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Preprint · March 2020

DOI: 10.13140/RG.2.2.20588.10886

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AI for the repurposing of approved or investigational drugs against COVID-19

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The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally since 2019 and reached the pandemic level in 2020. We utilized a deep neural network to search for host-target acting antivirals among experimental and approved drugs with potential activity against coronavirus-born diseases. To achieve the goal we searched for gene expression signatures of molecular perturbations most closely resembling the effects of the COBP2 gene knockout since COBP2 is required for replication of a genetically similar virus SARS-CoV. The majority of the top-scoring molecules were already suggested for repurposing as broad-spectrum antivirals. One of the approved drugs from the list, nitazoxanide, has recently demonstrated activity against SARS-CoV-2. We, therefore, urge prompt experimental characterization of the other predictions and highlight the potential of modern AI/ML technologies for prompt identification of human-trial ready therapeutics against the world's most urgent medical needs. We encourage academic and industrial collaborations to validate the results of this research and further develop the most successful compounds.

INTRODUCTION

On December 30, 2019, according to some sources, an artificial-intelligence (AI) company called BlueDot alerted clients to an unusual bump in pneumonia cases in Wuhan, China. It was nine days before the World Health Organization (WHO) officially flagged what we have all come to know as Coronavirus disease 2019 (COVID-19). This is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously referred to as 2019-nCoV). The disease has spread globally since 2019, resulting in the 2019–20 coronavirus pandemic. While the majority of cases result in mild symptoms, some progress to pneumonia and multi-organ failure [1].The death rate per the number of diagnosed cases is estimated at between 1% and 5% and varies by confounding health conditions and availability of healthcare resources [2].

The application of AI technologies is not limited to sophisticated natural language processing for outbreak monitoring. In just a few recent weeks we saw announcements from InSilico Medicine and DeepMind joining the global effort against the disease by contributing their AI/ML pipelines for the research and drug discovery community. The companies respectively produced and made public domain a set of putative small molecules inhibitors of one of the key virus targets, 3C-like Protease [3], and the structure predictions for six proteins associated with SARS-CoV-2 using the most up-to-date version of their AlphaFold system [4].

No matter how quickly the initial hits can be found with or without AI, it will take long years for any such novel molecule to progress through treacherous waters of clinical trials and end up as medicines in doctors' hands at the bedside. The much needed immediate relief can only be secured by repurposing approved or clinical-stage investigational drugs fast-tracked into clinical trials [5]. According to the report, most of the drugs currently tested against SARS-CoV-2 are Direct-acting antiviral agents (DAAs) and are representatives of a class of drugs targeting viral proteins. The repurposed drugs in the clinical trials were initially designed against HIV or influenza. A small minority of experimental treatments are the Host-targeting antivirals (HTA) acting against host factors, including inflammatory cytokines.

In this work, we utilized a deep neural network to mine gene expression signatures for experimental and approved drugs with potential activity against coronavirus-born diseases. To achieve this goal, we searched for gene expression profiles of the molecular perturbations most closely mimicking the gene expression signature of the COBP2 gene knockdown. The gene is required for replication of SARS-CoV [6], which is closely genetically related to SARS-Cov-2 with 79% identity [7].

We speculated that the same gene may be necessary for the replication of the genetically similar SARS-CoV-2. A large number of the top-scoring molecules were already suggested for repurposing as broad-spectrum antivirals based on the drug's performance in experimental models of viral diseases. One of the approved drugs, nitazoxanide, has recently demonstrated activity against SARS-CoV-2 [8]. According to the available literature, a few more drug compounds from our list have been already tested and found active in models involving related viruses in vitro, such as MERS-CoV or SARS-CoV. We, therefore, call for characterization of the remaining top-ranked compounds against SARS-CoV-2. All the drugs selected in our study have been already approved for clinical trials. Hence any experimental confirmation of the activities predicted here may build the rationale for a trial involving human subjects and, with some effort and luck, translated into a cost- and time- effective solution to the unfolding medical emergency.

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RESULTS

Deep neural network for batch removal in LINCS L1000 dataset

Deep learning with its capabilities to approximate general non-linear dependencies of input data was recently demonstrated as a powerful tool for gene expression data analysis and batch removal. We trained the deep neural network (DNN) with the architecture similar to that described in [9]. To enable identification of biologically similar molecular and genetic perturbations, we generated compressed 20-dimensional representations (embeddings) of the 978-dimensional differential gene expression signatures (LINCS L1000 data processing at Level 4 [10].

The DNN was constructed of the three blocks: DenseNet block, Embeddings, and Perturbagen classifier, see Fig. 1a. The DenseNet was implemented as suggested in [9] with 32 hidden layers and a growth rate of 48. The Embeddings layer is a dense layer with 2514 Input size and 20 output size. The perturbagen classifier was used to predict the perturbagen class (pert_iname label in the L1000 dataset) from the embedding vector using additive margin Softmax (AM-Softmax) [11] with the margin value was set to 0.2 as in [9].

The training data included profiles from LINCS PHASE I (GEO accession number GSE92742) and PHASE II (GEO accession number GSE70138). We removed samples related to cell lines in which less than 5000 profiles were measured. The preprocessed dataset involving 1467244 gene expression profiles corresponding to 27870 unique molecular perturbation classes was split into the training and test datasets at 80/20 ratio. The test dataset did not include gene expression signatures from the training dataset.

To validate the performance of the DNN we used the same metrics as proposed in [9]. The best model achieved the area under the receiver operating characteristic curve (ROC AUC) recovery of the molecular, 0.871, and genetic, 0.764, perturbations, respectively. Both numbers were significantly better than 0.656 and 0.616 for the same molecular perturbation classes in the raw LINCS L1000 data. The model was able to pull structurally similar compounds (with Tanimoto similarity score better than 0.85) with ROC AUC of 0.745.

To obtain the compressed representation of each molecular perturbation class we computed consensus profiles for each dose and time by averaging over all the available repeats and all cell lines. For the analysis, we used the measurements of the effects of small molecules produced at $10\mu M$ concentration at the time point of $24h$ (and $96h$ for the genetic perturbations).

Search for antivirals against SARS-CoV-2

A set of host factors relevant for SARS-coronavirus (SARS-CoV) replication was identified by means of a siRNA library screen targeting the human kinome in [6]. The depletion of the $\beta 2$ subunit of the coatomer protein complex (COPB2) in the followup experiment produced the strongest antiviral effect, reduced SARS-CoV protein expression, and produced a $>$ 2-log reduction in virus yield.

We assumed that the interactions between the virus and host may be shared by the genetically similar viruses and proceeded with the search for small molecules capable to recreate the effect of the COPB2 genetic knockout. Fortunately, LINCS L1000 database provides gene expression signatures of a series of shRNA knockouts of COPB2. We pooled the consensus signature from multiple shRNA experiments and searched for molecular perturbations most similar to the knockout. The similarity measure, the CoV similarity score, is the distance between the molecular perturbation and COPB2 knockout signatures in the latent variables space (see Fig. 1b for the distribution of the computed similarity scores).

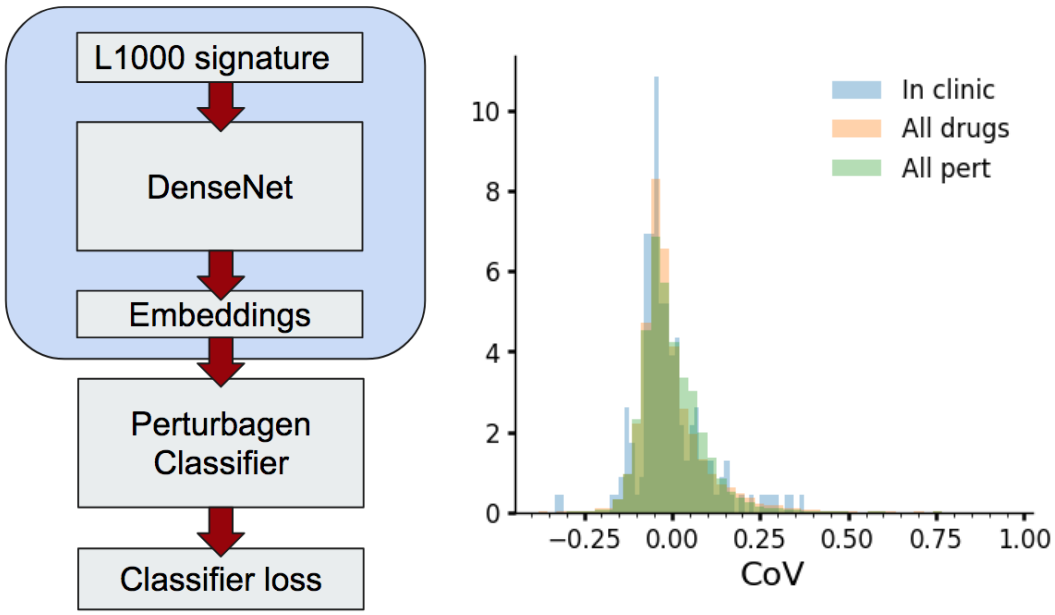
The results of the calculations are summarized in Table 1 and divided into categories reflecting their development status (including approved, and experimental drugs) according to the DrugBank database. For each of the drugs, we provided the Mechanism of Action (MoA) and the development status (if applicable). We also performed a literature search for evidence of antiviral activity in experiments involving coronaviruses (the "direct evidence" column) and other viral infections ("indirect evidence" column).

Of note, the top-scored molecular perturbation was Brefeldin A, which is a natural lactone antiviral compound produced by the fungus Penicillium brefeldianum. This is a good sanity check for the computational pipeline since according to [12], Brefeldin A treatment of SARS-CoV-infected cells significantly reduced replication as well as the accumulation of virus-induced membrane structures (see [6] for mechanistic details relating Brefeldin A activity and COPB2 knockout).

DISCUSSION

Direct-acting antiviral agents (DAAs) have been very successful against viral infections in medical practice. However, DAAs suffer from several inherent limitations, including narrow-spectrum antiviral profiles and liability to drug resistance. In comparison, host targeting antivirals (HTAs) target host proteins that are probably broadly required for various viral infections. This is why HTAs are not only perceived but also demonstrated to exhibit broad-spectrum antiviral activities. In addition, host proteins are not under the genetic control of the viral genome, and hence HTAs possess a much higher genetic barrier to drug resistance as compared with DAAs (see, e.g., [19] for the most recent review).

In this work, we focused on repurposing of approved or clinical-stage investigational drugs against COVID-19 and other coronavirus-borne diseases. We turned to the



(a) (b)

FIG. 1: a) Deep neural network (DNN) architecture employed for batch-removal and the construction of the compressed gene expression representation; b) the distributions of the CoV score (similarity to the gene-expression signature of COPB2 knockdown) for all, all molecular perturbations, and experimental drugs, respectively.

Broad Institute LINCS L1000 database of biological effects (gene expression signatures) of molecular and genetic perturbations. The resource is commonly used for MoA studies and drug repurposing. Unfortunately, most of gene expression variance in transcriptomes is typically associated with non-biological factors (commonly known as batch effects) and hence may be of limited use without sophisticated batch removal procedures [20].

We followed and improved on approach from [9] and reduced batch effects with the help of a deep neural network. We used the compressed low-dimensional representations of the gene expression data from LINCS L1000 dataset and searched for gene expression profiles of the molecular perturbations most closely mimicking the gene expression signature of the COBP2 gene knockdown. The gene was identified in a full-kinome iRNA screen and was confirmed as being required for the genetically similar SARS-CoV replication in vitro [6].

Based on the computed similarity to COBP2 knockout, we generated two lists of predicted antivirals separately among the approved and investigational drugs. Both tables were significantly enriched by HTAs with broad activity against viruses ranging from coronaviruses (MERS and SARS) to influenza and HCV.

Notably, the in vitro efficacy (EC50) of the investigational drugs in models of viral diseases are most of the time better than that of the approved drugs. This circumstance may reflect medicinal chemistry advances over the years as we shift our attention from the "old" and already approved to the "newer" investigational drugs.

Among the approved drugs, niclosamide and nitazoxanide are known for broad-spectrum antiviral action and exhibited low-micromolar range activities in vitro models of coronavirus diseases. Niclosamide is approved for the treatment of tapeworm infections and is listed in the WHO essential medicines. Nitazoxanide, a commercial antiprotozoal agent with an antiviral potential against a broad range of viruses including human and animal coronaviruses. Currently, the drug is listed in multiple clinical trials against viral diseases. In the most recent work, nitazoxanide inhibited the SARS-CoV-2, the virus behind the COVID-19, at a low-micromolar concentration ($EC_{50} = 2.12\mu M$; $CC_{50} > 35.53\mu M$; the selectivity index (SI)> 16.76) [8].

Although there is no data on the antiviral activity of ixazomib, a proteasome inhibitor, there is evidence that this class of compounds possesses a broad-spectrum antiviral activity. The clinically approved proteasome inhibitor bortezomib (PS-341) significantly reduces influenza A virus and vesicular stomatitis virus propagation at $EC_{50} = 50 - 100nM$, while exhibiting some cytotoxicity [21]. It is hypothesized that bortezomib may act as an antiviral agent via induction of the type I IFN response. Authors of [22] report an EC50 of influenza virus infection by bortezomib of $198nM$ in human non-malignant RPE cells (CC_{50} of bortezomib for these cells exceeds $10\mu M$). Bortezomib also inhibits herpes simplex virus (HSV) infection ($EC_{50} = 4 - 50nM$ for different strains) since proteasomal degradation activity is critical for early steps of HSV infection [23]. Proteasome

TABLE I: The top-scoring drugs according to the predicted antiviral effect.

Molecule	CoV-Score	MoA	Status	Direct evidence	Indirect evidence
Top LINCS L1000					
Brefeldin A		Arf inhibitor	N/A	$EC_{50} = 21.4\mu M$ (SARS-CoV) [12]	Herpes simplex, Newcastle disease, papillomavirus and polyomavirus [13]
Approved drugs					
Niclosamide	0.57	N/A	Approved for the treatment of tapeworm infections	$EC_{50} = 3.12\mu M$ (SARS-CoV) [14]	Rhinoviruses (HRV), influenza virus, Chikungunya virus, Zika virus [15]
Nitazoxanide	0.35	N/A	Approved antiprotozoan, currently is in clinical trials for influenza (Phase 3), rotavirus or norovirus (Phase 2), Hepatitis B and C, HIV	$EC_{50} = 2\mu M$ (MERS-CoV) [16], $EC_{50} = 2.12\mu M$ (SARS-CoV-2) [8]	Influenza $EC_{50} = 0.2 - 1.5\mu M$, syncytial virus, parainfluenza, rotavirus, norovirus, hepatitis B, hepatitis C, dengue, yellow fever, Japanese encephalitis virus and HIV [17]
Afatinib	0.34	EGFR	Approved for the treatment of non-small cell lung carcinoma	Drugs with the same MoA were effective in in vivo models of SARS-Cov	N/A
Ixazomib	0.33	Proteasome inhibitor	Approved for the treatment of multiple myeloma	Another inhibitor with the same MoA suppressed replication of SARS-Cov at $EC_{50} < 1\mu M$	Another inhibitor with the same MoA suppressed replication of influenza A virus at $EC50 < 1\mu M$
5 more drugs	$0.29 - 0.34$	Known MoA	2 approved, 3 withdrawn	N/A	Some active against Polyomaviruses
Reserpine	0.29	Vesicular monoamine transporters antagonist	Natural compound. Used as an antihypertensive (in combination). Was used as an antidepressant and to treat dyskinesia in Huntington's disease	$EC_{50} = 3.4\mu M$ (SARS-CoV) [18]	N/A
Investigational drugs					
Obatoclax	0.33	Mcl-1 (Bcl-2 family) inhibitor, senolytic	Phase 2 clinical trials for leukemia, lymphoma, myelofibrosis, and mastocytosis	N/A	Was effective in vitro against Influenza A and Zika viruses ($EC_{50} < 0.1\mu M$)
NVP-AUY922	0.23	Hsp90 inhibitor	Phase 2 clinical trials, oncology	N/A	Was effective in vitro against Influenza A and Measles ($EC_{50} < 0.1\mu M$)
7 more drugs	$0.20 - 0.38$	Known MoA	Phase 1/2	N/A	2 some active against Influenza and Dengue

inhibitor MG-132 inhibits the replication of hepatitis E and C viruses [24], cytomegalovirus [25].

Inhibition of the proteasome in sub-μM concentrations by different chemical compounds, such as MG-132 or bortezomib appeared to not only impair entry but also RNA synthesis and subsequent protein expression of different CoVs, including mouse hepatitis virus (MHV), feline infectious peritonitis virus, and, most notably, SARS-CoV [26]. Treatment of mice with SARS-like pneumonitis induced by murine hepatitis virus strain 1 (MHV-1) with the proteasome inhibitor PDTC (5 mg/kg daily s.c.), MG-132 (0.5 mg/kg daily s.c.), or PS-341 (or bortezomib, 0.25 mg/kg daily s.c.) led to 40% survival ($p < 0.01$), with a concomitant improvement of lung histology, reduced pulmonary viral replication, decreased pulmonary STAT phosphorylation, and reduced pulmonary inflammatory cytokine expression [27].

Reserpine is another predicted "hit" and a natural com-

pound used as an antihypertensive (in combination with other drugs). Previously, it was identified as a second most active ($EC_{50} = 3.4\mu M$) compound against SARS-CoV in a screening of 10,000 compounds [18].

One of the investigational compounds in our list is the Hsp90 inhibitor NVP-AUY922. This should not be surprising, since some viruses particularly depend on the cellular chaperoning apparatus. Accordingly, another HSP90 inhibitor, 17-DMAG, reduced the endpoint foot and mouth disease virus titer by more than 10-fold at $0.163\mu M$ concentration when applied prior to the infection [28]. Another HSP90 inhibitor geldanamycin exhibited broad-spectrum activity against viruses including SARS-CoV with EC50 ranging between 0.5 and $4\mu M$ (HIV-1 and SARS-CoV exhibited the highest sensitivity to geldanamycin in [29]).

Blocking EGFR receptor kinase activity by approved inhibitors broadly impaired infection by all major HCV genotypes and viral escape variants in cell culture and in a human liver chimeric mouse model in vivo [30]. In EGFR(DSK5) mice with constitutively active EGFR, SARS-CoV infection causes enhanced lung disease [31, 32]. In a separate work involving Respiratory syncytial virus (RSV) challenge model, EGFR activation suppresses IFN regulatory factor (IRF 1)-induced IFN-λ production and thus contributed to the viral infection. On the contrary, EGFR inhibition during viral infection augmented IRF1, IFN-λ, and decreased RSV titers [33].

Notably, many survivors of SARS-CoV and apprently SARS-Cov-2 infections develop pulmonary fibrosis (PF), with a higher prevalence in older patients. In mouse models of SARS-CoV pathogenesis, the wound repair pathway, controlled by the epidermal growth factor receptor (EGFR), is critical to recovery from SARS-CoV-induced tissue damage.

Age, as well as pre-existing chronic diseases, are risk factors for COVID-19 mortality. According to the proportional hazards model from [34], the mortality rate doubling time is approximately 10 years (HR = 1.10) and is consistent with mortality rate doubling time from the Gompertz mortality law. It is therefore intriguing to understand if there are common mechanisms through which the aging and the prevalence of age-related diseases may contribute to adverse outcomes.

One of the most interesting examples from our list in relation to aging is obatoclax, which is reported to stop influenza virus replication at a very decent $10nM$ concentration. Obatoclax is the discontinued Bcl-2 inhibitor similar to navitoclax. Both compounds have been investigated as a senolytics [35, 36], i.e. belong to a class of drugs reducing the number of so-called senescent cells (SCs) [37]. The number of SCs increase with age along with the level of inflammatory cytokines such as IL-6 as the part of the Senescence Associated Secretory Phenotype (SASP). SCs are implicated in the pathogenesis of multiple age-related diseases, including Idiopathic Pulmonary Fibrosis. IL-6 is the target of Tosilizumab and is now tested in clinical trials against COVID-19 [5].Since COVID-19 mortality is reported to be associated with cytokine storm and fibrosis (IPF), it would be interesting to see if senolytic drugs (including Hsp90 inhibitors with senolytic properties [38]) may provide benefits beyond reducing the virus replication rate (most probably by stimulating apoptosis).

In conclusion, we would like to assert that the presented work does not include any experimental validation of the predicted host-targeting antivirals. Nevertheless, the over-representation of the known with broad antiviral activities among our top-scoring compounds list is very encouraging. We believe that the calculations presented here highlight the capabilities of modern AI/ML pipelines for tackling the most challenging medical problems almost in real-time. The repurposing of existing drugs from this work could lead to meaningful solutions to the COVID-2019 pandemic and other more mundane diseases further down the road.

We encourage academic and industrial collaborations to validate the results of this research and further develop the most successful compounds against COVID-19. The regulatory and legal status of several identified drug candidates allow starting immediate clinical trials.

CONFLICT OF INTERESTS

KA, OB and POF are employees of Gero. PF is a shareholder of Gero. The company develops holds I.P. covering use of the drugs mentioned in this draft against a broad range of viral diseases

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