An integrative resource for network-based investigation of COVID-19 combinatorial drug repositioning and mechanism of action

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Abstract

Repurposing of the existing medications has become the mainstream focus of anti-COVID-19 drug discovery as it offers rapid and cost-effective solutions for therapeutic development. However, there is still a great deal to enhance efficacy of repurposing therapeutic options through combination therapy, in which promising drugs with varying mechanisms of action are administered together. Nonetheless, our ability to identify and validate effective combinations is limited due to the huge number of possible drug pairs. Yet, there is no available resource which can systematically guide to identify or choose the effective individual drugs or best possible synergistic drug combinations for the treatment of SARS-CoV-2 infection. To address this resource gap, we developed a web-based platform that displays the network-based mechanism of action of drug combinations, thus simultaneously giving a visual of the cellular interactome involved in the mode of action of the chosen drugs. The platform allows the freedom to choose two or more drug combinations and provides the options to investigate network-based efficacy of drug combinations and understand the similarity score, primary indications, and contraindications of using these drugs combinations. In a nutshell, the platform (accessible via: http://vafaeelab.com/COVID19_repositioning.html) is of the first of its type which provides a systematic approach for pre-clinical investigation of combination therapy for treating COVID-19 on the fingertips of the clinicians or researchers.

Introduction

The global pandemic caused by a novel coronavirus, SARS-CoV-2/COVID-19 has posed a grave threat to public health along with an unprecedented loss to countries economy [1]. Although considerable scientific attention has been focused on identifying a cure for COVID-19, yet there is no licensed/specific treatment available to prevent or treat the disease [2]. One of the hurdles in identifying one drug solution to cure this pandemic disease-causing virus is because of the plethora of symptoms it induces in human body. In critical patients in addition to neurological symptoms ranging from a loss of sense of smell to outright seizures, it can also lead to highly erratic gastrointestinal problems, elevated liver abnormalities, damage to the kidneys, and a likely fatal deranged immune system [3, 4]. The disease can also mess with a person's blood leading to the formation of clots, potentially leading up to the stroke, heart attack, lung damage and so on [5]. Indeed, these are far more detrimental than a typical respiratory virus [6] and thus, difficult to be treated with one single antiviral drug.

In the absence of approved therapeutics, clinicians rely on using repurposed drugs that is to use the drugs indicated for other diseases with some symptomatic similarity to COVID-19. Previously, repositioning of existing drugs based on drug-drug similarity, side-effect prediction, drug-drug interaction prediction [7-11] and drug target prediction has received an escalated interest as an innovative drug development strategy offering a quick solution for treatment for various diseases along with the additional benefits of reducing cost, saving time and avoiding risk as few phases of *de-novo* drug discovery can be bypassed for repositioning candidates [12]. Similarly, in the current situation, repositioning existing drugs seems to be the only timely solution for treating COVID-19. While using these repurposed drugs individually may yield clinical benefit, because of high virulence and complex pathological mechanism of COVID-19, carefully combined cocktails could be highly effective [13, 14]. In addition to increased therapeutic efficacy, repurposed combination therapy can also provide reduced toxicity of high dosing, thus providing a safer approach towards patients. However, due to a large number of possible drug pairs and dosage combinations our ability to find and verify effective combinations is limited by this combinatorial explosion [15]. Hence, the big question remained is how to identify effective drug combinations which can suppress viral replication and its mitigated life threatening symptoms at multi-level and can help in quick recovery of the patients [16]. To determine efficacious drug combinations as the choice of the treatment in the current pandemic situation, clinicians and the researchers need to have quick and easily accessible tool outlining the mechanism of the action of these drugs and importantly providing a systematic insight of dense biological networks, disease-related pathways, and drug-altered complex cellular processes, but no such tool is available yet.

To overcome this obstacle, we have developed a novel integrative computational platform, ***COVID-CDR*** (*COVID-19 Combinatorial Drug Repositioning*), which can visualize and analyze a range of potential repurposed drug combinations so to identify possibly efficacious multi-drug combinations for COVID-19 treatment and may help in the timely discovery of multicomponent therapy for the novel coronavirus disease. In this platform, we have utilized a systems pharmacology approach combined with a multitude of drug similarity measures to offer a rational multi-level, multi-evidence solution for investigation of drug combination strategy against COVID-19.

Systems pharmacology is a holistic network-centric view of drug actions which include network analyses at multiple scales of biological organization and provides additional insights into the mechanism of drug actions to explain both therapeutic and adverse effects of drugs. [17].

Mapping drug-target networks onto biological networks (host-pathogen interface), can not only help in prioritizing candidate drugs based on their network effects but can also help predict a drug's side-effects and efficacy. Network-based approaches have been effectively applied to numerous areas in pharmacology, comprising new target prediction for well-known drugs [8, 9, 11], identification of drug repurposing and combination, and inferring prospective drug-disease pathways [18-20]. Understanding that protein-protein interactions (PPIs) contain information of the inherent combinatorial complexity of cellular systems, we have incorporated direct drug targets (viral or human), and further overlaid with their associated protein-protein interactions from human interactome. We then quantified the topological interplay between the virus-host interactome and drug targets in the human PPI network following recent observations that network-based drug-drug and drug-disease proximities shed lights on the therapeutic efficacy of drug combinations [21, 22].

Further, we complemented the network-based measure of drug efficacy with a drug-disease *functional proximity* measure that quantifies the interplay between biological processes induced by drug targets with those impacted by SARS-COV-2 infection. This novel and intuitive functional proximity measure adjust for the limitations of existing studies which overlook the functional biological correlation of drug and disease targets.

Furthermore, pharmacological and biological similarities of drug pairs have been widely investigated to identify the efficacy of the compound pairs [23]. Accordingly, we evaluated drug-drug chemical similarity, drug target structural similarity, drug-induced pathway similarity and drug-target functional similarity to offer a resource for multi-modal, multi-evidence investigation of drug combinations in the context COVID-19. In addition to the network proximity measure, pharmacological and biological similarities of drug pairs have been widely investigated to identify the efficacy of the compound pairs [23]. Accordingly, we evaluated drug-drug chemical similarity, drug target structural similarity, drug-induced pathway similarity and drug-target functional similarity to offer a resource for multi-modal, multi-evidence investigation of drug combinations in the context COVID-19. Within few months of COVID-19 outbreak, an exceptionally large number of clinical trials commonly based on structurally different and often functionally unrelated drug combinations were launched to evaluate the safety and efficacy of these newly repurposed anti-COVID-19 therapies. We have listed some of these famous clinical trial combination (36 trials, accessed from ClinicalTrials.gov) on our platform with the focus to explain their molecular mechanisms and the foundation of the scientific rationale for their empirical use and evaluation in clinical trials. Further, to elucidate

the probability of drug combinations as synergistic or antagonistic, we utilized the results from high-throughput screening (HTS) of drug combination on 124 human cancer cell lines developed by Liu and colleagues [24].

Our web-based platform can automatically construct a PPI network for a given two or more set of drugs and build a drug-target/s, target-human and viral-human interactome and estimate drug-drug and drug-disease network proximity as well as multitude of drug-drug similarity measures. Such information has been complemented with drug side-effect, indications, and literature evidence, which together form a unique starting point for COVID-19 combinatorial drug repositioning. We have demonstrated the utility of the tool for bicombination of LY2275796 and cyclosporine and explained the mechanism of action and potency of such combination. To the best of our knowledge, this is the first computational tool to integrate COVID-19 drug information in the context of virus and human interaction networks, which may facilitate a better understanding of the molecular mechanisms of drug actions, for the identification effective drug combinations and can help in identifying better therapies of COVID-19 infection worldwide.

Results and discussions

COVID-CDR overview and statistics

COVID-CDR presents a computational workflow to choose candidate drugs combinations against COVID-19 and analyze their primary targets and associated human host and SARS-CoV-2 PPIs to provide a holistic view of the drug-target interactome and possible insights about the mechanism of action of drugs chosen. To this end, 867 drugs with reported evidence in treating COVID-19 symptoms or under investigation in trials were compiled (**Supplementary Table 1**), of them, 57% were approved for an indication, 41% are investigational, and >2% were vet-approved, nutraceutical or withdrawn. Compiled drugs cover a wide range of therapeutic classes (>200 categories) such as antivirals, antibiotics, anticancer, anti-inflammatory, immunomodulatory, immuno-suppressive, and anticoagulant agents, among others. Multiple drug-related information sources including drug's chemical structure, physiochemical and pharmacological properties, side effects, protein targets and their associated pathways were compiled from diverse resources (**Table 1**) and are accessible to explore from the web interface.

To enable network-based exploration of drug targets and their associations with SARS-CoV-2 proteins on human PPIs, we constructed a *multi-dimensional network*—i.e., a network representing multiple kinds of relationships—comprising drug-target interactions (867 drugs, 2,228 protein targets, and 4,866 interactions) and high-confidence binding associations between

SARS-CoV-2 and human proteins (28 viral proteins, 340 human proteins, and 414 interactions) overlaid on a comprehensive experimentally-validated human protein-protein interactome (469,515 PPIs). This multi-dimensional interactome (**Supplementary Table 2**) has been used to estimate the topological proximity of drug targets to COVID-19-related proteins and quantify the separation of drug targets on human protein-protein interactome for network-based exploration of efficacious drug combinations (see methods). In addition to network-based topological metrics, the functional relevance of drug targets with COVID-related cellular biological processes were estimated. Furthermore, for each drug pair, multiple structural and pharmacological similarity measures were estimated (**Supplementary Table 3**), and whenever available, complemented with results of drug combination screening studies on multiple cell-lines. **Figure 1** shows the *COVID-CDR* platform content and construction [25].

Network-based drug repositioning and quantification of potentially efficacious drug combinations for SARS-COV-2

In this study, we present a comprehensive SARS-CoV-2-host protein-protein interaction network (**Supplementary Table 2)** that is curated based on the known SARS-CoV-2 protein interactions [26, 27] in the literature and some important interaction databases [28]. We have also incorporated the SARS-CoV virus-host protein-protein interaction network which can serve as a valuable reference due to the close similarity between SARS-CoV and SARS-CoV-2 proteins [29-31]. The basis for this network-based drug repurposing methodology rests on the notion that for a drug with multiple targets to be efficacious, its target proteins should be within or in the immediate neighborhood of the corresponding subnetwork of the disease-related proteins in the human interactome, as demonstrated in multiple studies previously [15, 22, 32-35]. Using the network proximity framework, we measured the shortest distances of all drugs to SARS-CoV-2-related proteins using the existing knowledge of the drug-target interactions and the global map of the SARS-CoV-2-human interactome on the comprehensive human PPI network (see Methods). SARS-CoV-2-related proteins considered in this study include viral proteins, human proteins interacting with SARS-CoV-2, and virus entry factors. To quantify the significance of the shortest distances between drug targets and disease proteins, drug-disease proximity measures were then converted to z-scores (z) based on permutation tests as previously explained [21, 36], and the corresponding p-values were estimated. For $z < 0$, the drug–target subnetwork (i.e., drug module) and the SARS-CoV-2-related proteins (i.e., disease module) overlap; while for $z \geq 0$, the drug module and the disease module are separated. Overall, 543 drugs topologically overlap with SARS-CoV-2 module ($z < 0$), 118 of them show significant

exposure with the disease module ($z < 0$ and p-value < 0.05, permutation test, **Supplementary Table 3**).

Next, we used a recently-proposed network-based methodology to identify clinically efficacious drug combinations which relies on the assumption that a drug combination is therapeutically effective if follows *complementary exposure* pattern (**Figure 1C**) indicating that targets of the drugs overlap with the disease module but target separate neighborhoods on the interactome [15]. Accordingly, for each drug pair A and B, a network separation measure, s_{AB}, was estimated as the mean shortest distance within the interactome between the targets of two drugs (Equation 3, Methods). For $s_{AB} < 0$, drug target subnetworks overlap topologically, while for $s_{AB} \geq 0$, they are topologically separated on the interactome. Hence, complementary exposure implies that $s_{AB} \geq 0$, $z_A < 0$, and $z_B < 0$.

Functional proximity of drugs to COVID-19 biological processes

The network-based topological proximity of drug module to the disease module measures the immediate vicinity of drug targets to SARS-CoV-2 proteins on cellular interactome. However, it falls short in capturing the effect of drug's downstream changes in biological processes perturbed under the impact of the SARS-CoV-2 infection. To address this limitation, we complemented topological proximity with a measure of drug-disease *functional proximity* to quantify the relationship between biological processes induced by drug targets with those affected by SARS-COV-2-related proteins. We first performed Gene Ontology enrichment analysis to identify biological processes associated with drug protein targets and SARS-CoV-2-related proteins. Then, we estimated the similarity between drug- and disease-associated biological processes using Gene Ontology-based *semantic similarity* measure which leverages on the ontology graph structure and information content to estimate similarities among gene ontology terms [37]. **Supplementary Table 4** shows biological processes enriched by SARS-CoV-2 related proteins (FDR < 0.05). Drug-disease functional proximities are ranged between 0 and 1 with the mean value of $\mu = 0.29$ (**Supplementary Figure 1A**). Overall, the higher the similarity is, the greater the effect of the drug would be in perturbing disease-related mechanisms. Similarity measures were standardized to z-scores and the corresponding one-tailed p-values (i.e., $P[X > x]$) were estimated; 306 drugs hold z-score > μ, among them 82 have p-value < 0.05. SARS-CoV-2 functional proximities of drugs while inversely related to the corresponding topological proximities, hold weak linear relationship (Pearson's correlation

coefficient $= -0.413$) which indicates that these two measures are complementary rather than being redundant (**Supplementary Figure 1B**).

Structural and functional similarity of pairwise drug combinations

The use of structural and functional similarities is a common target-based approach for drug repurposing. Many studies suggest that synergy increases when targeting proteins with either strong functional similarity or dissimilarity [38, 39]. Multiple pairwise similarity measures for all the drug combinations were compiled were estimated as detailed in methods as being associated with COVID-19 treatment**.** ***COVID-CDR*** assesses drug–drug similarities derived from variety of direct and indirect sources of evidence and brings together the structural and functional drug similarity measures with molecular network analysis for combinatorial drug repurposing. Distinct drug-drug similarity matrices were generated estimating measures based on similarities of chemical structures, target protein sequences, induced pathways, and target protein function—i.e., cellular components, biological processes, and molecular functions (see Methods). The size of each matrix is 867 by 867, i.e. 751,689, and values range from 0 to 1. The individual similarity matrices were then mean-aggregated to form a combined-score similarity matrix and z-transformed for significance assessment (**Supplementary Table 3**). Overall, the network proximity of drug-drug pairs holds negative but insignificant correlation with structural and functional similarities (**Supplementary Figure 2**)

Drug combinations in trial for COVID-19 or FDA-approved for other indications

The existing COVID-19 outbreak lead to the rise of many COVID-19 clinical trials across the globe. Drug repurposing of existing antivirals drugs and the identification of a new antiviral activity for already known drugs, including approved, and discontinued one, is a key idea behind the design of large number of clinical trials launched for COVID-19. More than 500 different clinical trials were launched worldwide with multiple drug combinations with the hope to identify a promising treatment for this disease [40]. In order to provide in-action examples of studies likely to influence clinical practice, we incorporated in our platform 36 different drug combinations in various clinical trials designed for treating COVID-19 from clinicaltrials.gov database involving more than 20 medicines, e.g., human immunoglobulin, interferons, chloroquine, hydroxychloroquine, arbidol, remdesivir, favipiravir, lopinavir, ritonavir, oseltamivir, methylprednisolone, and bevacizumab (Supplementary Table X). The most common therapeutic agent being trialed currently is hydroxychloroquine (24 trials with potential sample size of over 25 000 participants), followed by lopinavir–ritonavir (7 trials) and remdesivir (5 trials). Additionally, we compiled 150 pairs of COVID-19-related drugs approved

by FDA for other indications (**Supplementary Table 5**). **Table 2** provides statistics and details of external drug combinations included in this platform.

Hight-throughput screening of drug combination synergy scores on cancer cell lines

Furthermore, in order to enable a better understanding and investigation of synergistic drug combinations on different cell types, we have incorporated the high-throughput screening results related to drug combinations assessed on more than 124 immortalized human cancer cell lines assembled by Liu and colleagues [24]. Cancer cell lines have been used in high-throughput drug screens against hundreds of compounds (both approved and experimental) to test their effect on cell viability. Given the minimal size of viral genome, all viruses including SARS-CoV-2 relies on host machinery to facilitate their replication, assembly, and release. It has been shown that the viruses interfere with multiple host cell-cycle components, metabolic pathways, epigenetic regulators and translational/posttranslational machinery via mechanisms co-opted by tumour cells [41]. It has recently been shown that infection of SARS-CoV-2 of lung cell lines induces metabolic and transcriptional changes consistent with epithelial mesenchymal transitions which is a key phenomenon observed in cancer cells implying a common mechanisms of SARS-CoV-2 pathogenesis and cancer cell proliferation and invasion [42]. This underlines the fact that cancer cell lines may make a novel model for understanding SARS-CoV-2 pathogenesis and identifying the drugs combination synergy/antagonism.

Database access and usage notes

Figure 2 shows the ***COVID-CDR*** web interface. The user can query drug combinations simply by using search option and can start with two drugs of the choice (**Figure 2A**). If required, additional drugs can be added on the top of the built network to explore a combination of three or even larger combinations (**Figure 2B**). When displaying the drug-targets network, each node type is highlighted with a specific color: pink nodes indicates drugs, blue nodes are human proteins directly targeted by the drug while green nodes are other human host proteins, and red nodes indicates SARS-CoV-2 proteins. Purple nodes indicate other viral proteins. Users can simply hover on the individual drugs to check the information link to the drugs such as drug's therapeutic class, primary indication, and disease topological and functional proximities. Details of drugs-target information can be assessed by clicking a small brain tab in the top right (**Figure 2B**) which displays physiochemical properties of the queried drug, its chemical structure in an interactive 3D view, and its pharmacological properties providing an all-in-one view for further investigation of the drug of interest. The platform also provides the flexibility of including or

not including the SARS-CoV network and drug-target and their PPI neighborhood via changing the “minimum distance” and” PPI hop” parameters.

Upon completion of network rendering, user can observe pair-wise multi-modal drug similarity information and their network separation score by interacting with the tab at the bottom of GUI (**Figure 2B**). The induced sub-network of the queried drug(s) in the network-view is also interactive and query-able, and upon selecting an edge, a PubMed query is made with its incident drugs, and the search results are displayed as a table in a modal window. Under the curated combination tabs user can also check the network for clinical drug combinations by clicking the clinical trial tab at top left, these 40 selected bi- or tri-drug combinations are currently under ongoing clinical trials for COVID-19 treatment (**Figure 2C**). Additionally, the network-based MOA of FDA approved potential COVID19 drug combinations can be explored. The sensitivities of the various cancer cell lines to the chosen drugs combinations can be viewed as well with the 'ranking' function of the tabular viewer, users can easily identify drug combinations with high sensitivity toward the specific cell lines with respect to certain types of synergy scores, such as Bliss, Loewe or ZIP. All these files can be downloaded from the download tabs at the top front page of GUI.

Case study: LY2275796 and cyclosporine combination therapy

We sought to use our platform in identifying drug combinations that may provide effective synergistic therapy in potentially treating SARS-CoV-2 infection along with displaying well-defined mechanism-of-action by the implemented functional and network-based analyses. The utility of COVID-CDR and its integrated network-based system medicine approaches is showcased by LY2275796 and cyclosporine combination: As shown in **Figure 3**, our network analysis indicates that LY2275796 and cyclosporine synergistically target SARS-CoV-2-associated host protein subnetwork by “*Complementary Exposure*” pattern, offering potential combination regimens for the treatment of SARS-CoV-2. The targets of both drugs hit the SARS-CoV2 host subnetwork (overlap with the disease module), but the targets separate neighborhoods in the human interactome network. Briefly, the negative value of topological network proximity for both the drugs suggests proximity with the disease module (LY2275796: z-score= –1.68, *p*-value = 0.01; cyclosporine: z-score=–2.24, *p*-value=0.01). Simultaneously, the higher positive value for functional proximity for both drugs (LY2275796: z-score=4.42, *p*-value=4.86E-06; cyclosporine: z-score=2.40, *p*-value=0.008) indicated significant similarity between the biological processes targeted by these drugs and the perturbed cellular processes in

SARS-CoV2–infection implying potentially very high effectiveness each drug. Besides, the two drugs denote positive separation score (s_{AB}=0.46) between the sub-modules suggesting no overlap between the targets of LY2275796 and cyclosporine, and thus the efficacy of the combination therapy.

All viruses enter and infect host cells to use the cell's protein-making machinery to make multiple copies of themselves before escaping to infect neighboring cells. Numerous promising antiviral therapies against SARS-CoV-2 are being investigated with the hope to stop the virus from utilizing host machinery, and thus preventing its replication and spread. The translation of most of the viral (sub-genomic) mRNAs is believed to be cap dependent which displays a requirement for eukaryotic initiation factor 4F (eIF4F), a heterotrimeric complex consisting of eIF4E, the cap-binding protein; eIF4A, an RNA helicase; and eIF4G, a large scaffolding protein needed for the recruitment of 40S ribosomes [44]. LY2275796 is a drug that inhibits eukaryotic initiation factor-4E, or eIF-4E, and is currently in Phase 1 development as the second antisense anti-cancer drug [45]. Inhibiting eIF4A or eIF4FE, the catalytic subunits of eIF4F is shown to lead apoptosis in selected cancer models. EIF4E, F and G proteins are involved in tumour progression, angiogenesis, and metastases. It inhibits eIF4E complex and its activating kinases, MNK1/2 [44, 46]. Inhibiting eIF4E inhibits Ras-Mnk and PI3-AKT-mTOR pathways, which are key nodes where the RAS and PI3K pathways come together and control the production of multiple oncoproteins [47] also shown to be important in SARS-COV2 infection. Targeting this translational pathway could lead to the development of new, more effective antiviral therapies to fight COVID-19.

In combination with LY2275796 we have added cyclosporine, an inhibitor of calcineurin inflammatory pathway via NF-κB, which has been used mainly for prophylaxis of organ rejection. Importantly, cyclosporine has demonstrated to improve outcomes in patients with severe H1N1 pneumonia and acute respiratory failure in SARSCOV2 infection via NF-κB [48] and mTOR signaling which plays an essential role for coronavirus infection in general [49]. Some studies have shown that cyclosporine may dramatically limit the severity of sepsis and/or inflammation-induced acute lung injury and post-cardiac arrest AR in SARS-COV-2 patients [43]. It has been consistently reported to improve lung function via mitochondrial processes, including PTP inhibition [50, 51]. Altogether our, network analyses and scientific data suggested that combining LY2275796 and cyclosporin can offer a potential therapeutic approach for SARS-CoV-2.

Materials and methods

COVID-19 drug collection and drug-related data sources

Drugs with reported evidence in treating COVID-19 symptoms or in clinical trials for COVID-19 were manually collected from the literature [ref], Clinicaltrials.gov, and DrugBank [44]. This list was further enriched with drugs from DrugBank whose protein targets physically interact with the SARS-Cov-2 proteins based on the recent report of SARS-CoV-2 protein interaction map [27]. For each drug, multiple drug-related data were then collected from different sources: drug identifiers, chemical structures (SDF format), physiochemical and pharmacological metadata, protein targets and their primary structure (FASTA format) were retrieved from DrugBank, version 5.1.56. Drug-induced pathways and their constituent genes were obtained from 'Kyoto Encyclopedia of Genes and Genomes' (KEGG), release 90 [45]. Gene ontology (GO) annotations (cellular components, biological processes and molecular functions) of protein targets for gene-set enrichment analysis were obtained from the EnrichR libraries which provides up-to-date annotations for gene-set enrichment analyses [46]. Information on recorded marketed drug side-effects were obtained from SIDER, version 4.1 [47]. Drugs' therapeutic class and indications—i.e., drug to disease mapping—were retrieved from Therapeutic Target Database (TTD), June 2020 update [48].

Virus-host-drug multi-dimensional network construction

To reveal the interplay between COVID-19 drug targets, and SARS-CoV-2-human protein interactions on human protein-protein interactome, a multi-dimensional network was fused from different data sources integrating drug-target, SARS-CoV-human, and human protein-protein interactions into a single network. Protein–protein interactions (PPIs) in humans were downloaded from 'Interologous Interaction Database' (I2D), version 2.9 [49]. High-confidence protein–protein interactions between SARS-CoV-2 and human proteins were obtained from Gordon *et al.* [27], and Saha *et al.* [50]. Drug-target interactions were compiled from DrugBank, version 5.1.5. Interactions between SARS-CoV-1 and human proteins were collected by searching through literature. Across different interaction data sources, protein names/identifiers were mapped into UniProt/Swiss-Prot IDs forming a unified multi-dimensional network.

Drug-drug similarity measures

Multiple pairwise similarity measures among 867 drugs compiled as being associated with COVID-19 treatment were estimated as detailed in our previous study [51]. Accordingly, multiple pairwise similarity measures among 869 867 drugs compiled as being associated with

COVID-19 treatment were estimated as detailed in our previous study [51]. Accordingly, drugs' *chemical structures*, *target protein sequences*, *induced pathways*, and *target functions*—i.e., GO term annotations of biological processes, molecular functions and cellular components—were used to estimate 6 heterogeneous measures of drug-drug similarities normalized between 0 and 1. In addition to individual similarities, mean-aggregated similarity score as well as its associated *p*-value (based on standardized z-score) and the corresponding false discovery rate adjusted *p*-value were reported. Missing values indicate no relevant information is available about the comparing drugs and were retained for consistency in dimensions.

Briefly, pairwise compound structural similarities were measured with atom pairs using the Tanimoto coefficient. To estimate target sequence similarities, the percentage of pairwise protein sequence identities upon global alignment was calculated and then 'best-match-averaged. In addition to sequence similarity, functional similarity of protein targets was estimated by GO term enrichment analysis followed by semantic similarity estimation between enriched GO terms. Similarities between pathways associated with each pair of drugs were estimated based on the similarity of their constituent genes using dice similarity and then max-aggregated to get pathway-induced drug-drug similarities. Details of different drug similarity estimation are provided in our recent study [51].

Network-based topological proximity measure

Disease-related proteins often form a localized region of connections on the protein interactome referred to as *disease module* which follows the frequently documented propensity of disease-related proteins to interact with each other [52]. As previously proposed [ref], to capture the network proximity between drug A and disease C, we used the average shortest path length between disease proteins to the nearest target of drug A on human PPI network using Equation 1, where $A = \{a\}$ is the set of targets of drug A, $C = \{c\}$ is the set of COVID-19-related proteins, and $d(a, c)$ is the shortest distance between a target a and a disease protein c.

$$d(A, C) = \frac{1}{\|C\|} \sum_{c \in C} \min_{a \in A} d(a, c) \tag{1}$$

The proximity measures were then converted to z-scores (i.e., $z = \frac{d(A,C) - \mu}{\sigma}$) by comparing the observed distance to a reference distance distribution (μ and σ) obtained by permutation test of 1000 iterations where at each iteration a randomly selected group of proteins of matching size

and degree distribution was generated as the disease proteins and drug targets in the human interactome.

Similarly, we measured the proximity of drug target modules of drugs A, B based on their target localizations on interactome using the previously introduced separation measure to compare the mean shortest distances within targets of each drug, i.e., d_{AA}, d_{BB}, to the mean shortest distance between targets of A and B, i.e, d_{AB}:

$$S_{AB} = d_{AB} - \frac{d_{AA} - d_{BB}}{2} \tag{2}$$

where d_{AB} was estimated based on the "closest" distance which basically measures the average shortest distance between targets of drug A and the nearest target of the drug B, and vice versa.

$$d_{AB} = \frac{1}{\|A\| + \|B\|}\left(\sum_{a \in A} \min_{b \in B} d(a,b) + \sum_{b \in B} \min_{a \in A} d(a,b)\right) \tag{3}$$

Functional proximity measure

Functional proximity measure between a drug and COVID-19 disease was estimated based on the similarity of Gene Ontology-based biological processes enriched by disease-related proteins and targets of drug A. The biological processes enriched by the drug targets and disease proteins (p-value<0.05) were then compared using the semantic similarity of the corresponding Gene Ontology (GO) terms using the topology and information content of the ontology graph [53]. Pairwise semantic similarities between any two GO terms associated with the drug and disease were then aggregated into a single functional proximity measure using a best-match average strategy [53].

Semantic similarity estimation was performed using the *GOSemSim* R package [37]. Enrichment analysis was performed using the right-sided Fisher's exact test whose p-value for the null hypothesis is computed based on the hypergeometric distribution. Nominal p-values were adjusted for multiple hypothesis tests using Benjamini and Hochberg (False Discovery Rate) correction and adjusted p-value were used for significance assessment of GO terms associated with a drug or the disease. Enrichment analyses were implemented in R using *stats* packages.

System design and implementation

The complete COVID-CDR framework – including data mining, pre-processing (noise removal and quality control), pair-wise drug similarity estimation, functional and network-based feature calculation of drugs and their target proteins, and visualization – was implemented in R. This unified codebase facilitates ease of reproducibility and ongoing maintenance. HPC (High performance computing)-powered parallel processing was leveraged for repetitive processing, e.g. similarity matrix, drug-disease proximity, and pair-wise network separation of drugs within their target interactome. The highly interactive web interface for COVID-CDR was developed using R Shiny [54]. This interface reports and visualizes some of the basic statistics of COVID19-related drugs and their reported combinations (as per Clinicaltrials.gov) using *ggplot2* [55] and *DT* [56] R packages. The interactive view of queried drug combination – the induced subnetwork of the multi-dimensional integrative network is visualized using *visnetwork* package in R, which includes all the features available in *vis.js* javascript library for R shiny applications [57]. For each drug, a three-dimensional visualization of its molecular structure is rendered using *MolView* API [58]. Drugs and their adverse side-effect information were retrieved via merging DrugBank [59] and SIDER [47] databases. Pathways induced by drugs were estimated via hypergeometric test from *stats* R package. Protein and their functional annotations (GO-terms) were retrieved from *QuickGO RESTful* API [60]. For any node-pair, e.g. drug-protein or protein-protein nodes, their literature co-occurrence in PubMed abstracts are sought and processed with *easyPubMed* R package [61]. All network-related processing is done via *igraph* package in R [62]. Overall, the whole pipeline is hosted in public repository aided with proper documentation and usage instruction. While this interface has been tested for most of the major internet browser, e.g. Google Chrome, Firefox, Safari, and Internet explorer 10, we recommend using the one which supports 3D graphs for MolView rendering.

Code and data availability

To ensure the reproducibility of ***COVID-CDR***, we have made the whole codebase (including any intermediate curation, processing, and the web application) freely available for non-commercial uses in GitHub (https://github.com/VafaeeLab/**COVID-CDR**). The code and interface are well documented, and the database update is implemented as a HPC-powered and parallel processing-enabled, semi-automated pipeline to accommodate anytime system upgradation.

Figure legends

Figure. 1. Schematic workflow for content and construction of *COVID-CDR*.

A. Multidimensional network construction. *COVID-CDR* encompasses a comprehensive multi-layer interactome that is curated based on the known SARS-CoV-2 protein-human host interactions; interactions of all drugs and their direct targets along with all experimentally validated human protein-protein interactions. **B. Drug-Drug similarity estimation.** A number of drug-drug similarity measures were calculated to determine the similarity index of each possible drug combinations (drug chemical structures to estimate drug pairwise chemical similarity, drug protein targets and protein sequences to estimate sequence-based target similarity, drug-induced pathways and their constituent genes to estimate pathway-based similarities, and GO annotations of protein targets and protein-protein interactions to identify functional similarities). **C. Network-based *complementary exposure* pattern** where the targets of the drugs both hit the virus subnetwork but target separate neighborhoods in the human interactome. **D. COVID-19 functional proximity estimation.** Functional proximity is an added measure which calculates the functional similarity of the COVID-19 related proteins and drug targets. **E. Curated drug combinations.** Users can explore curated drug combinations, i.e., drug combinations under investigation in COVID-19 clinical trials or FDA approved potential COVID-19 drug combinations. Synergistic scores of specific combinations can be assessed on various cell lines derived from HTS assays. **F. Comprehensive information on drugs.** Multiple drug-related information sources were compiled and are accessible to explore from the web interface. Abbreviations: GO: Gene Ontology.

Figure 2. An overview of *COVID-CDR* web interface and application scenarios.

A. The user can query drug combinations simply by using search option and can start with two drugs of the choice**.** **B.** Specific queried drug combination and drug-targets network gets displayed. Users can add on another drug on the same combination or query a different drug using a query or add tabs (top left). Details of drugs-target information can be assessed by clicking a small brain tab (top right) which displays detailed information of the queried drug. User can observe pair-wise multi-modal drug similarity information and their network separation score using the tab at the bottom of GUI. **C.** Under the curated combination tabs, user can also check the network for COVID-19 clinical drug combinations by clicking the clinical trial tab at top (C, top panel). Additionally, the network-based MOA of FDA approved potential COVID19 drug combinations can be explored (C, middle panel). The sensitivities of the various

cancer cell lines to the chosen drugs combinations can be viewed as well with the 'ranking' function of the tabular viewer (C down panel).

Figure 3. Integrated network visualization generated for pairwise combination of LY2275796 (Cap independent translation inhibitor-Glycosides) and Cyclosporine (Calceinurin inhibitor-immunosuppressant). The top panel indicates possible exposure mode of the SARS-CoV2-associated protein module to the drug cyclosporine. The top left plot shows pathways significantly enriched by direct and indirect targets of cyclosporine (i.e., proteins directly interacting with targets on human PPI). The bottom panel shows the drug-disease module for LY2275796 and pathways significantly enriched by direct and indirect targets of LY2275796.

Supplementary table legends

Supplementary Table 1. List of all drugs included in this platform along with all drug properties as well as disease topological and functional proximity measures.

Supplementary Table 2. All types of interactions incorporated into the multi-dimensional network constructed in this platform.

Supplementary Table 3. All possible drug pairs along with network separation measure (s_{AB}) and pairwise similarity measures.

Supplementary Table 4. Gene Ontology based (biological processes) enrichment analysis of COVID-19-related human proteins.

Supplementary Table 5. Curated drug combinations included in this platform.

Tables

Table 1: Data types, statistics and details of data sources used to generate ***COVID-CDR***

Data type	Statistics	Details	Data source
Drug Identifiers, drug names and clinical status	**867** drugs including **487** approved drugs	—	DrugBank [59], ClinicalTrials.gov[63], Literature (Supplementary Table X)
Drug physicochemical properties	**16** distinct properties per drug	Molecular weight, Hydrogen bond acceptors/donors, Ring count, Molecular Refractivity and polarizability, CAS number, SMILES, lnChl, IUPAC name, etc.	DrugBank [59]
Drug pharmacological properties	**16** distinct properties per drug	Description, indication, mechanism of action, target names, toxicity, pharmacodynamics, metabolism, half-life, route of elimination, etc.	"
Drug Chemical structures	**726** structures	SDF format	"
Drug target-protein sequences	**2,393** unique protein sequences	FASTA format	“
Drug-target network	**2,228** and **4,866** drug -target pairs	Composed of drugs and their targets from human and other organisms (e.g. SARS-CoV2, SARS-CoV, etc.)	DrugBank [59]
Drug-induced pathways	**298, 459,** and **226, 1530, 112,** pathways from KEGG, WikiPathways, BioCarta, Reactome, and Pather databases, respectively	Based on the over-representation analyses of drug-targets with pathway constituents (Hypergeometric test, p-value <= 0.05)	KEGG [64], WikiPathway [65], and BioCarta [46], Reactome [66], Panther [67]
Gene ontology terms and annotations	**446** CC, **1,151** MF, and **5,103** BP terms, and a total of **250,734** protein-GO term associations	Gene ontology terms across categories of Cellular components (CC), molecular functions (MF) and biological processes (BP)	EnrichR [67]

Protein-protein Interactions (PPIs)	**469,515** PPIs	Validated and computationally predicted human PPIs	I2D [68]
Drug indications and therapeutic classes			TTD [69], DrugBank [59]
Drug side effects	**139,756** drug-side effect associations	Information on marketed medicines and their recorded adverse drug reactions	SIDER [47]

Table 2: Details about external drug-combinations that are used in ***COVID-CDR*** interface

Data type	**Statistics**	**Combination Type**	**Details**	**Data source**
Experimental Drug-combinations	**6,181** drug-combinations	Dual combinations only	Combinations experimented in various cell-lines with different settings	drugCombDB [70]
Combinations in clinical trials	**36** drug-combinations	Dual, tri-, and tetra-combinations	Combinations that are related to 867 COVID-19 drugs found in clinical trials in various phases	ClinicalTrials.gov [63]
FDA approved combinations	**150** drug combinations	Dual, tri-, and tetra-combinations	FDA approved combinations that are related to 867 COVID-19 drugs	drugCombDB [70]

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