. The host interactome consists of human

proteins as nodes and their interactions as edges, drawing upon various repositories of protein–protein interactions (PPI). The virus–host interactome extends this network by including viral proteins and their interactions with host proteins, typically leveraging high-throughput experiments. Additional data, such as transcriptomics, are used to derive subnetworks that are relevant to the disease under study, in this case COVID-19. Finally, databases of drug targets are utilized to predict druggable nodes in these subnetworks, identifying potential therapeutics that can perturb key processes of COVID-19 pathology.

Early papers that aimed to identify COVID-19 disease-relevant subnetworks needed to overcome the lack of data on interactions between SARS-CoV-2 and human proteins. Alakwaa[85] and Cava et al.[86] focused solely on host networks centered around ACE2, which is broadly expressed and is critical for SARS-CoV-2 cellular entry. They identified ACE2-associated networks derived from the analysis of gene expression in lung tissue transcriptomes in the public domain (e.g. GTEx[87]), and mapped databases of drug perturbations onto these gene sets. The work of Zhou et al.[88] built upon a similar strategy and constructed a broader pan Coronavirus–host interactome network, which included a set of 119 host proteins associated with previously characterized human, mouse, and avian Coronaviruses. The drug repurposing methodology rested on the idea that for a drug to be effective, its targets should be either in the Coronavirus–host interactome or in close proximity to the interactome within the global human PPI network. Guided by this idea, alongside additional information such as transcriptomics data, literature-reported antiviral evidence and known side effects, the authors prioritized four classes of drugs. These included estrogen receptor modulators, angiotensin receptor blockers, immunosuppressant or antineoplastic agents, and anti-inflammatory agents. Finally, Zhou et al.[88] predicted three potentially synergistic drug combinations for COVID-19: sirolimus (immunosuppressor) + dactinomycin (RNA synthesis inhibitor), toremifene (estrogen receptor modulator) + emodin (antiviral agent), and mercaptopurine (antineoplastic agent) + melatonin (anti-inflammatory agent).

Network-based repurposing strategies require high-confidence information on interactions between viral and human proteins. In contrast to the computationally derived interactome in the Zhou et al.[88] study, Gordon et al.[89] experimentally identified 332 interactions between SARS-CoV-2 and human proteins. For each viral protein, a set of interacting host proteins was determined using affinity purification mass spectrometry, and assessed via immunological pathway analysis. This analysis revealed that the interacting host proteins participate in major cellular processes including DNA replication, epigenetic and transcriptional regulation, multiple innate immune pathways, and host translational machinery. Next, the authors predicted 69 agents, including FDA-approved drugs, that would disrupt host proteins and cellular processes potentially hijacked during SARS-CoV-2 infection. Further experiments revealed the antiviral activity of two broad classes of active compounds: those impinging on the translational machinery of the host needed for viral biogenesis, and those modulating the sigma1 and sigma2 receptors (chaperone proteins at the endoplasmic reticulum). Translation inhibitors (such as zotatifin and aplidin/plitidepsin) and sigma receptor ligands that have antiviral activity (such as

haloperidol and clemastine/cloperastine) were identified as potential candidates for repurposing of drugs against COVID-19.

Bouhaddou et al.[90] performed the first proteomics and phosphoproteomics analysis to explore how host pathways rewire upon SARS-CoV-2 infection. The study revealed a prominent role of phosphorylation events in modulating the cell cycle and cytoskeletal organization of infected cells. The strategy for drug repurposing hinged on detecting changes in phosphorylation states between SARS-CoV-2-infected and control cells. These identified changes were then mapped to changes in the activity of 97 kinases linked by database knowledge with their substrates.[91] Of note, several inferred kinases were members of the virus–host PPI map generated by Gordon et al.[89] Finally, Bouhaddou et al.[90] looked for drugs that were able to inhibit the identified kinases, producing 87 drug candidates. In vitro assays involving 68 out of these 87 kinase inhibitors, including silmitasertib (an inhibitor of CK2), gilteritinib (an inhibitor of AXL), and ARRY-797 (an inhibitor of p38) demonstrated strong antiviral activity.

More recent studies took advantage of the increasing availability of transcriptomics data, which make it possible to identify SARS-CoV-2-regulated genes and pathways, and their overlap with drug-modulated genes.[92,93] By applying network proximity measures to multi-omics data from diverse tissues, Zhou et al.[94] revealed similarities between COVID-19 and other pathologies, including inflammatory bowel disease and asthma. The shared pathological processes could suggest candidates for repurposing in COVID-19.

Hybrid methodologies

An important study of Bojkova et al.,[95] which makes and validates multiple predictions, does not fit the standard computational drug repurposing classification. We place this study in the 'Hybrid' category because it integrates diverse computational techniques as well as experimental work.

To identify host pathways that are modulated by SARS-CoV-2 infection, Bojkova et al.[95] established a novel cell culture model using a human epithelial carcinoma cell line. The SARS-CoV-2 infection profile, comprising both viral and host proteins, was quantified through translatome and proteome analysis at multiple time points within 2–24 hours after infection. First, the authors identified host proteins whose translation kinetics showed high correlation with those of viral proteins. Network and enrichment analyses of these proteins showed a strong increase in the host translation machinery, suggesting that translation inhibitors may reduce SARS-CoV-2 replication. This hypothesis was validated using two translation inhibitors, cycloheximide and emetine. To gain further insight into host proteome changes after infection, Bojkova et al.[95] performed hierarchical clustering of the host proteins' expression profiles over time. This revealed an upregulated cluster of proteins that was enriched in spliceosome components and carbon metabolism, suggesting that targeting these two pathways may prevent SARS-CoV-2 replication. Both hypotheses were validated using, respectively, pladienolide B (a spliceosome inhibitor) and 2-deoxy-D-glucose (an inhibitor of hexokinase implicated in carbon metabolism). Additional correlation analysis of the kinetics of host and viral proteins showed that SARS-CoV-2 replication can be also inhibited using ribavirin and NMS-873 (a compound targeting the protein homeostasis machinery). Altogether, this work revealed that SARS-CoV-2 infection modulates critical host functions such as splicing, diverse metabolism sub-pathways, and proteostasis. Drugs that interfere with these pathways can be successfully repurposed to prevent SARS-CoV-2 replication in a human cell line and are good candidates for further testing in clinical settings for COVID-19.

Mining of text and healthcare records

The compilation of knowledge on COVID-19 has grown exponentially since the beginning of the pandemic. Several initiatives, such as the COVID-19 Open Research Dataset (CORD-19) and LitCovid, have made the published work more easily accessible.[96,97] This opens up great opportunities for analysis based on text mining and natural language processing. A recent publication by Wang et al.[97] provides a review of the different text-mining systems and their applications to COVID-19 research, including information retrieval, automated annotation, and drug repurposing.[98] The COVID-19 Drug Repository is the first significant work on computational drug repurposing based on text mining.[36] The goal of this repository, which integrates data from PubMed, clinical trials and drug databases, is to centralize information on drugs against COVID-19 in a structured framework. The available information includes drug descriptions, side effects, pharmacology-oriented data, and drug–gene interactions. The resource makes it possible to identify putative repurposing candidates by analyzing omics data in conjunction with mined drug–target interactions.

More generally, text mining can be used to derive 'knowledge graphs'. These are models of entities and relationships in a particular domain (for example, COVID-19 research) that can support the inference of novel relationships. In our context, a novel relationship could represent the potential efficacy of an existing drug against COVID-19.[98] Finally, another promising research direction is the mining of electronic health records, prescription records and medical insurance claims.[99] As these data types accumulate in the context of COVID-19, frameworks that identify new uses for on-market prescription drugs by systematically analyzing healthcare databases can be applied.[100] Although still in their early stages, the mining of text and healthcare records will become an increasingly important tool in addressing the information overload, and in generating new hypotheses for drug repurposing.

Summary and conclusions

Computational drug repurposing for SARS-CoV-2 has homed in on two main mechanisms of action (Table 1). The most frequent mechanism is the direct inhibition of SARS-CoV-2 viral proteins (Fig. 2A, seen in 31 of 44 reviewed works). The criterion for repurposing is the high binding affinity of the drugs to viral proteins, which is estimated using molecular docking or machine learning. This strategy has previously led to successful repurposing of antimicrobial drugs, including inhibitors of the Zika Virus.[17] In the context of SARS-CoV-2, potentially repurposable drugs include multiple inhibitors of RdRp, Mpro/3CL protease, and

TABLE 1

List of FDA-approved and investigational compounds predicted by computational drug repurposing methods to be effective against COVID-19. The predicted mechanism of action and current indication is included where available. Hyperlinks are provided for compounds in clinical trials. *Compound failing experimental validation or clinical trial.

Drug Name	Predicted MOA	Predicted Class	Current indication	Reference	Validation
Bedaquiline	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Antibacterial	[101]	In vitro (cell culture)
Carmofur	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Antineoplastic	[61]	In vitro (cell culture & FRET assay)
Cinanserin	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	No current pharmaceutical use	[63]	In vitro (tissue culture)
Disulfiram	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Alcoholism medication	[61]	In vitro (cell culture & FRET assay)
Ebselen	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Potential diabetes medication	[61]	In vitro (cell culture & FRET assay)
N3	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	No current pharmaceutical use	[61]	In vitro (cell based assays)
PX-12	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Potential antineoplastic medication	[61]	In vitro (cell culture & FRET assay)
Shikonin	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Homeopathic medication	[61]	In vitro (cell culture & FRET assay),
TDZD-8	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Potential Alzheimer's medication	[61]	In vitro (cell culture & FRET assay)
Tideglusib	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Potential Alzheimer's medication	[61]	In vitro (cell culture & FRET assay)
Baloxavir marboxil	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Antiviral for influenza	[102]	In vivo (clinical trial)
Mefloquine	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Antimalarial agent	[103]	In vitro (cell culture)
Almitrine	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Potential agent for the treatment of COPD	[104]	In vivo
Ritonavir	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Antiviral for HIV	[105]	In vivo (clinical trial)*
Indinavir	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Antiviral for HIV	[106]	In vitro (cell culture)*
Telmisartan	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Anti-hypertensive	clinical trial	In vivo (clinical trial)
Atazanavir	inhibitor of MPro/3CL, RdRp, Helicase	inhibitor of SARS-CoV-2 protein(s)	Antiviral for HIV	[107]	In vitro (cell culture)
Remdesivir	inhibitor of MPro/3CL, RdRp	inhibitor of SARS-CoV-2 protein(s)	Antiviral for Ebola, approved for use for SARS CoV-2	[18]	In vivo (clinical trial)
Ciclesonide	inhibitor of MPro/3CL, NSP15	inhibitor of SARS-CoV-2 protein(s)	Agent for the treatment of Asthma (anti-inflammatory)	[108]	In vitro (cell culture)
Sofosbuvir	inhibitor of RdRp	inhibitor of SARS-CoV-2 protein(s)	Antiviral for HepC	clinical trial	In vivo (clinical trial)
Hydroxychloroquine (HCQ)	inhibitor of RdRp	inhibitor of SARS-CoV-2 protein(s)	Antimalarial agent	[109]	In vivo (clinical trial)*
Favipiravir	inhibitor of RdRp	inhibitor of SARS-CoV-2 protein(s)	Antiviral agent	clinical trial	In vivo (clinical trial)
Ribavirin	inhibitor of PLpro	inhibitor of SARS-CoV-2 protein(s)	Antiviral, broad-spectrum	[110]	In vivo (clinical trial)*
Amodiaquine	based on similarity to HCQ	inhibitor of SARS-CoV-2 protein(s)	Anti-malarial	[111]	In vitro (cell culture)
Cycloheximide	protein translation inhibitor	inhibitor of host protein(s)/pathway(s)	No current pharmaceutical use	[95]	In vitro (cell culture)
Emetine	protein translation inhibitor	inhibitor of host protein(s)/pathway(s)	Antiprotozoal	[112]	In vitro (cell culture)
Rapamycin	mTOR inhibitor	inhibitor of host protein(s)/pathway(s)	Immunosuppressant with antifungal and antineoplastic properties	clinical trial	In vivo (clinical trial)
Toremifene	estrogen receptor modulators	inhibitor of host protein(s)/pathway(s)	Selective estrogen receptor modulator	[113]	In vitro (cell culture)
Tamoxifen	estrogen receptor modulators	inhibitor of host protein(s)/pathway(s)	Selective estrogen receptor modulator	[114]	In vitro (cell culture)
Chloroquine	sigma1 receptor of Endoplasmic Reticulum	inhibitor of host protein(s)/pathway(s)	Antiparasitic	[115]	In vitro (cell culture)
Merimepodib	inhibitor of host proteins interacting with SARS-CoV-2 Nsp14	inhibitor of host protein(s)/pathway(s)	IMPDH inhibitor	clinical trial	In vivo (clinical trial)
Mycophenolic acid	inhibitor of host proteins interacting with SARS-CoV-2 Nsp14	inhibitor of host protein(s)/pathway(s)	Immunosuppressant	[116]	In vitro (cell culture)

TABLE 1 (*CONTINUED*)

Drug Name	Predicted MOA	Predicted Class	Current indication	Reference	Validation
Silmitasertib	Kinase inhibitor	inhibitor of host protein(s)/pathway(s)	Potential antineoplastic	90	In vitro (cell culture)
Gilteritinib	Kinase inhibitor	inhibitor of host protein(s)/pathway(s)	Antineoplastic	90	In vitro (cell culture)
ARRY-797	Kinase inhibitor	inhibitor of host protein(s)/pathway(s)	Potential cardiovascular agent	90	In vitro (cell culture)
MAPK13-IN-1	Kinase inhibitor	inhibitor of host protein(s)/pathway(s)	Potential antineoplastic	90	In vitro (cell culture)
SB203580	Kinase inhibitor	inhibitor of host protein(s)/pathway(s)	Potential antineoplastic	90	In vitro (cell culture)
Ralimetinib	Kinase inhibitor	inhibitor of host protein(s)/pathway(s)	Potential antineoplastic	90	In vitro (cell culture)
Apilimod	Kinase inhibitor	inhibitor of host protein(s)/pathway(s)	Antiviral and antineoplastic	90	In vitro (cell culture)
Imatinib	Kinase inhibitor	inhibitor of host protein(s)/pathway(s)	Antineoplastic	116	In vitro (cell culture)
Dinaciclib	Kinase inhibitor	inhibitor of host protein(s)/pathway(s)	Potential antineoplastic	90	In vitro (cell culture)
Camostat mesylate	TMPRSS2 inhibitor	inhibitor of host protein(s)/pathway(s)	Agent for treatment of pancreatitis	117	In vitro (cell culture)
Nafamostat mesylate	TMPRSS2 inhibitor	inhibitor of host protein(s)/pathway(s)	Anticoagulant	clinical trial	In vivo (clinical trial)
Lopinavir	Protease inhibitor	inhibitor of host protein(s)/pathway(s)	Antiretroviral	112	In vitro (cell culture)
Zotatifin	translation inhibitor	inhibitor of host protein(s)/pathway(s)	Potential antineoplastic	clinical trial	in vivo (clinical trial)
Colchicine	Anti-inflammatory	inhibitor of host protein(s)/pathway(s)	Anti-inflammatory	clinical trial	In vivo (clinical trial)
Melatonin	Anti-inflammatory	inhibitor of host protein(s)/pathway(s)	Anti-inflammatory	clinical trial	In vivo (clinical trial)
Siltuximab	IL6 inhibitor	inhibitor of host protein(s)/pathway(s)	Anti-inflammatory agent	118	In vivo
Tetrandrine	Calcium channel blocker	inhibitor of host protein(s)/pathway(s)	Agent for the treatment of hypertension	119	In vitro (cell culture)
				Lacking validation	
Carvedilol	inhibitor of SARS-CoV-2 protein(s), MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Treatment of high blood pressure, congestive heart failure		
Conivaptan	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Treatment for hyponatremia		
Chloroxine	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Antibacterial		
Demexiptiline	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Antidepressant		
Fluorouracil	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Antineoplastic		
Debio-1347	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Antineoplastic		
Mercaptopurine	inhibitor of MPro/3CL	inhibitor of SARS-CoV-2 protein(s)	Antineoplastic agent with immunosuppressant properties		
Emodin	inhibitor of MPro/3CL, Spike protein	inhibitor of SARS-CoV-2 protein(s)	Treatment of Polycystic kidney		
Ganciclovir	inhibitor of MPro/3CL, RdRp, Helicase	inhibitor of SARS-CoV-2 protein(s)	Antiviral		
Idarubicin	inhibitor of RdRp	inhibitor of SARS-CoV-2 protein(s)	Antineoplastic		
Valaciclovir	inhibitor of Spike protein & Spike protein - ACE2 interface complex	inhibitor of SARS-CoV-2 protein(s)	Antiviral		
Sulfamethoxazole	inhibitor of Spike protein & Spike protein - ACE2 interface complex	inhibitor of SARS-CoV-2 protein(s)	Antibacterial		
Dactinomycin	RNA synthesis inhibitor	inhibitor of host protein(s)/pathway(s)	Antineoplastic		
Plitidepsin	translation inhibitor	inhibitor of host protein(s)/pathway(s)	Antineoplastic		
Haloperidol	sigma1/2 receptor of Endoplasmic Reticulum	inhibitor of host protein(s)/pathway(s)	Antipsychotic		
Clemastine	sigma1/2 receptor of Endoplasmic Reticulum	inhibitor of host protein(s)/pathway(s)	Anti allergy		
Cloperastine	sigma1/2 receptor of Endoplasmic Reticulum	inhibitor of host protein(s)/pathway(s)	Cough suppressant		
Pladienolide B	spliceosome inhibitor	inhibitor of host protein(s)/pathway(s)	Potential antineoplastic		
2-deoxy-D-glucose	carbon metabolism	inhibitor of host protein(s)/pathway(s)	Potential antineoplastic and antiviral		
NMS-873	protein homeostasis machinery	inhibitor of host protein(s)/pathway(s)	No current pharmaceutical use		

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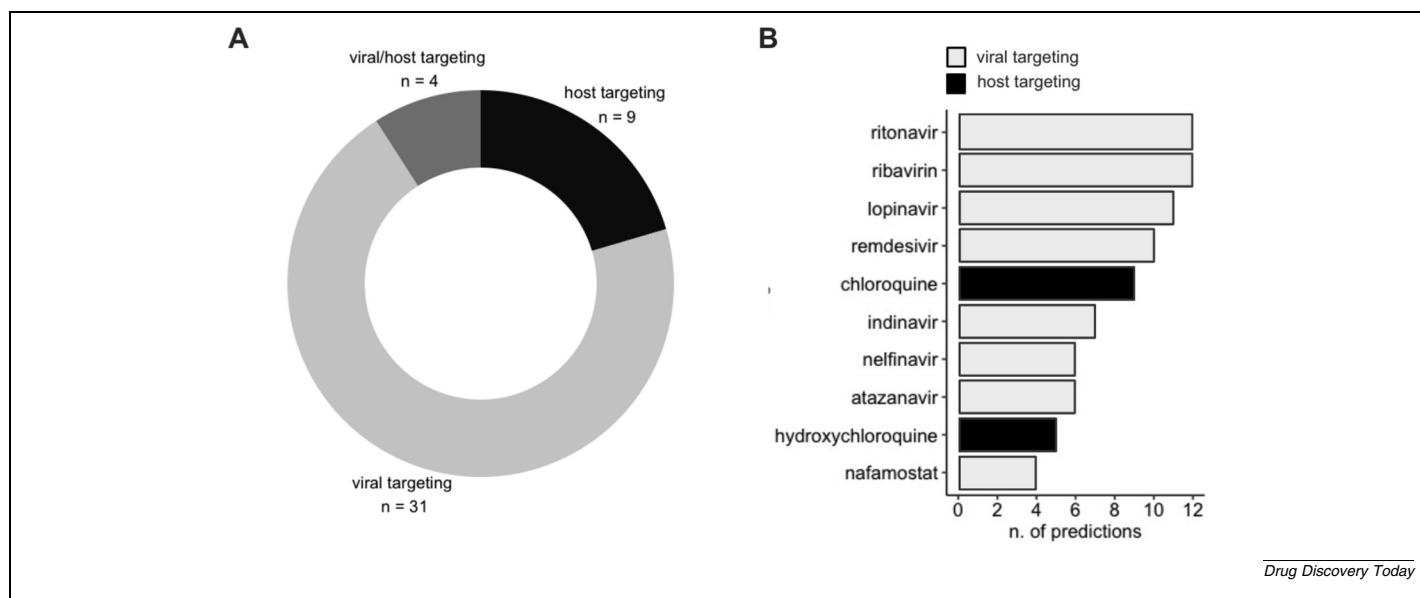
FIGURE 2

Classification of predictions based on the mechanism of action. A. Proportions of reviewed works predicting drugs that target viral proteins, host proteins, or both. B. The most commonly predicted drugs, classified as either virus or host targeting. Several drugs have been predicted by multiple works.

other viral proteins. We found extensive overlap between the drug compounds predicted by the reviewed works. Many commonly used antivirals that have garnered international attention and have been used clinically in the treatment of COVID-19,[101,102] such as ritonavir and ribavirin, were predicted by up to 12 different computational approaches (Fig. 2B).

The second mechanism is the inhibition of host pathways predicted by network-based and hybrid approaches (Fig. 2A, seen in 9 of 44 reviewed works). These methods identified host targets involved in virus life cycle, particularly entry and RNA synthesis. Progress in identifying inhibitors of host pathways that contribute to pathogenesis is critical, particularly for a virus that has already mutated enough to render some previously effective therapeutics significantly less potent. Of note, current methods are less effective in identifying drugs that target other key host pathways that contribute to pathology, such as aberrant immune responses and thrombosis, whose therapeutic manipulation showed promising results.[103–106] This may be due to a poor molecular understanding of the systems-level effects of SARS-CoV-2 infection. Finally, a few studies have identified both viral and host proteins as potential targets (Fig. 2A, seen in 4 of 44 reviewed works). These predictions were produced by docking and structure-based machine learning, which are not intrinsically limited to the identification of viral proteins as targets.

The overall strengths, limitations, and successful applications of the methodologies included in this review have been discussed previously.[19–25] In the context of COVID-19, an additional challenge is the lack of solid prior biological knowledge. The knowledge required for each of the different method classes is being accumulated at different rates. For example, the SARS-CoV-2 protein structure, which is required for docking, was quickly solved for several viral proteins. On the other hand, the mapping of the virus–host interactome, which is needed for network approaches, is a research objective that will require

longer-term effort. Therefore, efforts to assess the success rates of the different methods for COVID-19 drug repurposing are still premature. Regardless of the specific method being used, the preconditions for success go beyond target activity to encompass other key pharmacological aspects, such as safety, toxicity and drug–drug interactions. Furthermore, as noted by Edwards,[107] the success rate of hypothesis-driven repurposing research far exceeds that of large-scale, hypothesis-free screenings. This concept is also evident in works of Gordon *et al.*,[89] Jin *et al.*[61] and Bojkova *et al.*[95] reviewed here, which first produced data specifically for hypothesis generation, before validating the predictions *in vitro*. Going forward, the increasing accumulation of data, as well as improved knowledge of COVID-19 pathology, should enhance our ability to strike the right balance between hypothesis-driven screenings and the predominantly data-driven repurposing strategies reviewed here.

With this objective in mind, we have curated a list of COVID-19-specific data portals. We also include a list of other relevant resources typically employed by computational repurposing methods, both for COVID-19 and more broadly (Table 2). These repositories contain data describing gene and protein sequences and structures; drugs and drug targets; properties of chemical compounds; and biological networks and pathways. Furthermore, several -omics datasets, profiling SAR-CoV-2 infection in various tissues, have been published.[108–113] Although not exhaustive, our curated lists include the most commonly utilized repositories and provides a basis for future work.

Effective treatment of complex diseases, such as viral infections, may require the targeting of multiple host and viral processes. Severity and mortality of COVID-19 are highly dependent upon biological factors, such as older age, and upon pre-existing conditions, such as hypertension, diabetes, cardiovascular disease, or chronic obstructive pulmonary disease (COPD).[114–117] The optimal treatment is likely to depend on a

TABLE 2

Curated list of COVID-19-specific resources and repositories relevant to computational drug repurposing.

Resource/ data type	Resource name	Website	Description	Reference
COVID-19 platform	CORD-19	https://www.kaggle.com/allen-institute-for-ai/CORD-19-research-challenge	Scholarly articles on COVID-19, SARS-CoV-2, and other related coronaviruses, with a focus on natural language processing and other AI techniques	97
	COVID-19 portfolio	https://icite.od.nih.gov/covid19/search/	Publications and preprints on COVID-19 and SARS-CoV-2	–
	COVIDScholar	https://covidscholar.org/	Search engine that utilizes natural language processing to aid in the search for COVID-19 articles	–
	COVID-19 research explorer	https://covid19-research-explorer.appspot.com/	Search engine for COVID-19 that operates on question-based searches	–
	SPIKE-CORD	https://spike.covid-19.apps.allenai.org/search/covid19	Search engine for CORD-19 which operates on query modes to perform extractive searches	–
	Virus-CKB	https://www.cbligand.org/g/virus-ckb	Knowledgebase for research on COVID-19 and similar viral infections	123
	SciSight	https://scisight.apps.allenai.org/	Tool used to visualize the directions of the emerging literature network related to COVID-19	–
	KnetMiner	https://knetminer.org/COVID-19/	Search engine that aids in COVID-19 related search queries based on keywords, gene lists, and genomic regions	–
	COVID-19 Primer	https://covid19primer.com/dashboard	Tool that uses natural language processing (NLP) to summarize research trends, news coverage, and social media discussions on the topic of COVID-19 and SARS-CoV-2	–
	COVID-19 drug and gene set library	https://maayanlab.cloud/covid19/	A collection of drug and gene sets related to COVID-19 research contributed by the community	35
	CDC COVID-19 Databases and Journals	https://www.cdc.gov/library/researchguides/2019novelcoronavirus/databasesjournals.html	Compilation of selected databases and journals that can help researchers to find scholarly articles and data relating to COVID-19	–
	LitCovid	https://www.ncbi.nlm.nih.gov/research/coronavirus/	A curated literature hub for tracking up-to-date scientific information about SARS-CoV-2	124
	iSearch COVID-19 portfolio	https://icite.od.nih.gov/covid19/search/	An expert-curated database containing published papers and preprints	–
	WHO COVID-19 research article database	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov	A database gathering the latest international multilingual scientific findings and knowledge on COVID-19	–
	COVID-KOP	https://covidkop.renci.org/	Biomedical reasoning system for data collected about the COVID-19 pandemic, including information on drugs, literature co-occurrences and phenotypes	125
	HIT-COVID	https://akuko.io/post/covid-intervention-tracking	Quantification of the effectiveness of public health measures on SARS-CoV-2 transmission	126
	COVID Moonshot	https://covid.postera.ai/covid	Crowdsourced initiative to accelerate the development of a COVID-19 antiviral	127
	CIDO	http://www.ontobee.org/ontology/CIDO	Community-based ontology that supports COVID-19 knowledge and data standardization, integration, sharing, and analysis	128
	COVEX	https://exbio.wzw.tum.de/covex/about	Online network and systems medicine platform for data analysis that integrates virus–human interactions for SARS-CoV-2 and SARS-CoV-1	129
	The COVIDome Project	https://www.ncbi.nlm.nih.gov/sars-cov-2/	Collaborative effort to generate multidimensional datasets from biospecimens from COVID-19 patients and controls	–
	NCBI SARS-CoV-2 Resource	https://www.ncbi.nlm.nih.gov/sars-cov-2/	An expert-curated database which was developed to increase the useability of existing resources	–
	PDBe COVID-19	https://www.ebi.ac.uk/pdbe/covid-19	3D-structure data for large biological molecules, such as proteins and nucleic acids, that are specific to SARS-CoV-2	130

(continued on next page)

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TABLE 2 (CONTINUED)

Resource/ data type	Resource name	Website	Description	Reference
Compound database	ZINC15	https://zinc15.docking.org/	3D formats of purchasable compounds and their different properties, such as rings, substances, tranches, and patterns	[45]
Drug response	PharmGKB	https://www.pharmgkb.org/	Data on the impact of genetic variations on drug response and annotated information on drugs	[131]
Drugs and drug targets	IUPHAR/BPS guide to pharmacology	https://www.guidetopharmacology.org/	Information on drug targets, and on prescription and experimental medications that act on them	–
	DrugBank	https://www.drugbank.ca/	Information on drugs and their chemical and pharmacological properties; this resource also contains information on drug targets and their sequences, structures, and pathways	[132]
	Drug Target Commons Database	https://drugtargetcommons.fimm.fi/	Bioactivity data for drugs and their targets	[84]
Drugs	Drug repurposing for COVID-19	http://covid19.md.biu.ac.il/	Database of existing drugs that have potential or proven efficacy against SARS-CoV-2	–
Binding affinities	BindingDB	https://www.bindingdb.org/bind/index.jsp	Information on the binding affinities between molecular entities and protein targets	[83]
Gene	GenBank	https://www.ncbi.nlm.nih.gov/genbank/	Publicly available DNA sequences	[133]
	EMBL-ENA	https://www.ebi.ac.uk/ena	Nucleotide sequencing information	[134]
	GeneCards	https://www.genecards.org/	Annotated and predicted human genes	[135]
	CMAP	https://www.broadinstitute.org/connectivity-map-cmap	Gene expression profiles and disease-associated genes	[136]
	MSigDB	https://www.gsea-msigdb.org/gsea/msigdb/index.jsp	Annotated gene sets that can be utilized with Gene Set Enrichment Analysis (GSEA) software	[137]
Protein	UniProt	https://covid-19.uniprot.org/uniprotkb?query=*	Information on protein sequence and annotation of SARS-CoV-2	[138]
	Swiss-Prot	https://www.uniprot.org/statistics/Swiss-Prot	Part of UniProt, this resource includes protein sequences and their functional information	[139]
	PDB	https://www.rcsb.org/	3D structure data for large biological molecules, such as proteins and nucleic acids	[130]
	PRIDE	https://www.ebi.ac.uk/pride/	Mass spectrometry proteomics and genomic data	[140]
	CORUM	http://mips.helmholtz-muenchen.de/corum/	Protein complexes, protein subunits, literature references, and experimental reports	[141]
Multi type	KEGG	https://www.genome.jp/kegg	Information on drugs, genes, proteins and pathways	[142]

specific patient's characteristics, so future repurposing methods may account for variation in risk factors, leading to personalized treatments.

Combination therapies increase the spectrum of disease modulation, improving drug efficacy/toxicity ratios and combating drug resistance.[118] A synergistic effect can be created by using several drugs that target different disease pathways.[119] For example, combination drug therapy has become the gold standard in the treatment of cancer[120] and in the treatment of several virus infections, notably HIV.[121] The principle of 'complementary exposure',[122] which optimizes drug effects over a large portion of the disease network, has predicted several synergistic drug combinations for the treatment of COVID-19. One example is sirolimus and dactinomycin, which inhibit mTOR signaling and RNA synthesis pathways, respectively. An important challenge and a promising objective for future computational drug repurposing is the ability to design effective drug combinations that target multiple COVID-19 pathological pathways.

Computational drug repurposing has led to remarkable success stories in several disease areas, including cancer, autoimmune diseases, and viral infections. Despite the many challenges, our review lays out the early promising steps towards successful computational repurposing for COVID-19.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1 M.Z. Tay, C.M. Poh, L. Rénia, P.A. MacAry, L.F.P. Ng, The trinity of COVID-19: immunity, inflammation and intervention, Nat Rev Immunol 20 (6) (2020) 363–374, https://doi.org/10.1038/s41577-020-0311-8.

2 H. Wang, X. Li, T. Li, S. Zhang, L. Wang, X. Wu, J. Liu, The genetic sequence, origin, and diagnosis of SARS-CoV-2, Eur J Clin Microbiol Infect Dis 39 (9) (2020) 1629–1635, https://doi.org/10.1007/s10096-020-03899-4.

3 G. Nitulescu, H. Paunescu, S. Moschos, D. Petrakis, G. Nitulescu, G. Ion, D. Spandidos, T. Nikolouzakis, N. Drakoulis, A. Tsatsakis, Comprehensive analysis of drugs to treat SARS-CoV-2 infection: mechanistic insights into current COVID-19 therapies (Review), Int J Mol Med 46 (2) (2020) 467–488, https://doi.org/10.3892/ijmm10.3892/ijmm.2020.4608.

4 J.R. Lechien, T. Radulesco, C. Calvo-Henriquez, C.M. Chiesa-Estomba, S. Hans, M.R. Barillari, et al., ACE2 & TMPRSS2 expressions in head & neck tissues: a systematic review, Head Neck Pathol 15 (2021) 225–235, https://doi.org/10.1007/s12105-020-01212-5.

5 L. Mousavizadeh, S. Ghasemi, Genotype and phenotype of COVID-19: their roles in pathogenesis, J Microbiol Immunol Infect 54 (2) (2021) 159–163, https://doi.org/10.1016/j.jmii.2020.03.022.

6 W. Dai, B. Zhang, X.-M. Jiang, H. Su, J. Li, Y. Zhao, X. Xie, Z. Jin, J. Peng, F. Liu, C. Li, Y. Li, F. Bai, H. Wang, X.i. Cheng, X. Cen, S. Hu, X. Yang, J. Wang, X. Liu, G. Xiao, H. Jiang, Z. Rao, L.-K. Zhang, Y. Xu, H. Yang, H. Liu, Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease, Science 368 (6497) (2020) 1331–1335, https://doi.org/10.1126/science:abb4489.

7 A. Mittal, K. Manjunath, R.K. Ranjan, S. Kaushik, S. Kumar, V. Verma, T.C. Hobman, COVID-19 pandemic: insights into structure, function, and hACE2 receptor recognition by SARS-CoV-2, PLoS Pathog 16 (8) (2020) e1008762, https://doi.org/10.1371/journal.ppat.1008762.

8 Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol 17: 46–64. doi:10.1038/s41581-020-00357-4

9 K. Yuki, M. Fujiogi, S. Koutsogiannaki, COVID-19 pathophysiology: a review, Clin Immunol 215 (2020) 108427, https://doi.org/10.1016/j.clim.2020.108427.

10 M.U. Ahmed, M. Hanif, M.J. Ali, M.A. Haider, D. Kherani, G.M. Memon, A.H. Karim, A. Sattar, Neurological manifestations of COVID-19 (SARS-CoV-2): a review, Front Neurol 11 (2020), https://doi.org/10.3389/fneur.2020.00518.

11 A.N. Kochi, A.P. Tagliari, G.B. Forleo, G.M. Fassini, C. Tondo, Cardiac and arrhythmic complications in patients with COVID-19, J Cardiovasc Electrophysiol 31 (5) (2020) 1003–1008, https://doi.org/10.1111/jce.v31.510.1111/jce.14479.

12 F. Amanat, F. Krammer, SARS-CoV-2 vaccines: status report, Immunity 52 (4) (2020) 583–589, https://doi.org/10.1016/j.immuni.2020.03.007.

13 D. Zhou, W. Dejnirattisai, P. Supasa, C. Liu, A.J. Mentzer, H.M. Ginn, Y. Zhao, H.M.E. Duyvesteyn, A. Tuekprakhon, R. Nutalai, B. Wang, G.C. Paesen, C. Lopez-Camacho, J. Slon-Campos, B. Hallis, N. Coombes, K. Bewley, S. Charlton, T.S. Walter, D. Skelly, S.F. Lumley, C. Dold, R. Levin, T. Dong, A.J. Pollard, J.C. Knight, D. Crook, T. Lambe, E. Clutterbuck, S. Bibi, A. Flaxman, M. Bittaye, S. Belij-Rammerstorfer, S. Gilbert, W. James, M.W. Carroll, P. Klenerman, E. Barnes, S.J. Dunachie, E.E. Fry, J. Mongkolsapaya, J. Ren, D.I. Stuart, G.R.

Screaton, Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera, Cell 184 (9) (2021) 2348–2361.e6, https://doi.org/10.1016/j.cell.2021.02.037.

14 A.D. Paltiel, J.L. Schwartz, A. Zheng, R.P. Walensky, Clinical outcomes of a COVID-19 vaccine: implementation over efficacy, Health Aff (Millwood) 40 (1) (2021) 42–52, https://doi.org/10.1377/hlthaff.2020.02054.

15 J.A. DiMasi, M.I. Florez, S. Stergiopoulos, Y. Peña, Z. Smith, M. Wilkinson, K.A. Getz, Development times and approval success rates for drugs to treat infectious diseases, Clin Pharmacol Ther 107 (2) (2020) 324–332, https://doi.org/10.1002/cpt.v107.210.1002/cpt.1627.

16 S. Pushpakom, F. Iorio, P.A. Eyers, K.J. Escott, S. Hopper, A. Wells, A. Doig, T. Guilliams, J. Latimer, C. McNamee, A. Norris, P. Sanseau, D. Cavalla, M. Pirmohamed, Drug repurposing: progress, challenges and recommendations, Nat Rev Drug Discov 18 (1) (2019) 41–58, https://doi.org/10.1038/nrd.2018.168.

17 B. Mercorelli, G. Palù, A. Loregian, Drug repurposing for viral infectious diseases: how far are we?, Trends Microbiol 26 (10) (2018) 865–876, https://doiorg/10.1016/j.tim.2018.04.004.

18 J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M.-D. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, H.C. Lane, Remdesivir for the treatment of Covid-19 – final report, N Engl J Med 383 (19) (2020) 1813–1826, https://doi.org/10.1056/NEJMoa2007764.

19 S. D'Souza, K.V. Prema, S. Balaji, Machine learning models for drug-target interactions: current knowledge and future directions, Drug Discov Today 25 (4) (2020) 748–756, https://doi.org/10.1016/j.drudis.2020.03.003.

20 Y. Masoudi-Sobhanzadeh, Y. Omidi, M. Amanlou, A. Masoudi-Nejad, Drug databases and their contributions to drug repurposing, Genomics 112 (2) (2020) 1087–1095, https://doi.org/10.1016/j.ygeno.2019.06.021.

21 M. Lotfi Shahreza, N. Ghadiri, S.R. Mousavi, J. Varshosaz, J.R. Green, A review of network-based approaches to drug repositioning, Brief Bioinformatics 19 (2018) 878–892, https://doi.org/10.1093/bib/bbx017.

22 Q. Vanhaelen, P. Mamoshina, A.M. Aliper, A. Artemov, K. Lezhnina, I. Ozerov, I. Labat, A. Zhavoronkov, Design of efficient computational workflows for in silico drug repurposing, Drug Discov Today 22 (2) (2017) 210–222, https://doi.org/10.1016/j.drudis.2016.09.019.

23 L.B. Tari, J.H. Patel, Systematic drug repurposing through text mining, Methods Mol Biol 1159 (2014) 253–267, https://doi.org/10.1007/978-1-4939-0709-0_14.

24 G. Sliwoski, S. Kothiwale, J. Meiler, E.W. Lowe, E.L. Barker, Computational methods in drug discovery, Pharmacol Rev 66 (1) (2014) 334–395, https://doi.org/10.1124/pr.112.007336.

25 M.D. Paranjpe, A. Taubes, M. Sirota, Insights into computational drug repurposing for neurodegenerative disease, Trends Pharmacol Sci 40 (8) (2019) 565–576, https://doi.org/10.1016/j.tips.2019.06.003.

Reviews • KEYNOTE REVIEW

26 T.U. Singh, S. Parida, M.C. Lingaraju, M. Kesavan, D. Kumar, R.K. Singh, Drug repurposing approach to fight COVID-19, Pharmacol Rep 72 (6) (2020) 1479–1508, https://doi.org/10.1007/s43440-020-00155-6.

27 V. Parvathaneni, V. Gupta, Utilizing drug repurposing against COVID-19 – efficacy, limitations, and challenges, Life Sci 259 (2020) 118275, https://doi.org/10.1016/j.lfs.2020.118275.

28 Naveja JJ, Madariaga-Mazón A, Flores-Murrieta F, Granados-Montiel J, Maradiaga-Ceceña M, Alaniz VD, et al. Union is strength: antiviral and anti-inflammatory drugs for COVID-19. Drug Discov Today 26: 229–39. doi:10.1016/j.drudis.2020.10.018

29 K. Mohamed, N. Yazdanpanah, A. Saghazadeh, N. Rezaei, Computational drug discovery and repurposing for the treatment of COVID-19: a systematic review, Bioorg Chem 106 (2021) 104490, https://doi.org/10.1016/j.bioorg.2020.104490.

30 A. Keshavarzi Arshadi, J. Webb, M. Salem, E. Cruz, S. Calad-Thomson, N. Ghadirian, J. Collins, E. Diez-Cecilia, B. Kelly, H. Goodarzi, J.S. Yuan, Artificial Intelligence for COVID-19 drug discovery and vaccine development, Front Artif Intell 3 (2020), https://doi.org/10.3389/frai.2020.00065.

31 Y. Zhou, F. Wang, J. Tang, R. Nussinov, F. Cheng, Artificial intelligence in COVID-19 drug repurposing, Lancet Digit Health 2 (12) (2020) e667–e676, https://doi.org/10.1016/S2589-7500(20)30192-8.

32 S. Dotolo, A. Marabotti, A. Facchiano, R. Tagliaferri, A review on drug repurposing applicable to COVID-19, Brief Bioinformatics 22 (2021) 726–741, https://doi.org/10.1093/bib/bbaa288.

33 G. Galindez, J. Matschinske, T.D. Rose, S. Sadegh, M. Salgado-Albarrán, J. Späth, J. Baumbach, J.K. Pauling, Lessons from the COVID-19 pandemic for advancing computational drug repurposing strategies, Nat Comput Sci 1 (1) (2021) 33–41, https://doi.org/10.1038/s43588-020-00007-6.

34 X. Wang, Y. Guan, COVID-19 drug repurposing: a review of computational screening methods, clinical trials, and protein interaction assays, Med Res Rev 41 (1) (2021) 5–28, https://doi.org/10.1002/med.v41.110.1002/med.21728.

35 M.V. Kuleshov, D.J. Stein, D.J.B. Clarke, E. Kropiwnicki, K.M. Jagodnik, A. Bartal, J.E. Evangelista, J. Hom, M. Cheng, A. Bailey, A. Zhou, L.B. Ferguson, A. Lachmann, A. Ma'ayan, The COVID-19 Drug and Gene Set Library, Patterns (N Y) 1 (6) (2020) 100090, https://doi.org/10.1016/j.patter.2020.100090.

36 Tworowski D, Gorohovski A, Mukherjee S, Carmi G, Levy E, Detroja R, et al. COVID19 Drug Repository: text-mining the literature in search of putative COVID19 therapeutics. Nucleic Acids Res 2021; 49: D1113–21. doi:10.1093/nar/gkaa969

37 R.A. Friesner, J.L. Banks, R.B. Murphy, T.A. Halgren, J.J. Klicic, D.T. Mainz, et al., Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy, J Med Chem 47 (2004) 1739–1749, https://doi.org/10.1021/jm0306430.

38 O. Trott, A.J. Olson, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading, J Comput Chem 31 (2010) 455–461, https://doi.org/10.1002/jcc.21334.

39 A. Grosdidier, V. Zoete, O. Michielin, SwissDock, a protein-small molecule docking web service based on EADock DSS, Nucleic Acids Res 39 (suppl) (2011) W270–W277, https://doi.org/10.1093/nar/gkr366.

40 E.G. Phimister, J.M. Parks, J.C. Smith, How to discover antiviral drugs quickly, N Engl J Med 382 (23) (2020) 2261–2264, https://doi.org/10.1056/NEJMcibr2007042.

41 X. Liu, X.-J. Wang, Potential inhibitors against 2019-nCoV coronavirus M protease from clinically approved medicines, J Genet Genomics 47 (2) (2020) 119–121, https://doi.org/10.1016/j.jgg.2020.02.001.

42 C.N. Cavasotto, S.S. Phatak, Homology modeling in drug discovery: current trends and applications, Drug Discov Today 14 (13-14) (2009) 676–683, https://doi.org/10.1016/j.drudis.2009.04.006.

43 Waterhouse A, Bertoni M, Bienert S, Studer G, Tauriello G, Gumienny R, et al. SWISS-MODEL: homology modelling of protein structures and complexes. Nucleic Acids Res 2018; 46: W296–303. doi:10.1093/nar/gky427

44 C. Wu, Y. Liu, Y. Yang, P. Zhang, W.u. Zhong, Y. Wang, Q. Wang, Y. Xu, M. Li, X. Li, M. Zheng, L. Chen, H. Li, Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods, Acta Pharm Sin B 10 (5) (2020) 766–788, https://doi.org/10.1016/j.apsb:2020.02.008.

45 T. Sterling, J.J. Irwin, ZINC 15 – ligand discovery for everyone, J Chem Inf Model 55 (11) (2015) 2324–2337, https://doi.org/10.1021/acs.jcim.5b00559.

46 A.A. Elfiky, Anti-HCV, nucleotide inhibitors, repurposing against COVID-19, Life Sci 248 (2020) 117477, https://doi.org/10.1016/j.lfs.2020.117477.

47 A.A. Elfiky, Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study, Life Sci 253 (2020) 117592, https://doi.org/10.1016/j.lfs.2020.117592.

48 Chen YW, Yiu C-PB, Wong K-Y. Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CL pro) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates. F1000Res 2020; 9: 129. doi:10.12688/f1000research.22457.2

49 C.N. Cavasotto, J.I. Di Filippo, In silico drug repurposing for COVID-19: targeting SARS-CoV-2 proteins through docking and consensus ranking, Mol Inform 40 (1) (2021) 2000115, https://doi.org/10.1002/minf.v40.110.1002/minf.202000115.

50 J.F. Borgio, H.S. Alsuwat, W.M. Al Otaibi, A.M. Ibrahim, N. Almandil, L.I. Al Asoom, M. Salahuddin, B. Kamaraj, S. AbdulAzeez, State-of-the-art tools unveil potent drug targets amongst clinically approved drugs to inhibit helicase in SARS-CoV-2, Arch Med Sci 16 (3) (2020) 508–518, https://doi.org/10.5114/aoms.2020.94567.

51 A. Basu, A. Sarkar, U. Maulik, Molecular docking study of potential phytochemicals and their effects on the complex of SARS-CoV2 spike protein and human ACE2, Sci Rep 10 (2020) 17699, https://doi.org/10.1038/s41598-020-74715-4.

52 N. Rahman, Z. Basharat, M. Yousuf, G. Castaldo, L. Rastrelli, H. Khan, Virtual screening of natural products against type II transmembrane serine protease (TMPRSS2), the priming agent of Coronavirus 2 (SARS-CoV-2), Molecules 25 (2020) 2271, https://doi.org/10.3390/molecules25102271.

53 A.D. Elmezayen, A. Al-Obaidi, A.T. Şahin, K. Yelekçi, Drug repurposing for coronavirus (COVID-19): in silico screening of known drugs against coronavirus 3CL hydrolase and protease enzymes, J Biomol Struct Dyn 39 (8) (2021) 2980–2992, https://doi.org/10.1080/07391102.2020.1758791.

54 R. Yu, L. Chen, R. Lan, R. Shen, P. Li, Computational screening of antagonists against the SARS-CoV-2 (COVID-19) coronavirus by molecular docking, Int J Antimicrob Agents 56 (2) (2020) 106012, https://doi.org/10.1016/j.ijantimicag.2020.106012.

55 M. Sencanski, V. Perovic, S.B. Pajovic, M. Adzic, S. Paessler, S. Glisic, Drug repurposing for candidate SARS-CoV-2 main protease inhibitors by a novel in silico method, Molecules 25 (2020) 3830, https://doi.org/10.3390/molecules25173830.

56 B. Shah, P. Modi, S.R. Sagar, In silico studies on therapeutic agents for COVID-19: drug repurposing approach, Life Sci 252 (2020) 117652, https://doi.org/10.1016/j.lfs.2020.117652.

57 A. Gimeno, J. Mestres-Truyol, M.J. Ojeda-Montes, G. Macip, B. Saldivar-Espinoza, A. Cereto-Massagué, G. Pujadas, S. Garcia-Vallvé, Prediction of novel inhibitors of the main protease (M-pro) of SARS-CoV-2 through consensus docking and drug reposition, Int J Mol Sci 21 (11) (2020) 3793, https://doi.org/10.3390/ijms21113793.

58 Liu S, Zheng Q, Wang Z. Potential covalent drugs targeting the main protease of the SARS-CoV-2 coronavirus. Bioinformatics 2020; 36: 3295–8. doi:10.1093/bioinformatics/btaa224

59 M. Kandeel, M. Al-Nazawi, Virtual screening and repurposing of FDA approved drugs against COVID-19 main protease, Life Sci 251 (2020) 117627, https://doi.org/10.1016/j.lfs.2020.117627.

60 Kouznetsova VL, Zhang A, Tatineni M, Miller MA, Tsigelny IF. Potential COVID-19 papain-like protease PLpro inhibitors: repurposing FDA-approved drugs. Peer J 2020; 8: e9965. doi:10.7717/peerj.9965

61 Z. Jin, X. Du, Y. Xu, Y. Deng, M. Liu, Y. Zhao, B. Zhang, X. Li, L. Zhang, C. Peng, Y. Duan, J. Yu, L. Wang, K. Yang, F. Liu, R. Jiang, X. Yang, T. You, X. Liu, X. Yang, F. Bai, H. Liu, X. Liu, L.W. Guddat, W. Xu, G. Xiao, C. Qin, Z. Shi, H. Jiang, Z. Rao, H. Yang, Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors, Nature 582 (7811) (2020) 289–293, https://doi.org/10.1038/s41586-020-2223-y.

62 H. Yang, W. Xie, X. Xue, K. Yang, J. Ma, W. Liang, Q.i. Zhao, Z. Zhou, D. Pei, J. Ziebuhr, R. Hilgenfeld, K.Y. Yuen, L. Wong, G. Gao, S. Chen, Z. Chen, D. Ma, M. Bartlam, Z. Rao, P. Bjorkman, Design of wide-spectrum inhibitors targeting coronavirus main proteases, PLoS Biol 3 (10) (2005) e324, https://doi.org/10.1371/journal.pbio.0030324.

63 L. Chen, C. Gui, X. Luo, Q. Yang, S. Günther, E. Scandella, C. Drosten, D. Bai, X. He, B. Ludewig, J. Chen, H. Luo, Y. Yang, Y. Yang, J. Zou, V. Thiel, K. Chen, J. Shen, X.u. Shen, H. Jiang, Cinanserin is an inhibitor of the 3C-like proteinase of severe acute respiratory syndrome coronavirus and strongly reduces virus replication in vitro, J Virol 79 (11) (2005) 7095–7103, https://doi.org/10.1128/JVI.79.11.7095-7103.2005.

64 D.-W. Zhang, H.-L. Yan, X.-S. Xu, L. Xu, Z.-H. Yin, S. Chang, H. Luo, The selenium-containing drug ebselen potently disrupts LEDGF/p75-HIV-1 integrase interaction by targeting LEDGF/p75, J Enzyme Inhib Med Chem 35 (1) (2020) 906–912, https://doi.org/10.1080/14756366.2020.1743282.

65 S. Mukherjee, W.S. Weiner, C.E. Schroeder, D.S. Simpson, A.M. Hanson, N.L. Sweeney, R.K. Marvin, J. Ndjomou, R. Kolli, D. Isailovic, F.J. Schoenen, D.N.

Frick, Ebselen inhibits hepatitis C virus NS3 helicase binding to nucleic acid and prevents viral replication, ACS Chem Biol 9 (10) (2014) 2393–2403, https://doi.org/10.1021/cb500512z.

66 Y. Simanjuntak, J.-J. Liang, S.-Y. Chen, J.-K. Li, Y.-L. Lee, H.-C. Wu, Y.-L. Lin, T. C. Pierson, Ebselen alleviates testicular pathology in mice with Zika virus infection and prevents its sexual transmission, PLoS Pathog 14 (2) (2018) e1006854, https://doi.org/10.1371/journal.ppat.1006854.

67 D. Van Der Spoel, E. Lindahl, B. Hess, G. Groenhof, A.E. Mark, H.J.C. Berendsen, GROMACS: fast, flexible, and free, J Comput Chem 26 (16) (2005) 1701–1718, https://doi.org/10.1002/(ISSN)1096-987X10.1002/jcc.v26:1610.1002/jcc.20291.

68 D.A. Case, T.E. Cheatham, T. Darden, H. Gohlke, R. Luo, K.M. Merz, A. Onufriev, C. Simmerling, B. Wang, R.J. Woods, The Amber biomolecular simulation programs, J Comput Chem 26 (16) (2005) 1668–1688, https://doi.org/10.1002/(ISSN)1096-987X10.1002/jcc.v26:1610.1002/jcc.20290.

69 L. Mittal, A. Kumari, M. Srivastava, M. Singh, S. Asthana, Identification of potential molecules against COVID-19 main protease through structure-guided virtual screening approach, J Biomol Struct Dyn 39 (10) (2021) 3662–3680, https://doi.org/10.1080/07391102.2020.1768151.

70 K. Al-Khafaji, D. Al-Duhaidahawi, T.T. Taskin, Using integrated computational approaches to identify safe and rapid treatment for SARS-CoV-2, J Biomol Struct Dyn 39 (2021) 3387–3395, https://doi.org/10.1080/07391102.2020.1764392.

71 S. Pant, M. Singh, V. Ravichandiran, U.S.N. Murty, H.K. Srivastava, Peptide-like and small-molecule inhibitors against Covid-19, J Biomol Struct Dyn 39 (8) (2021) 2904–2913, https://doi.org/10.1080/07391102.2020.1757510.

72 N. Muralidharan, R. Sakthivel, D. Velmurugan, M.M. Gromiha, Computational studies of drug repurposing and synergism of lopinavir, oseltamivir and ritonavir binding with SARS-CoV-2 protease against COVID-19, J Biomol Struct Dyn 39 (7) (2021) 2673–2678, https://doi.org/10.1080/07391102.2020.1752802.

73 H.A. Odhar, S.W. Ahjel, A.A.M.A. Albeer, A.F. Hashim, A.M. Rayshan, S.S. Humadi, Molecular docking and dynamics simulation of FDA approved drugs with the main protease from 2019 novel coronavirus, Bioinformation 16 (2020) 236–244, https://doi.org/10.6026/97320630016236.

74 S.A. Khan, K. Zia, S. Ashraf, R. Uddin, Z. Ul-Haq, Identification of chymotrypsin-like protease inhibitors of SARS-CoV-2 via integrated computational approach, J Biomol Struct Dyn 39 (7) (2021) 2607–2616, https://doi.org/10.1080/07391102.2020.1751298.

75 A.A. Elfiky, SARS-CoV-2 RNA dependent RNA polymerase (RdRp) targeting: an in silico perspective, J Biomol Struct Dyn 39 (2021) 3204–3212, https://doi.org/10.1080/07391102.2020.1761882.

76 J.A. Encinar, J.A. Menendez, Potential drugs targeting early innate immune evasion of SARS-Coronavirus 2 via 2'-O-methylation of viral RNA, Viruses 12 (2020) 525, https://doi.org/10.3390/v12050525.

77 I. Abdelli, F. Hassani, S. Bekkel Brikci, S. Ghalem, In silico study the inhibition of angiotensin converting enzyme 2 receptor of COVID-19 by Ammoides verticillata components harvested from Western Algeria, J Biomol Struct Dyn 39 (2021) 3263–3276, https://doi.org/10.1080/07391102.2020.1763199.

78 A. Trezza, D. Iovinelli, A. Santucci, F. Prischi, O. Spiga, An integrated drug repurposing strategy for the rapid identification of potential SARS-CoV-2 viral inhibitors, Sci Rep 10 (2020) 13866, https://doi.org/10.1038/s41598-020-70863-9.

79 Gao K, Nguyen DD, Chen J, Wang R, Wei G. Repositioning of 8565 existing drugs for COVID-19. J Phys Chem Lett June 2020; 11: 5373–82. doi:10.1021/acs.jpclett.0c01579

80 R. Batra, H. Chan, G. Kamath, R. Ramprasad, M.J. Cherukara, S.K.R.S. Sankaranarayanan, Screening of therapeutic agents for COVID-19 using machine learning and ensemble docking studies, J Phys Chem Lett 11 (17) (2020) 7058–7065, https://doi.org/10.1021/acs.jpclett.0c0227810.1021/acs.jpclett.0c02278.s00110.1021/acs.jpclett.0c02278.s002.

81 B.R. Beck, B. Shin, Y. Choi, S. Park, K. Kang, 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 18 (2020) 784–790, https://doi.org/10.1016/j.csbj.2020.03.025.

82 A.-T. Ton, F. Gentile, M. Hsing, F. Ban, A. Cherkasov, Rapid identification of potential inhibitors of SARS-CoV-2 main protease by deep docking of 1.3 billion compounds. Mol, Inform 39 (8) (2020) 2000028, https://doi.org/10.1002/minf.v39.810.1002/minf.202000028.

83 T. Liu, Y. Lin, X. Wen, R.N. Jorissen, M.K. Gilson, BindingDB: a web-accessible database of experimentally determined protein-ligand binding affinities, Nucleic Acids Res 35 (Database) (2007) D198–D201, https://doi.org/10.1093/nar/gkl999.

84 Z. Tanoli, Z. Alam, M. Vähä-Koskela, B. Ravikumar, A. Malyutina, A. Jaiswal, et al., Drug Target Commons 2.0: a community platform for systematic analysis of drug-target interaction profiles, Database (Oxford) 2018 (2018) 1–13, https://doi.org/10.1093/database/bay083.

85 F.M. Alakwaa, Repurposing didanosine as a potential treatment for COVID-19 using single-cell RNA sequencing data, mSystems 5 (2020) e00297–e320, https://doi.org/10.1128/mSystems.00297-20.

86 C. Cava, G. Bertoli, I. Castiglioni, In silico discovery of candidate drugs against Covid-19, Viruses 12 (2020) 404, https://doi.org/10.3390/v12040404.

87 M. Mele, P.G. Ferreira, F. Reverter, D.S. DeLuca, J. Monlong, M. Sammeth, T.R. Young, J.M. Goldmann, D.D. Pervouchine, T.J. Sullivan, R. Johnson, A.V. Segre, S. Djebali, A. Niarchou, T.G. Consortium, F.A. Wright, T. Lappalainen, M. Calvo, G. Getz, E.T. Dermitzakis, K.G. Ardlie, R. Guigo, The human transcriptome across tissues and individuals, Science 348 (6235) (2015) 660–665, https://doi.org/10.1126/science:aaa0355.

88 Y. Zhou, Y. Hou, J. Shen, Y. Huang, W. Martin, F. Cheng, Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2, Cell Discov 6 (2020) 14, https://doi.org/10.1038/s41421-020-0153-3.

89 D.E. Gordon, G.M. Jang, M. Bouhaddou, J. Xu, K. Obernier, K.M. White, M.J. O'Meara, V.V. Rezelj, J.Z. Guo, D.L. Swaney, T.A. Tummino, R. Hüttenhain, R.M. Kaake, A.L. Richards, B. Tutuncuoglu, H. Foussard, J. Batra, K. Haas, M. Modak, M. Kim, P. Haas, B.J. Polacco, H. Braberg, J.M. Fabius, M. Eckhardt, M. Soucheray, M.J. Bennett, M. Cakir, M.J. McGregor, Q. Li, B. Meyer, F. Roesch, T. Vallet, A. Mac Kain, L. Miorin, E. Moreno, Z.Z.C. Naing, Y. Zhou, S. Peng, Y. Shi, Z. Zhang, W. Shen, I.T. Kirby, J.E. Melnyk, J.S. Chorba, K. Lou, S.A. Dai, I. Barrio-Hernandez, D. Memon, C. Hernandez-Armenta, J. Lyu, C.J.P. Mathy, T. Perica, K.B. Pilla, S.J. Ganesan, D.J. Saltzberg, R. Rakesh, X.i. Liu, S.B. Rosenthal, L. Calviello, S. Venkataramanan, J. Liboy-Lugo, Y. Lin, X.-P. Huang, YongFeng Liu, S.A. Wankowicz, M. Bohn, M. Safari, F.S. Ugur, C. Koh, N.S. Savar, Q.D. Tran, D. Shengjuler, S.J. Fletcher, M.C. O'Neal, Y. Cai, J.C.J. Chang, D.J. Broadhurst, S. Klippsten, P.P. Sharp, N.A. Wenzell, D. Kuzuoglu-Ozturk, H.-Y. Wang, R. Trenker, J.M. Young, D.A. Cavero, J. Hiatt, T.L. Roth, U. Rathore, A. Subramanian, J. Noack, M. Hubert, R.M. Stroud, A.D. Frankel, O.S. Rosenberg, K. A. Verba, D.A. Agard, M. Ott, M. Emerman, N. Jura, M. von Zastrow, E. Verdin, A. Ashworth, O. Schwartz, C. d'Enfert, S. Mukherjee, M. Jacobson, H.S. Malik, D. G. Fujimori, T. Ideker, C.S. Craik, S.N. Floor, J.S. Fraser, J.D. Gross, A. Sali, B.L. Roth, D. Ruggero, J. Taunton, T. Kortemme, P. Beltrao, M. Vignuzzi, A. García-Sastre, K.M. Shokat, B.K. Shoichet, N.J. Krogan, A SARS-CoV-2 protein interaction map reveals targets for drug repurposing, Nature 583 (7816) (2020) 459–468, https://doi.org/10.1038/s41586-020-2286-9.

90 M. Bouhaddou, D. Memon, B. Meyer, K.M. White, V.V. Rezelj, M. Correa Marrero, B.J. Polacco, J.E. Melnyk, S. Ulferts, R.M. Kaake, J. Batra, A.L. Richards, E. Stevenson, D.E. Gordon, A. Rojc, K. Obernier, J.M. Fabius, M. Soucheray, L. Miorin, E. Moreno, C. Koh, Q.D. Tran, A. Hardy, R. Robinot, T. Vallet, B.E. Nilsson-Payant, C. Hernandez-Armenta, A. Dunham, S. Weigang, J. Knerr, M. Modak, D. Quintero, Y. Zhou, A. Dugourd, A. Valdeolivas, T. Patil, Q. Li, R. Hüttenhain, M. Cakir, M. Muralidharan, M. Kim, G. Jang, B. Tutuncuoglu, J. Hiatt, J.Z. Guo, J. Xu, S. Bouhaddou, C.J.P. Mathy, A. Gaulton, E.J. Manners, E. Félix, Y. Shi, M. Goff, J.K. Lim, T. McBride, M.C. O'Neal, Y. Cai, J.C.J. Chang, D.J. Broadhurst, S. Klippsten, E. De wit, A.R. Leach, T. Kortemme, B. Shoichet, M. Ott, J. Saez-Rodriguez, B.R. tenOever, R.D. Mullins, E.R. Fischer, G. Kochs, R. Grosse, A. García-Sastre, M. Vignuzzi, J.R. Johnson, K.M. Shokat, D.L. Swaney, P. Beltrao, N.J. Krogan, The global phosphorylation landscape of SARS-CoV-2 infection, Cell 182 (3) (2020) 685–712.e19, https://doi.org/10.1016/j.cell.2020.06.034.

91 D. Ochoa, A.F. Jarnuczak, C. Viéitez, M. Gehre, M. Soucheray, A. Mateus, A.A. Kleefeldt, A. Hill, L. Garcia-Alonso, F. Stein, N.J. Krogan, M.M. Savitski, D.L. Swaney, J.A. Vizcaíno, K.-M. Noh, P. Beltrao, The functional landscape of the human phosphoproteome, Nat Biotechnol 38 (3) (2020) 365–373, https://doi.org/10.1038/s41587-019-0344-3.

92 Z. Jia, X. Song, J. Shi, W. Wang, K. He, Transcriptome-based drug repositioning for coronavirus disease 2019 (COVID-19), Pathog Dis 78 (2020) ftaa036, https://doi.org/10.1093/femspd/ftaa036.

93 Y.-h. Taguchi, T. Turki, Q. Li, A new advanced in silico drug discovery method for novel coronavirus (SARS-CoV-2) with tensor decomposition-based unsupervised feature extraction, PLoS ONE 15 (9) (2020) e0238907, https://doi.org/10.1371/journal.pone.0238907.

94 Y. Zhou, Y. Hou, J. Shen, R. Mehra, A. Kallianpur, D.A. Culver, M.U. Gack, S. Farha, J. Zein, S. Comhair, C. Fiocchi, T. Stappenbeck, T. Chan, C. Eng, J.U. Jung, L. Jehi, S. Erzurum, F. Cheng, N. Soranzo, A network medicine approach to investigation and population-based validation of disease manifestations and

drug repurposing for COVID-19, PLoS Biol 18 (11) (2020) e3000970, https://doi.org/10.1371/journal.pbio.3000970.

95 D. Bojkova, K. Klann, B. Koch, M. Widera, D. Krause, S. Ciesek, J. Cinatl, C. Münch, Proteomics of SARS-CoV-2-infected host cells reveals therapy targets, Nature 583 (7816) (2020) 469–472, https://doi.org/10.1038/s41586-020-2332-7.

96 Q. Chen, A. Allot, Z. Lu, Keep up with the latest coronavirus research, Nature 579 (2020) 193, https://doi.org/10.1038/d41586-020-00694-1.

97 Lu Wang L, Lo K, Chandrasekhar Y, Reas R, Yang J, Eide D, et al. CORD-19: The Covid-19 Open Research Dataset. ArXiv 2020; 2004.10706v2.

98 L.L. Wang, K. Lo, Text mining approaches for dealing with the rapidly expanding literature on COVID-19, Brief Bioinform 22 (2021) 781–799, https://doi.org/10.1093/bib/bbaa296.

99 D. Gurwitz, Repurposing current therapeutics for treating COVID-19: a vital role of prescription records data mining, Drug Dev Res 81 (2020) 777–781, https://doi.org/10.1002/ddr.21689.

100 M. Ozery-Flato, Y. Goldschmidt, O. Shaham, S. Ravid, C. Yanover, Framework for identifying drug repurposing candidates from observational healthcare data, JAMIA Open 3 (2020) 536–544, https://doi.org/10.1093/jamiaopen/ooaa048.

101 B. Cao, Y. Wang, D. Wen, W. Liu, J. Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L.i. Zhang, C. Li, Y.e. Yuan, H. Chen, H. Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y.i. Zhang, H. Li, L. Shang, K.e. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L.u. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, J. Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L.i. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, C. Wang, A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19, N Engl J Med 382 (19) (2020) 1787–1799, https://doi.org/10.1056/NEJMoa2001282.

102 S. Tong, Y. Su, Y. Yu, C. Wu, J. Chen, S. Wang, J. Jiang, Ribavirin therapy for severe COVID-19: a retrospective cohort study, Int J Antimicrob Agents 56 (3) (2020) 106114, https://doi.org/10.1016/j.ijantimicag.2020.106114.

103 M.W. Lo, C. Kemper, T.M. Woodruff, COVID-19: complement, coagulation, and collateral damage, J Immunol 205 (6) (2020) 1488–1495, https://doi.org/10.4049/jimmunol.2000644.

104 J. Villar, C. Ferrando, D. Martínez, A. Ambrós, T. Muñoz, J.A. Soler, G. Aguilar, F. Alba, E. González-Higueras, L.A. Conesa, C. Martín-Rodríguez, F.J. Díaz-Domínguez, P. Serna-Grande, R. Rivas, J. Ferreres, J. Belda, L. Capilla, A. Tallet, J.M. Añón, R.L. Fernández, J.M. González-Martín, G. Aguilar, F. Alba, J. àlvarez, A. Ambrós, J.M. Añón, M.J. Asensio, J. Belda, J. Blanco, M. Blasco, L. Cachafeiro, R. del Campo, L. Capilla, J.A. Carbonell, N. Carbonell, A. Cariñena, D. Carriedo, M. Chico, L.A. Conesa, R. Corpas, J. Cuervo, F.J. Díaz-Domínguez, C. Domínguez-Antelo, L. Fernández, R.L. Fernández, C. Ferrando, J. Ferreres, E. Gamboa, E. González-Higueras, R.I. González-Luengo, J.M. González-Martín, D. Martínez, C. Martín-Rodríguez, T. Muñoz, R. Ortiz Díaz-Miguel, R. Pérez-González, A.M. Prieto, I. Prieto, R. Rivas, L. Rojas-Viguera, M.A. Romera, J. Sánchez-Ballesteros, J.M. Segura, P. Serna-Grande, A. Serrano, R. Solano, J.A. Soler, M. Soro, A. Tallet, J. Villar, Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial, Lancet Respir Med 8 (3) (2020) 267–276, https://doi.org/10.1016/S2213-2600(19)30417-5.

105 H. Farne, K. Kumar, A.I. Ritchie, L.J. Finney, S.L. Johnston, A. Singanayagam, Repurposing existing drugs for the treatment of COVID-19, Ann Am Thorac Soc 17 (10) (2020) 1186–1194, https://doi.org/10.1513/AnnalsATS.202005-566FR.

106 J.J. DiNicolantonio, J. Barroso-Aranda, Harnessing adenosine A2A receptors as a strategy for suppressing the lung inflammation and thrombotic complications of COVID-19: potential of pentoxifylline and dipyridamole, Med Hypotheses 143 (2020) 110051, https://doi.org/10.1016/j.mehy.2020.110051.

107 A. Edwards, What are the odds of finding a COVID-19 frug from a lab repurposing screen?, J Chem Inf Model 60 (2020) 5727–5729, https://doiorg/10.1021/acs.jcim.0c00861.

108 Y. Han, X. Duan, L. Yang, B.E. Nilsson-Payant, P. Wang, F. Duan, X. Tang, T.M. Yaron, T. Zhang, S. Uhl, Y. Bram, C. Richardson, J. Zhu, Z. Zhao, D. Redmond, S. Houghton, D.-H. Nguyen, D. Xu, X. Wang, J. Jessurun, A. Borczuk, Y. Huang, J. L. Johnson, Y. Liu, J. Xiang, H. Wang, L.C. Cantley, B.R. tenOever, D.D. Ho, F.C. Pan, T. Evans, H.J. Chen, R.E. Schwartz, S. Chen, Identification of SARS-CoV-2 inhibitors using lung and colonic organoids, Nature 589 (7841) (2021) 270–275, https://doi.org/10.1038/s41586-020-2901-9.

109 J.A. Pérez-Bermejo, S. Kang, S.J. Rockwood, C.R. Simoneau, D.A. Joy, G.N. Ramadoss, et al., SARS-CoV-2 infection of human iPSC-derived cardiac cells predicts novel cytopathic features in hearts of COVID-19 patients, BioRxiv (2020), https://doi.org/10.1101/2020.08.25.265561.

110 N. Desai, A. Neyaz, A. Szabolcs, A.R. Shih, J.H. Chen, V. Thapar, L.T. Nieman, A. Solovyov, A. Mehta, D.J. Lieb, A.S. Kulkarni, C. Jaicks, K.H. Xu, M.J. Raabe, C.J. Pinto, D. Juric, I. Chebib, R.B. Colvin, A.Y. Kim, R. Monroe, S.E. Warren, P.

Danaher, J.W. Reeves, J. Gong, E.H. Rueckert, B.D. Greenbaum, N. Hacohen, S. M. Lagana, M.N. Rivera, L.M. Sholl, J.R. Stone, D.T. Ting, V. Deshpande, Temporal and spatial heterogeneity of host response to SARS-CoV-2 pulmonary infection, Nat Commun 11 (1) (2020), https://doi.org/10.1038/s41467-020-20139-7.

111 R. Nienhold, Y. Ciani, V.H. Koelzer, A. Tzankov, J.D. Haslbauer, T. Menter, N. Schwab, M. Henkel, A. Frank, V. Zsikla, N. Willi, W. Kempf, T. Hoyler, M. Barbareschi, H. Moch, M. Tolnay, G. Cathomas, F. Demichelis, T. Junt, K.D. Mertz, Two distinct immunopathological profiles in autopsy lungs of COVID-19, Nat Commun 11 (1) (2020), https://doi.org/10.1038/s41467-020-18854-2.

112 J.-Y. Zhang, X.-M. Wang, X. Xing, Z. Xu, C. Zhang, J.-W. Song, X. Fan, P. Xia, J.-L. Fu, S.-Y. Wang, R.-N. Xu, X.-P. Dai, L. Shi, L. Huang, T.-J. Jiang, M. Shi, Y. Zhang, A. Zumla, M. Maeurer, F. Bai, F.-S. Wang, Single-cell landscape of immunological responses in patients with COVID-19, Nat Immunol 21 (9) (2020) 1107–1118, https://doi.org/10.1038/s41590-020-0762-x.

113 A.J. Wilk, A. Rustagi, N.Q. Zhao, J. Roque, G.J. Martínez-Colón, J.L. McKechnie, G.T. Ivison, T. Ranganath, R. Vergara, T. Hollis, L.J. Simpson, P. Grant, A. Subramanian, A.J. Rogers, C.A. Blish, A single-cell atlas of the peripheral immune response in patients with severe COVID-19, Nat Med 26 (7) (2020) 1070–1076, https://doi.org/10.1038/s41591-020-0944-y.

114 X. Li, S. Xu, M. Yu, K.e. Wang, Y.u. Tao, Y. Zhou, J. Shi, M. Zhou, B.o. Wu, Z. Yang, C. Zhang, J. Yue, Z. Zhang, H. Renz, X. Liu, J. Xie, M. Xie, J. Zhao, Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan, J Allergy Clin Immunol 146 (1) (2020) 110–118, https://doi.org/10.1016/j.jaci.2020.04.006.

115 G. Pascarella, A. Strumia, C. Piliego, F. Bruno, R. Del Buono, F. Costa, S. Scarlata, F.E. Agrò, COVID-19 diagnosis and management: a comprehensive review, J Intern Med 288 (2) (2020) 192–206, https://doi.org/10.1111/joim.v288.210.1111/joim.13091.

116 V. Jain, J.-M. Yuan, Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis, Int J Public Health 65 (5) (2020) 533–546, https://doi.org/10.1007/s00038-020-01390-7.

117 R. Miller, K. Englund, Transmission and risk factors of OF COVID-19, Cleve Clin J Med (2020), https://doi.org/10.3949/ccjm.87a.ccc029.

118 X. Li, G. Qin, Q. Yang, L. Chen, L. Xie, Biomolecular network-based synergistics drug combination discovery, Biomed Res Int 2016 (2016) 8518945, https://doi.org/10.1155/2016/8518945.

119 W. Sun, P.E. Sanderson, W. Zheng, Drug combination therapy increases successful drug repositioning, Drug Discov Today 21 (7) (2016) 1189–1195, https://doi.org/10.1016/j.drudis.2016.05.015.

120 R.B. Mokhtari, T.S. Homayouni, N. Baluch, E. Morgatskaya, S. Kumar, B. Das, H. Yeger, Combination therapy in combating cancer, Oncotarget 8 (23) (2017) 38022–38043, https://doi.org/10.18632/oncotarget.v8i2310.18632/oncotarget.16723.

121 T. Cihlar, M. Fordyce, Current status and prospects of HIV treatment, Curr Opin Virol 18 (2016) 50–56, https://doi.org/10.1016/j.coviro.2016.03.004.

122 F. Cheng, I.A. Kovács, A.-L. Barabási, Network-based prediction of drug combinations, Nat Commun 10 (2019) 1197, https://doi.org/10.1038/s41467-019-09186-x123.

123 Z. Feng, M. Chen, T. Liang, M. Shen, H. Chen, X.-Q. Xie, Virus-CKB: an integrated bioinformatics platform and analysis resource for COVID-19 research, Brief Bioinformatics 22 (2021) 882–895, https://doi.org/10.1093/bib/bbaa155.

124 Q. Chen, A. Allot, Z. Lu, LitCovid: an open database of COVID-19 literature, Nucleic Acids Res 49 (2021) D1534–D1540, https://doi.org/10.1093/nar/gkaa952.

125 D. Korn, T. Bobrowski, M. Li, Y. Kebede, P. Wang, P. Owen, et al., COVID-KOP: integrating emerging COVID-19 data with the ROBOKOP database, Bioinformatics 37 (2021) 586–587, https://doi.org/10.1093/bioinformatics/btaa718.

126 Q. Zheng, F.K. Jones, S.V. Leavitt, L. Ung, A.B. Labrique, D.H. Peters, E.C. Lee, A. S. Azman, HIT-COVID, a global database tracking public health interventions to COVID-19, Sci Data 7 (1) (2020), https://doi.org/10.1038/s41597-020-00610-2.

127 J. Chodera, A.A. Lee, N. London, F. von Delft, Crowdsourcing drug discovery for pandemics, Nat Chem 12 (2020) 581, https://doi.org/10.1038/s41557-020-0496-2.

128 Y. He, H. Yu, E. Ong, Y. Wang, Y. Liu, A. Huffman, H.-H. Huang, J. Beverley, J. Hur, X. Yang, L. Chen, G.S. Omenn, B. Athey, B. Smith, CIDO, a community-based ontology for coronavirus disease knowledge and data integration, sharing, and analysis, Sci Data 7 (1) (2020), https://doi.org/10.1038/s41597-020-0523-6.

129 S. Sadegh, J. Matschinske, D.B. Blumenthal, G. Galindez, T. Kacprowski, M. List, R. Nasirigerdeh, M. Oubounyt, A. Pichlmair, T.D. Rose, M. Salgado-Albarrán, J.

Späth, A. Stukalov, N.K. Wenke, K. Yuan, J.K. Pauling, J. Baumbach, Exploring the SARS-CoV-2 virus-host-drug interactome for drug repurposing, Nat Commun 11 (1) (2020), https://doi.org/10.1038/s41467-020-17189-2.

130 H.M. Berman, T. Battistuz, T.N. Bhat, W.F. Bluhm, P.E. Bourne, K. Burkhardt, Z. Feng, G.L. Gilliland, L. Iype, S. Jain, P. Fagan, J. Marvin, D. Padilla, V. Ravichandran, B. Schneider, N. Thanki, H. Weissig, J.D. Westbrook, C. Zardecki, The protein data bank, Acta Crystallogr D Biol Crystallogr 58 (6) (2002) 899–907, https://doi.org/10.1107/S0907444902003451.

131 M. Hewett, D.E. Oliver, D.L. Rubin, K.L. Easton, J.M. Stuart, R.B. Altman, T.E. Klein, Pharmgkb: the Pharmacogenetics Knowledge Base, Nucleic Acids Res 30 (2002) 163–165, https://doi.org/10.1093/nar/30.1.163.

132 D.S. Wishart, Y.D. Feunang, A.C. Guo, E.J. Lo, A. Marcu, J.R. Grant, et al., DrugBank 5.0: a major update to the DrugBank database for 2018 D1074–82, Nucleic Acids Res 46 (2018), https://doi.org/10.1093/nar/gkx1037.

133 D.A. Benson, M. Cavanaugh, K. Clark, I. Karsch-Mizrachi, D.J. Lipman, J. Ostell, E.W. Sayers, GenBank, Nucleic Acids Res 45 (D1) (2017) D37–D42, https://doi.org/10.1093/nar/gkw1070.

134 P.W. Harrison, B. Alako, C. Amid, A. Cerdeño-Tárraga, I. Cleland, S. Holt, et al., The European nucleotide archive in 2018 D84–8, Nucleic Acids Res 47 (2019), https://doi.org/10.1093/nar/gky1078.

135 Safran M, Dalah I, Alexander J, Rosen N, Stein TI, Shmoish M, et al. GeneCards Version 3: the human gene integrator. Database (Oxford) 2010; 2010: baq020. doi:10.1093/database/baq020

136 K. Yang, A.R. Dinasarapu, E.S. Reis, R.A. Deangelis, D. Ricklin, S. Subramaniam, J.D. Lambris, CMAP: Complement Map Database, Bioinformatics 29 (2013) 1832–1833, https://doi.org/10.1093/bioinformatics/btt269.

137 A. Liberzon, A. Subramanian, R. Pinchback, H. Thorvaldsdottir, P. Tamayo, J.P. Mesirov, Molecular signatures database (MSigDB) 3.0, Bioinformatics 27 (12) (2011) 1739–1740, https://doi.org/10.1093/bioinformatics/btr260.

138 UniProt Consortium, UniProt: a hub for protein information, Nucleic Acids Res 43 (2015) D204–D212, https://doi.org/10.1093/nar/gku989.

139 A. Bairoch, B. Boeckmann, The SWISS-PROT protein sequence data bank, Nucleic Acids Res 20 (Suppl) (1992) 2019–2022, https://doi.org/10.1093/nar/20.suppl.2019.

140 L. Martens, H. Hermjakob, P. Jones, M. Adamski, C. Taylor, D. States, K. Gevaert, J. Vandekerckhove, R. Apweiler, PRIDE: the proteomics identifications database, Proteomics 5 (13) (2005) 3537–3545, https://doi.org/10.1002/(ISSN)1615-986110.1002/pmic.v5:1310.1002/pmic.200401303.

141 A. Ruepp, B. Brauner, I. Dunger-Kaltenbach, G. Frishman, C. Montrone, M. Stransky, B. Waegele, T. Schmidt, O.N. Doudieu, V. Stumpflen, H.W. Mewes, CORUM: the comprehensive resource of mammalian protein complexes, Nucleic Acids Res 36 (Database) (2008) D646–D650, https://doi.org/10.1093/nar/gkm936.

142 H. Ogata, S. Goto, K. Sato, W. Fujibuchi, H. Bono, M. Kanehisa, KEGG: Kyoto encyclopedia of genes and genomes, Nucleic Acids Res 27 (1) (1999) 29–34, https://doi.org/10.1093/nar/27.1.29.

Further reading

143 Y.-Y. Ke, T.-T. Peng, T.-K. Yeh, W.-Z. Huang, S.-E. Chang, S.-H. Wu, H.-C. Hung, T.-A. Hsu, S.-J. Lee, J.-S. Song, W.-H. Lin, T.-J. Chiang, J.-H. Lin, H.-K. Sytwu, C.-T. Chen, Artificial intelligence approach fighting COVID-19 with repurposing drugs, Biomed J 43 (4) (2020) 355–362, https://doi.org/10.1016/j.bj.2020.05.001.

144 N.A. Murugan, S. Kumar, J. Jeyakanthan, V. Srivastava, Searching for target-specific and multi-targeting organics for Covid-19 in the Drugbank database with a double scoring approach, Sci Rep 10 (2020) 19125, https://doi.org/10.1038/s41598-020-75762-7.

145 M. Gendrot, J. Andreani, M. Boxberger, P. Jardot, I. Fonta, M. Le Bideau, I. Duflot, J. Mosnier, C. Rolland, H. Bogreau, S. Hutter, B. La Scola, B. Pradines, Antimalarial drugs inhibit the replication of SARS-CoV-2: an in vitro evaluation, Travel Med Infect Dis 37 (2020) 101873, https://doi.org/10.1016/j.tmaid.2020.101873.

146 R. Barthélémy, P.-L. Blot, A. Tiepolo, A. Le Gall, C. Mayeur, S. Gaugain, L. Morisson, E. Gayat, A. Mebazaa, B.G. Chousterman, Efficacy of almitrine in the treatment of hypoxemia in SARS-Cov-2 acute respiratory distress syndrome, Chest 158 (5) (2020) 2003–2006, https://doi.org/10.1016/j.chest.2020.05.573.

147 M. Mahdi, J.A. Mótyán, Z.I. Szojka, M. Golda, M. Miczi, J. Tőzsér, Analysis of the efficacy of HIV protease inhibitors against SARS-CoV-2's main protease, Virol J 17 (2020) 190, https://doi.org/10.1186/s12985-020-01457-0.

148 N. Fintelman-Rodrigues, C.Q. Sacramento, C. Ribeiro Lima, F. Souza da Silva, A.C. Ferreira, M. Mattos, C.S. de Freitas, V. Cardoso Soares, S. da Silva Gomes Dias, J.R. Temerozo, M.D. Miranda, A.R. Matos, F.A. Bozza, N. Carels, C.R. Alves, M.M. Siqueira, P.T. Bozza, T.M.L. Souza, Atazanavir, alone or in combination with ritonavir, inhibits SARS-CoV-2 replication and proinflammatory cytokine production, Antimicrob Agents Chemother 64 (10) (2020), https://doi.org/10.1128/AAC.00825-20.

149 S. Matsuyama, M. Kawase, N. Nao, K. Shirato, M. Ujike, W. Kamitani, M. Shimojima, S. Fukushi, T. Gallagher, The inhaled steroid ciclesonide blocks SARS-CoV-2 RNA replication by targeting the viral replication-transcription complex in cultured cells, J Virol 95 (1) (2020), https://doi.org/10.1128/JVI.01648-20.

150 C.P. Skipper, K.A. Pastick, N.W. Engen, A.S. Bangdiwala, M. Abassi, S.M. Lofgren, D.A. Williams, E.C. Okafor, M.F. Pullen, M.R. Nicol, A.A. Nascene, K. H. Hullsiek, M.P. Cheng, D. Luke, S.A. Lother, L.J. MacKenzie, G. Drobot, L.E. Kelly, I.S. Schwartz, R. Zarychanski, E.G. McDonald, T.C. Lee, R. Rajasingham, D.R. Boulware, Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial, Ann Intern Med 173 (8) (2020) 623–631, https://doi.org/10.7326/M20-4207.

151 G. Bocci, S.B. Bradfute, C. Ye, M.J. Garcia, J. Parvathareddy, W. Reichard, S. Surendranathan, S. Bansal, C.G. Bologa, D.J. Perkins, C.B. Jonsson, L.A. Sklar, T.I. Oprea, Virtual and in vitro antiviral screening revive therapeutic drugs for COVID-19, ACS Pharmacol Transl Sci 3 (6) (2020) 1278–1292, https://doi.org/10.1021/acsptsci.0c00131.

152 K.-T. Choy, A.-L. Wong, P. Kaewpreedee, S.F. Sia, D. Chen, K.P.Y. Hui, D.K.W. Chu, M.C.W. Chan, P.-H. Cheung, X. Huang, M. Peiris, H.-L. Yen, Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro, Antiviral Res 178 (2020) 104786, https://doi.org/10.1016/j.antiviral.2020.104786.

153 K. Watashi, Identifying and repurposing antiviral drugs against severe acute respiratory syndrome coronavirus 2 with in silico and in vitro approaches, Biochem Biophys Res Commun 538 (2021) 137–144, https://doi.org/10.1016/j.bbrc.2020.10.094.

154 S. Yuan, J.F.W. Chan, K.K.H. Chik, C.C.Y. Chan, J.O.L. Tsang, R. Liang, J. Cao, K. Tang, L.-L. Chen, K. Wen, J.-P. Cai, Z.-W. Ye, G. Lu, H. Chu, D.-Y. Jin, K.-Y. Yuen, 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 159 (2020) 104960, https://doi.org/10.1016/j.phrs.2020.104960.

155 M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, Z. Shi, Z. Hu, W.u. Zhong, G. Xiao, Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro, Cell Res 30 (3) (2020) 269–271, https://doi.org/10.1038/s41422-020-0282-0.

156 M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T.S. Schiergens, G. Herrler, N.-H. Wu, A. Nitsche, M.A. Müller, C. Drosten, S. Pöhlmann, SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2) (2020) 271–280.e8, https://doi.org/10.1016/j.cell.2020.02.052.

157 Y. Song, M. Zhang, L. Yin, K. Wang, Y. Zhou, M.i. Zhou, Y. Lu, COVID-19 treatment: close to a cure? A rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2), Int J Antimicrob Agents 56 (2) (2020) 106080, https://doi.org/10.1016/j.ijantimicag.2020.106080.