Identification of Repurposable Drugs and Adverse Drug Reactions for Various Courses of Coronavirus Disease 2019 (COVID-19) Based on Single-cell RNA Sequencing Data

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ABSTRACT

With more than 3.8 million people infected Coronavirus Disease 2019 (COVID-19), caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses a critical threat to human health. There is no proven vaccine or specific drug to date, which highlights the urgent need for rapid development of therapeutics for COVID-19. To identify potentially repurposable drugs, we employed a systematic approach to mine candidates from U.S. FDA approved drugs and pre-clinical small-molecule compounds by integrating the gene expression perturbation data by chemicals from the Library of Integrated Network-Based Cellular Signatures (LINCS) project with publically available single-cell RNA sequencing dataset from mild and severe COVID-19 patients. We identified 281 FDA approved drugs that have the potential to be effective against SARS-CoV-2 infection, 10 of which are currently undergoing clinical trials to evaluate their efficacy against COVID-19. In conclusion, we have identified a list of repurposable anti-SARS-CoV-2 drugs using a systems biology approach.
INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a highly contagious respiratory disease resulting from a life-threatening novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has spread rapidly throughout the globe, causing 3.8 million infections and 260 thousand of deaths by early May 2020[1, 2]. SARS-CoV-2 is an enveloped RNA virus that belongs to the genus Betacoronavirus of the family Coronaviridae, which includes well-known severe acute respiratory syndrome coronavirus (SARS-CoV) as well as middle east respiratory syndrome coronavirus (MERS-CoV)[3]. The advancement in the management of these coronaviruses and other viruses like influenza virus H1N1 and Ebola infections have provided insight into treating COVID-19. More than 300 active clinical trials for COVID-19 are being performed[4, 5]. Chloroquine[6, 7] and its hydroxyl analogue Hydroxychloroquine[8], Lopinavir/Ritonavir[9-11], and Remdesivir[7, 12], developed for treating Malaria, human immunodeficiency virus (HIV) and Ebola virus, respectively, have provided some benefits to treat COVID-19 and are being tested in ongoing trials.

Although COVID-19 is less fatal than the SARS and MERS, older patients with co-morbidities tend to experience more severe symptoms, making them more vulnerable. The majority of SARS-CoV-2 infected patients displayed mild symptoms and generally have a good prognosis, classified as mild COVID-19[9, 13]. However, a large proportion of patients, especially among older men with underlying chronic diseases, have rapidly progressed to severe COVID-19 and suffered from respiratory distress requiring emergent medical interventions[14]. Unfortunately, there is no evidence from randomized clinical trials supporting vaccines or efficient treatment for COVID-19[4, 5].

Additionally, recent studies have shown the important roles of host immune responses in protection and the pathogenesis of respiratory viral infections, for instance, SARS-CoV, MERS-CoV, and influenza A viruses[15, 16]. Liao et al.[17] reported that increased immune cell recruitment in COVID-19 patients suggested a crucial role of CD8+ T cells in successful viral control, and proposed support therapeutic strategies that target the myeloid cell compartment to treat COVID-19-associated inflammation. However, little is known about drug screens of disease-relevant cell types.
Drug repurposing is an essential and universal strategy in the development of new drugs\cite{18}. It may facilitate the discovery of new mechanisms of action for existing drugs, which is less time-consuming and cost-effective let alone the existing pharmaceutical supply chains for formulation and distribution\cite{19, 20}. Considering that an RNA virus exhibits a considerable degree of sequence variation, drugs targeting host factors may cause less mutational resistance with more effective and broad anti-virus spectrum potential. Hence, there is an urgent need to identify potential therapeutics with new strategies for emerging infectious diseases, and repurposing clinically assessed drugs represents one of the most practicable strategies for the rapid identification of treatments to combat COVID-19.

In this study, we analyzed a publicly available single-cell RNA sequencing (scRNA-seq) dataset of bronchoalveolar lavage fluid (BALF) collected from mild and severe cases as well as bulk RNA-Seq of BALF in COVID-19 patients from different experiments (Figure 1). Data mining was performed by using the Library of Integrated Network-Based Cellular Signatures (LINCS)\cite{21}, a drug perturbation database, to identify potential therapies for COVID-19 disease. A total of 281 candidates of different courses of COVID-19 independent of cell subtypes were identified, 10 of which were in clinical trials of COVID-19, including lopinavir/ritonavir\cite{22}, dexamethasone, niclosamide, lenalidomide, hydrocortisone, metformin, atorvastatin, sildenafil, and verapamil. Subsequently, we utilized the side effect prediction based on L1000 (SEP-L1000) project to predict adverse drug reactions (ADRs) and constructed drug-ADR association \cite{23, 24}. Our findings may aid in the rapid preclinical and clinical evaluation of these therapeutics and can provide an important drug discovery pipeline to accelerate and facilitate the development of potential treatments for COVID-19.

MATERIALS AND METHODS

ScRNA-seq data analysis and sample aggregation

The gene-barcode matrix files of all 6 donors containing 3 mild cases and 3 severe cases (lung BALF) and 3 healthy control (lung tissues) were downloaded from the NCBI Gene Expression Omnibus database (Accession ID: GSE145926)\cite{17}. All expression matrices were loaded in R statistical analysis platform using Seurat v3\cite{25} and keeping cells with gene number between 200 and 6000, unique molecular identifier (UMI) count above 1000 and mitochondrial gene percentage below 0.1. A total of 43,914 cells collected from three healthy subjects, three mild COVID-19 patients, and three severe COVID-19 patients, were used for the analyses. We also
collected a list of differentially expressed genes (DEGs) in SARS-CoV-2-infected lung BALF using a bulk RNA-Seq analysis to compare against the single-cell-based data. This DEG list was obtained from the Chinese National Genomics Data Center (https://bigd.big.ac.cn/; Accession ID: CRA002390)[26].

**Dimensionality reduction and clustering**

The LogNormalize method in Seurat was used for normalizing filtered gene-barcode matrix. Principal component analysis (PCA) was done by using the top 2,000 most variable genes. Then Uniform Manifold Approximation and Projection (UMAP) was performed on the top 50 principal components for visualizing the cells, and graph-based clustering was performed on the PCA-reduced data with Seurat v3[27].

**Differential analysis for clusters between the three groups**

MAST in Seurat v3 was used to perform differential analysis. DEGs were identified by comparing each cluster between all of the three groups. Genes with average log2FC > 0.25 and adjusted p-value < 0.05 were deemed as DEGs.

**Drug repurposing using the LINCS drug-perturbation data**

DEGs were first sorted by the log2FC values and then the upregulated and downregulated genes were chosen to identify drugs and compounds against the LINCS database using the Connectivity Map Linked User Environment (CLUE) platform[21]. The drug connectivity score (CS) with a negative value smaller than -90 was used to determine candidate drugs and compounds. COVID-19 database from the International Clinical Trials Registry Platform (ICTRP) (https://www.who.int/ictrp/en/, updated on May 5th, 2020) was searched for clinical trials information associated with these drugs.

**Adverse drug reactions analysis**
Both on-label and off-label adverse drug reactions (ADRs) of the candidate drugs were collected from the SEP-L1000 database (https://maayanlab.net/SEP-L1000/). The SEP-L1000 data include on-label ADRs of FDA-approved drugs collected from SIDER\textsuperscript{[28]} and off-label ADRs from the PharmGKB database\textsuperscript{[29]} based on the post-marketing ADR reports in the FDA Adverse Event Report System (FAERS).

**RESULTS**

*Study design and analysis of single-cell data*

Our study highlighted the identification of different therapeutic effects in the varied disease course. With the high variability of the cellular compartments underlying disease progression, our drug repurposing profiles from major cell subtypes included T, B, and NK cells, macrophages, and epithelial cells. A total of 9 scRNA-seq BALF samples, including 3 healthy cases, 3 mild cases, and 3 severe cases, were collected from publicly available scRNA-seq data (Supplemental Table S1). After quality filtering, approximately 250,000 gene expression values from 44,000 cells were collected. The clustering analysis identified six major clusters of macrophage, NK cells, CD4+ T cells, CD8+ T cells, B cells and epithelial cells (Supplemental Figure S1), which was determined based on the unique signature genes CD68 (macrophage cell), IL7R and CD4 (CD4+ T cell), CD8A (CD8+ T cell), MS4A1 (B cells), TPPP3 (epithelial cells), respectively (Supplemental Figure S2). We then compared these six major clusters across the healthy, mild, and severe COVID-19 cases and identified differentially expressed genes between any of the two courses (Supplemental Tables S2-S4).

*An overview of drug repurposing on the LINCS database*

Connecting to the LINCS database of small-molecule perturbations on gene expression, we identified candidate drugs and compounds that can reverse these upregulated and downregulated genes via the CLUE platform. The closer the CS is to -100, a score indicating a complete reversal, the higher chance identification of drug-adverse effect associations with upregulated or downregulated DEGs, in other words, drugs may show a better response to reverse expression of DEGs upregulated or downregulated in major cell subtypes in the BALF. There were a total of 281 candidates selected out by CLUE with CS lower than -90 based on DEGs among all three comparisons between two courses (Supplementary Table S5). To enable prioritization of known
Repurposing analysis in mild COVID-19 patients

To select candidates for mild cases, drugs and compounds were ranked according to their CSs (Supplementary Table S6), 133 candidate drugs were identified compared to controls (mild vs healthy group), and 53 of them involved in more than one cell subtype (Figure 2A, Supplementary Table S7). The top 10 drugs (Table 1), which appeared in three or more cell types, were tubulin inhibitor (flubendazole, mebendazole, nocodazole, and vincristine), DNA methyltransferase inhibitor (azacytidine), BCL inhibitor (ABT-737), M5 modulator (VU-0365114-2), calcium channel blocker (calmidazolium), apoptosis stimulant (kinetin-riboside), and opioid receptor antagonist (JTC-801). Beyond that, five drugs in this group are undergoing evaluation in COVID-19 clinical trials (Table 1), including HIV protease inhibitors lopinavir/ritonavir\(^{[22]}\) combination (phase 4), glucocorticoid receptor agonist dexamethasone (Phase 3/4)\(^{[30]}\), DNA replication inhibitor niclosamide (Phase 2/3) and antineoplastic lenalidomide (Phase 4).

The tubulin inhibitor flubendazole, widely used in treating intestinal parasites, is a potent inducer of autophagy initiation and can decrease infection of dendritic cells with the HIV\(^{[31]}\). Azacytidine could partially reverse the aberrant DNA methylation, a phase I clinical trial in combination with chemotherapy has been conducted to assess its therapeutic effects in children with leukemia, and in combination with APR-246 for myelodysplastic syndrome is in phase 3 clinical trial\(^{[32]}\). The BCL inhibitor ABT-737 exhibits potential pro-apoptotic and antineoplastic activities\(^{[33, 34]}\). Lopinavir is widely used for the treatment of HIV, formulated in combination with ritonavir that can increase the half-life of lopinavir\(^{[9-11]}\).

Repurposing analysis in severe COVID-19 patients

Drugs for preclinical and clinical evaluation for the therapy efficiency of SARS-CoV-2, a summary of the most among major cell subtypes during the patients’ disease course and the publicly disclosed clinical trial phases are annotated in Tables 1-3. Supplementary Table S5 provides the complete list of potential anti-coronavirus agents from the current analysis, focusing on the FDA approved drugs and experimental agents that have been already tested in clinical trials.
60 potent drugs were also selected in severe cases compared to controls (severe vs healthy group) according to their average CS between the replicates, and 25 of them involved in more than one cell subtype (Figure 2B, Supplementary Tables S8 & S9). As listed in Table 2, nine drugs presented at least in three separate cell types, including ABT-737 (BCL inhibitor), brefeldin-a (Protein synthesis inhibitor), indirubin (CDK inhibitor), TPCA-1 (IKK inhibitor), lopinavir (HIV protease inhibitor), GW-441756 (Growth factor receptor inhibitor), treprostinil (Prostacyclin analog), tyrphostin-AG-1478 (EGFR inhibitor) and epoxycholesterol (LXR agonist). In this group, lopinavir/ritonavir and hydrocortisone are ongoing in COVID-19 clinical trials.

Protein synthesis inhibitor brefeldin-a has used inhibit entry of some viruses, like human papillomavirus and polyomavirus[35], and egress of others, such as herpesviruses and paramyxoviruses[36]. Indirubin, an active ingredient of traditional Chinese medicine (TCM) “Danggui Longui Wan”, has potent activity against myelocytic leukemia[37] and therapeutic potential on IAV-infection[38].

*Repurposing analysis in severe COVID-19 patients compared to mild patients*

A total of 111 candidate drugs were identified in severe cases compared to mild ones (severe vs mild group), 39 of them involved in more than one cell subtype (Figure 2C, Supplementary Tables S10 & S11). As listed in Table 3, nine drugs (those for which drugs selected out in three separate cell types or more), including fostamatinib (SYK inhibitor), VER-155008 (HSP inhibitor), KU-0063794 (MTOR inhibitor), PIK-90 (PI3K inhibitor), linsitinib (IGF-1 inhibitor), TAK-715 (p38 MAPK inhibitor), Y-27632 (Rho-associated kinase inhibitor), AZ-628 (RAF inhibitor) and lestaurtinib (FLT3 inhibitor). In this group, except lopinavir, we also following listed 4 drugs in clinical trials for the treatment of COVID-19 in Table 3, including insulin sensitizer metformin (Phase 3), HMGCR inhibitor atorvastatin (Phase 2/3), phosphodiesterase inhibitor sildenafil (Phase 3) and calcium channel blocker verapamil (Phase 2/3).

SYK inhibitor fostamatinib produced clinically-meaningful responses for adult persistent and chronic immune thrombocytopenia in two parallel, phase 3 randomized trials[39]. HSP inhibitor VER-155008 regulates Kaposi’s sarcoma-associated herpesvirus lytic replication and highlights the potential to be a novel antiviral agent[40]. FLT3 inhibitor lestaurtinib obtained orphan drug approval from the FDA for acute myeloid leukemia[41] and in a phase II trial of advanced multiple myeloma and phase I trials of prostate cancer.
Common candidates through mild and severe COVID-19 patients

As shown in Figures 3A & 3B and Supplemental Table S5, lopinavir was the only one identified in all three comparisons, and interestingly, ritonavir was common in two analyses. There were 23 additional common drugs, such as SB-216763, ABT-737, JTE-907, brefeldin-a, PKCbeta-inhibitor, indirubin, GW-441756, flubendazole, tyrphostin-AG-1478, memantine, calyculin, kinetin-riboside, ascorbyl-palmitate, ON-01910, mirin, verrucarin-a, emetine, TPCA-1, RHO-kinase-inhibitor-III[rockout], PD-158780 and NVP-AUY922. For example, the glycogen synthase kinase inhibitor SB-216763 acts as neuroprotectant[42] and prevents cardiac ischemia[43]. JTE-907 is a cannabinoid receptor inverse agonist producing anti-inflammatory effects[44].

To further demonstrate the usefulness of this strategy, we have accomplished the identification of therapeutic drugs by transcriptional changes in BALF of COVID-19 patients with a bulk RNA-seq data[26]. Ten efficient candidates were identified using the same analysis pipeline, two of which, including glycogen synthase kinase inhibitor SB-216763 and PPAR receptor antagonist GW-6471, were also included in the single-cell-based candidate lists (Supplemental Table S12).

Adverse drug reactions analysis

Further investigations are necessary to characterize the ADRs which are a central consideration during drug development[45]. Therefore, we conducted a computational approach using the SEP-L1000 database to predictive relationships between drugs and the emergence of ADRs (Supplemental Tables S13 S14). Figure 4 shows a heatmap of the top 50 drug-ADR association for On-label (Figure 4A) and Off-label (Figure 4B) ADRs. These findings highlighted drug-ADR associations and may lead to inform clinical decisions regarding treatments for COVID-19.

DISCUSSION

COVID-19 has spread rapidly, and no proven vaccine or drug has yet been identified to treat it. Generally speaking, there are several ways to control or prevent emerging coronavirus disease, including antivirals, small-molecule drugs, biologics, and vaccines[4, 5]. Due to the lack of
effective therapeutic agents and long development cycles of vaccines, it is, therefore, reasonable to consider repurposing existing drugs and compounds for COVID-19.

Drug repurposing is a potentially important strategy for the discovery of existing medicines to tackle COVID-19\[18\]. Gordon et al.\[46\] identified 332 high-confidence SARS-CoV-2-human protein-protein interactions for drug repurposing. An additional study\[47\] tested the antiviral activity of 20 FDA approved drugs against SARS-CoV-2 that previously shown to inhibit SARS-CoV and MERS-CoV. Another research team\[48\] conducted a high-throughput analysis of the ReFRAME library to identify 30 candidates existing drugs that prevent the COVID-19 virus from replicating in mammalian cells. In a study\[49\] based on public data of patients with pulmonary fibrosis and the database LINCS, several drugs were identified on COVD-19 targets ACE2.

Host immune responses are particularly important in the protection and pathogenesis of the respiratory viral infections like SARS-CoV, MERS-CoV, and influenza A viruses\[15, 16\]. Liao et al.\[17\] observed that T and NK cells accumulated, epithelial cells decreased in COVID-19 patients compared to controls, meanwhile, macrophages dysregulated and the cell compartments differed in mild and severe disease courses, more T and NK cells decreased in severe cases but CD8+ T cells increased in mild cases. However, drug screening of disease-relevant cell types is still unclear.

Here, we analyzed publicly available data of COVID-19 patients and performed data mining by using the LINCS L1000 database to identify potential therapies for COVID-19 disease and SEP-L1000 database to predict side effects. Our approach is different from previous methods for drug repurposing for coronavirus, since it does not merely rapidly identify likely effective therapeutic agents in preventing or treating COVID-19, but tries to filter out specific medications during the patients’ disease courses. Furthermore, the data and transcriptome are derived from human samples from real patients, two independent sets of experiments. Lastly, we explore the underlying risk factors associated with some side effects of the candidates. Overall, our data will guide the future development of therapies for the different durations of COVID-19 and other viral respiratory infections.

This study has several limitations to note. First, the public scRNA-Seq data had a small number of clinical samples (n=9) without available patient information, which makes comparisons between studies difficult. With the fast pace and expected large number of published literature using other patient samples, our candidate lists may need to be revised. Second, our
findings may not apply to children because all the sequencing data were from adults. Future work on large-scale data mining would help us in better identification of antiviral drugs.

CONCLUSIONS

The pandemic of COVID-19 represents the greatest global public health crisis in this generation. So far, no proven vaccines and therapies have been identified. Based on the study, we thoroughly investigated potential candidates for the treatment in COVID-19 progression and predicted some possible adverse effects. The findings can guide additional repurposing studies, tailored for different stages of disease progression.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

JH, CH, MW and KG designed the project, collected data, performed analysis, and prepared figures. KG and ZW collected data, prepared figures, and wrote the manuscript. PG performed analysis and prepared tables. QP revised the manuscript.

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CODE AVAILABILITY

All the codes and data are available at https://github.com/guokai8/COVID19/

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Table 1. A list of potential drugs for treating COVID-19 based on LINCS database and DEGs between mild and healthy samples in B, CD4+ T, CD8+ T, Epithelial, NK cells, and Macrophage. Connectivity scores were calculated from the CLUE platform. Asterisk (*) represents the clinical trial for its efficacy in COVID-19 disease. (+) indicates drugs meeting the SC < -90 criteria, while (-) indicates drugs not meeting the criterion.

| Drug          | LINCS ID      | B  | CD4+T cells | CD8+ T cells | Epithelial cells | Macrophage cells | NK cells | SharedSets | Description                  | Phase     |
|---------------|---------------|----|--------------|--------------|------------------|------------------|----------|------------|--------------------------------|-----------|
| flubendazole  | BRD-K86003836 | +  | +            | +            | +                | -                | +        |            | Tubulin inhibitor             |           |
| azacitidine   | BRD-K03406345 | -  | +            | +            | +                | +                | -        |            | DNA methyltransferase inhibitor | Phase 1/3 |
| ABT-737       | BRD-K56301217 | +  | +            |             | -                | +                | -        |            | BCL inhibitor                  |           |
| VU-0365114-2  | BRD-K37456065 | -  | +            | +            | -                | -                | -        |            | M5 modulator                   |           |
| calmidazolium | BRD-A98283014 | +  | +            | +            | +                | +                | -        |            | Calcium channel blocker         |           |
| mebendazole   | BRD-K77987382 | -  | +            | -            | +                | +                | -        |            | Tubulin inhibitor              |           |
| kinetin-ribose| BRD-K94325918 | -  | -            | +            | -                | -                | -        |            | Apoptosis stimulant            |           |
| nocodazole    | BRD-K12539581 | -  | +            | -            | +                | +                | -        |            | Tubulin inhibitor              |           |
| JTC-801       | BRD-K17705806 | -  | +            | +            | +                | +                | -        |            | Opioid receptor antagonist      |           |
| vincristine   | BRD-K82109576 | -  | -            | +            | +                | -                | +        |            | Tubulin inhibitor              |           |
| lopinavir     | BRD-K99451608 | +  | -            | -            | -                | -                | +        |            | HIV protease inhibitor          | Phase 4*  |
| ritonavir     | BRD-K51485625 | +  | -            | -            | -                | -                | +        |            | HIV protease inhibitor          | Phase 4*  |
| dexamethasone | BRD-A35108200 | -  | +            | -            | -                | -                | -        |            | Glucocorticoid receptor agonist | Phase 3/4* |
| niclosamide   | BRD-K35960502 | -  | -            | -            | -                | +                | -        |            | DNA replication inhibitor       | Phase 2/3* |
| lenalidomide  | BRD-K05926469 | -  | -            | -            | -                | -                | +        |            | Antineoplastic                 | Phase 4*  |
Table 2. A list of potential drugs for treating COVID-19 based on LINCS database and DEGs between severe and healthy samples in B, CD4⁺ T, CD8⁺ T, Epithelial, NK cells, and Macrophage. Connectivity scores were calculated from the CLUE platform. Asterisk (*) represents the clinical trial for its efficacy in COVID-19 disease. (+) indicates drugs meeting the SC < -90 criteria, while (-) indicates drugs not meeting the criterion.

| Drug         | LINCS ID        | B  | CD4⁺T cells | CD8⁺ T cells | Epithelial cells | Macrophage cells | NK cells | SharedSets | Description               | Phase     |
|--------------|-----------------|----|-------------|-------------|-----------------|------------------|----------|------------|---------------------------|-----------|
| ABT-737      | BRD-K56301217   | +  | +           | -           | +               | +                |          |            | BCL inhibitor             | 5         |
| brefeldin-a  | BRD-A17065207   | +  | +           | +           | -               | +                |          |            | Protein synthesis inhibitor | 5         |
| indirubin    | BRD-K53959060   | +  | +           | +           | -               | +                | +        |            | CDK inhibitor              | 5         |
| TPCA-1       | BRD-K51575138   | +  | +           | +           | -               | +                |          |            | IKK inhibitor              | 4         |
| lopinavir    | BRD-K99451608   | +  | -           | -           | +               | -                | +        |            | HIV protease inhibitor     | 3         |
| GW-441756    | BRD-K04146668   | -  | -           | -           | +               | -                | +        |            | Growth factor receptor inhibitor | 3         |
| treprostinil | BRD-A67438293   | +  | -           | +           | -               | +                |          |            | Prostacyclin analog        | 3         |
| tyrphostin-AG-1478 | BRD-K68336408 | -  | +           | +           | -               | +                | -        |            | EGFR inhibitor             | 3         |
| epoxycholesterol | BRD-K61480498 | -  | +           | +           | +               | -                | -        |            | LXR agonist                | 3         |
| ritonavir    | BRD-K51485625   | -  | -           | -           | +               | +                |          |            | HIV protease inhibitor      | 2         |
| hydrocortisone | BRD-A07000685  | -  | +           | -           | -               | -                | -        |            | Glucocorticoid receptor agonist | 1         |

*Note: BRD stands for BioRxiv Database.
Table 3. A list of potential drugs for treating COVID-19 based on LINCS database and DEGs between severe and mild samples in B, CD4+ T, CD8+ T, Epithelial, NK cells, and Macrophage. Connectivity scores were calculated from the CLUE platform. Asterisk (*) represents the clinical trial for its efficacy in COVID-19 disease. (+) indicates drugs meeting the SC < -90 criteria, while (-) indicates drugs not meeting the criterion.

| Drug        | LINCS ID       | B cells | CD4+ T cells | CD8+ T cells | Epithelial cells | Macrophage cells | NK cells | SharedSets | Description               | Phase |
|-------------|----------------|---------|--------------|--------------|------------------|-------------------|----------|------------|---------------------------|-------|
| fostamatinib| BRD-K20285085  | +       | +            | +            | +                | +                 | +        | 6          | SYK inhibitor             | Phase 3 |
| VER-155008  | BRD-K32330832  | +       | +            | +            | +                | +                 | +        | 6          | HSP inhibitor             |        |
| KU-0063794  | BRD-K67566344  | +       | -            | -            | -                | +                 | +        | 3          | MTOR inhibitor            |        |
| PIK-90      | BRD-K99818283  | +       | +            | -            | -                | -                 | +        | 3          | PI3K inhibitor            |        |
| linstitinib | BRD-K08589866  | +       | -            | -            | -                | +                 | +        | 3          | IGF-1 inhibitor           |        |
| TAK-715     | BRD-K52751261  | -       | +            | +            | -                | -                 | +        | 3          | p38 MAPK inhibitor        |        |
| Y-27632     | BRD-K44084986  | -       | +            | +            | -                | -                 | +        | 3          | Rho associated kinase inhibitor |        |
| AZ-628      | BRD-K05804044  | -       | +            | +            | -                | -                 | +        | 3          | RAF inhibitor             |        |
| lestaurtinib| BRD-K23192422  | -       | -            | -            | +                | +                 | +        | 3          | FLT3 inhibitor            | Phase 1/2|
| metformin   | BRD-K79602928  | -       | +            | -            | -                | -                 | -        | 1          | Insulin sensitizer        | Phase 3* |
| atorvastatin| BRD-U88459701  | -       | -            | +            | -                | -                 | -        | 1          | HMGCR inhibitor           | Phase 2/3*|
| sildenafil   | BRD-K50128260  | -       | -            | +            | -                | -                 | -        | 1          | Phosphodiesterase inhibitor | Phase 3* |
| verapamil   | BRD-A09533288  | -       | -            | +            | -                | -                 | -        | 1          | Calcium channel blocker    | Phase 2/3*|
| lopinavir   | BRD-K99451608  | -       | -            | +            | -                | -                 | -        | 1          | HIV protease inhibitor     | Phase 4*  |
FIGURE LEGENDS

Figure 1. Workflow of drug repurposing for treating different durations of COVID-19.
Input publicly available scRNA-seq data and transcriptomic data of BALF in COVID-19 patients against the LINCS database by using the CLUE platform. Candidates are selected which can reverse expression of upregulated DEGs upon drug treatment and are compared by connectivity score and the number in major cell subtypes cross healthy, mild, and severe groups.
Figure 2. UpSet plots showing the overlap among the drug candidates for treating COVID-19 based on the LINCS database. DEGs between (A) mild and healthy, (B) severe and healthy, and (C) severe and mild samples in B, CD4⁺ T, CD8⁺ T, Epithelial, NK cells, and Macrophages.
**Figure 3.** Common drug candidates. Venn Diagram showing the overlap among the drug candidates for treating COVID-19 between three sets across control, mild, and severe COVID-19 groups (A) and heatmap showing the 25 drugs shared by at least two sets (B).
Figure 4. Heatmap of drug-ADR association. On-label (A) and off-label (B) ADRs are illustrated in heatmaps. White color means no association between drug and ADRs.
SUPPLEMENTARY INFORMATION

Supplementary Figure S1. The UMAP presentation of single-cell atlas of BALFs showing 6 major cell types.

Supplementary Figure S2. The violin plot shows the signature genes (CD68, IL7R, CD4, CD8A, MS4A1, TPPP3) expression from major cell types.

Supplemental Table S1. Clinical data of the enrolled subjects (SARS-COVID 2 confirmed).

Supplemental Table S2. Differentially expressed genes between severe and mild samples in B, CD4+ T, CD8+ T, Epithelial, NK cells and Macrophage.

Supplemental Table S3. Differentially expressed genes between mild and healthy samples in B, CD4+ T, CD8+ T, Epithelial, NK cells and Macrophage.

Supplemental Table S4. Differentially expressed genes between severe and healthy samples in B, CD4+ T, CD8+ T, Epithelial, NK cells and Macrophage.

Supplemental Table S5. Full list of overlap potential drugs among three comparisons (Mild vs Healthy, Severe vs Healthy and Severe vs Mild).

Supplemental Table S6. Full list of potential drugs for treating COVID-19 based on LINCS database and DEGs between mild and healthy samples in B, CD4+ T, CD8+ T, Epithelial, NK cells and Macrophage. Connectivity scores were calculated from CLUE platform.

Supplemental Table S7. Overlap potential drugs based on DEGs among different cell clusters between mild and healthy patients.

Supplemental Table S8. Full list of potential drugs for treating COVID-19 based on LINCS database and DEGs between severe and healthy samples in B, CD4+ T, CD8+ T, Epithelial, NK cells and Macrophage. Connectivity scores were calculated from CLUE platform.

Supplemental Table S9. Overlap potential drugs based on DEGs among different cell clusters between severe and healthy patients.

Supplemental Table S10. Full list of potential drugs for treating COVID-19 based on LINCS database and DEGs between severe and mild samples in B, CD4+ T, CD8+ T, Epithelial, NK cells and Macrophage. Connectivity scores were calculated from CLUE platform.

Supplemental Table S11. Overlap potential drugs based on DEGs among different cell clusters between severe and mild patients.
**Supplemental Table S12.** A list of potential drugs for treating COVID-19 based on DEGs from RNA-seq data between patient and healthy samples and LINCS database.

**Supplemental Table S13.** A complete list of on-label ADRs of all candidates. On-label ADRs of drugs were downloaded from the Side Effect Resource (SIDER). The ADR terms are mapped to Preferred Terms (PTs) coded in MedDRA v16.0.

**Supplemental Table S14.** A complete list of off-label ADRs of all candidates. Off-label ADRs were processed data from the post-market ADR reports within the FDA Adverse Event Report System (FAERS). The ADR terms are mapped to Preferred Terms (PTs) coded in MedDRA v16.0.