Viribus Unitis: Drug Combinations as a Treatment against COVID-19

Eugene N. Muratov[a,*] and Alexey Zakharov[b]

[a] Laboratory for Molecular Modeling, Division of Chemical Biology and Medicinal Chemistry, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC, 27599, USA.

[b] National Center for Advancing Translational Sciences (NCATS), 9800 Medical Center Drive, Rockville, Maryland 20850, United States

Corresponding Authors

* Address for correspondence: 301 Beard Hall, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC, 27599, USA; Telephone: (919) 966-3459; FAX: (919) 966-0204; E-mail: murik@email.unc.edu

Abstract

The opportunities that may be provided by synergistic antiviral action of drugs for battling SARS-CoV2 are currently underestimated. Modern AI technologies realized as text, data, and knowledge mining and analytics tools provide the researchers with unprecedented opportunities for “smart” design of drug combinations with synergistic antiviral activities. The goal of this study is to emphasize the combination therapy as a potential treatment against COVID-19 and to utilize the combination of modern machine learning and AI technologies with our expertise to select the most promising drug combinations with further experimental validation. To the best of our knowledge, we are the first who applied the combination of data, text, and knowledge mining and modeling towards identification of drug combinations against SARS-CoV2. As a result, we have identified 281 combinations of 38 drugs that may serve as potential treatment for COVID-19. Among them, we selected twenty binary combinations that were submitted to experimental testing and twenty treble drug combinations that will be submitted for experimental testing as soon as necessary infrastructure will be developed. We hope that this study will promote the combination therapy as an efficient treatment for COVID-19.

Introduction

As of today, there are more than two and a half thousand publications in both peer-reviewed scientific journals and arXives devoted to COVID-19.[1] The number of clinical trials worldwide is already close to 500 and will exceed this number very soon.[1] However, to the best of our knowledge, almost none of them consider the application of combination therapy against the virus, except the Lopinavir-Ritonavir pair that is known as Kaletra (there are also other brand names) and used for the treatment and prevention of HIV/AIDS and combinations of Chloroquine/Hydroxychloroquine and/or antivirals like Kaletra, Remdesivir, etc., with antibiotics to battle the COVID-19 both in the hospitals and clinical trials (in lesser degree) worldwide.[2] Meanwhile, the Kaletra as well as some other successful examples of combination therapy inspired us to think in this direction. Moreover, rapid development of Artificial Intelligence (AI) technologies[3] and text, data, and knowledge mining and analytics tools supported by initiatives like Biomedical Data Translator[4–6] provide the researchers with unprecedented opportunities for targeted design of drug combinations with desired synergistic effects. Certainly, such technologies may led you astray and should not be used blindly. For instance, the authors of recent study[7] made correct statement about benefits of combining antiviral and anti-inflammatory treatments. However, as an outcome of their analysis, they suggested baricitinib, an anti-inflammatory drug that can make you more likely to get infections or may worsen any current infections and the following statement at package insert: “You should not take OLUMIANT (Baricitinib) if you have any kind of infection”.[8] Therefore, all the hypotheses generated using AI tools should be critically analyzed and triaged.

Such AI technologies as, machine learning, text mining and knowledge mining, were already applied in computer-aided drug design, mostly for pure (single) compounds.[9] However,

because of extreme urgency in finding a treatment against COVID-19, we gave the priority to drug repurposing, because it is faster to repurpose existing drug to treat COVID-19 rather than to develop it de novo. We decided to focus on drug combinations not only because of the reasons described above but also because most of antivirals and other drugs were already tried in the hospitals in China, Italy, Russia, US, and other countries, but no successful treatment was found. To the best of our knowledge, we are first who applied the combination of data, text, and knowledge mining and modeling towards searching of combinations of existing drugs against SARS-CoV2. The goal of this study is to emphasize the combination therapy as a potential treatment against COVID-19 and to utilize the combination of modern machine learning and AI technologies with our expertise to select the most promising drug combinations with further experimental validation. We do hope that this study will provide useful insights as to how to utilize the combination therapy both in general and specifically, considering the combinations recommended in this paper as potential treatments for COVID-19.

Materials and Methods

Chemotext is a publicly-available Webserver that mines the published literature in PubMed in the form of Medical Subject Headings (MeSH) terms.[10] Chemotext was used for elucidation of the relationships between drugs and their combinations, targets, and SARS-CoV2 and COVID-19 from the papers annotated Medline/PubMed database. Mining this database affords rapid identification of all published studies that confirm connections between vertices of this triangle or enable new inferences of such connections. Chemotext mines the entire compendium of published literature in PubMed annotated by Medline Subject Heading (MeSH) terms. We use

Chemotext to identify all known drug-target-disease relationships and infer missing links between vertices of the DTD triangle.

ROBOKOP[11] is a data-mining tool developed within Biomedical Data Translator Initiative[4–6] to efficiently query, store, rank and explore sub-graphs of a complex knowledge graph (KG) for hypothesis generation and scoring. ROBOKOP provides a unique query mechanism based on meta-graphs and a novel ranking algorithm. The ROBOKOP software stack includes a web server, application programming interface (API) and a web-based UI that together enable users to create queries in an easy-to-use format, store the results of those queries, rank the relevance of the queries and graphically explore the results. We have used ROBOKOP in a similar fashion as Chemotext; The combination of these two tools is synergistic – Chemotext could help the user to find and impute the connections between drugs, targets and diseases and ROBOKOP could help to explore and score them. Moreover, ROBOKOP, because of larger variety of implemented knowledge sources, is more suitable for working with drug combinations than Chemotext.

QSAR models developed by us earlier were used for selection of drugs[12] that could be repurposed as combinations and exclusion of potential drug-drug interactions.[13] All the models were developed according to the best practices of QSAR modeling[14,15] with a special attention paid for data curation[16–18] and rigorous external validation.[19] Mixture-specific descriptors and validation techniques[20] specially developed for modeling of drug combinations were utilized for modeling of drug-drug interactions.[13]

Results and Discussion

We focused our study towards combination therapy against COVID-19 powered by AI-driven selection of drug combinations. To the best of our knowledge, we are first who applied the

combination of text mining (Chemotext), knowledge mining (ROBOKOP knowledge graphs) and machine learning (QSAR) towards searching of combinations of existing drugs against SARS-CoV2. We achieved this by the following study design: First, we applied Chemotext and ROBOKOP to identify the drug-target-disease[21] relations and the papers describing them. In addition to this, we have screened DrugBank[22] and NPC[23] collections with QSAR models for SARS MPro inhibition developed by us earlier and identified the compounds potentially active against CoV-SARS-2. These two lists had certain overlap, so the duplicated records were removed. We also analyzed the PubMed hits from Chemotext, e.g., study and found certain overlap between our hit compounds and the compounds suggested as potential treatment by others, e.g., in study Li and DeClercq.[24] This resulted in the list of ca. 70 drug candidates for repurposing in combination therapy against COVID-19. Then we applied Chemotext and ROBOKOP to evaluate and score the potential combinations of drugs identified at previous stage as a treatment to coronavirus. Here we considered the mechanism of action (if known), targets that the drugs hit, potential synergy between them as well as undesired side effects. We prioritized the combinations of drugs with different mechanisms of action, hitting virus in the different stages of its lifecyle (preferably) or at least the different viral targets. This will increase the probability of synergy between drugs.[25,26] Then we applied the cheminformatics models developed by us earlier to exclude the undesired Drug-Drug Interactions.[13] After this, we applied our joint expertise in cheminformatics, data science, and computational antiviral research to carefully triage obtained results to exclude the artifacts and compounds undesired or contraindicated in case of pneumonia (e.g., paclitaxel, bleomycin, etc.), or viral infection (e.g., baricitinib).

Overall, we identified 281 binary combinations of 37 drugs that may be useful against COVID-19 (See Figure 1 and Supplementary Table 1 as bigger and editable version). Please interpret the Figure 1 as follows: It has been developed as a matrix of all possible binary combinations of 38 drugs. This will give us 703 combinations in total because the matrix is symmetric – a combination Drug X-Drug Y is the same thing as a combination Drug Y-Drug X. Drugs a grouped by potential mechanism of action, source, etc. We tried to mix only the drugs that may possess a synergistic antiviral effect. This resulted in 281 combinations highlighted by red. Then, we would like to specify that we were targeting different combinations for different types of assays. For phenotypic assays we considered the combinations that may result in a synergistic antiviral effect, whilst for *in vivo* assays we added Primaquine and Atovaquone – two drugs (highlighted by grey color) that may work for the whole organism. Thus, we have 261 binary combinations for phenotypic assays and these 261 plus 20 more combinations that may work *in vivo*. The combination of Lopinavir and Ritonavir is highlighted by orange because it is already known as anti-HIV medication Kaletra.[2]

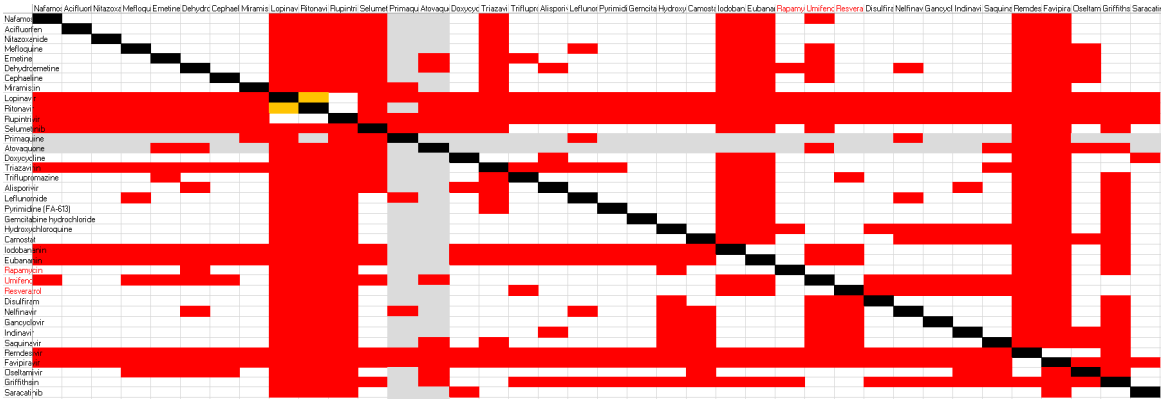

Figure 1. *Matrix of all possible binary combinations of 38 drugs identified by our analysis. Combinations that we consider as promising are highlighted by red. Combinations of*

Primaquine and Atovaquone are not recommended for phenotypic assays (grey color). Kaletra, known anti-HIV medication, is a combination of Lopinavir and Ritonavir (orange color).

We do hope that the combinations depicted in Figure 1 will be useful for researches considering the options of combination therapy based on their experience. In turn, to move further, we have prioritized twenty binary combinations to be tested in phenotypic assays developed in NCATS. List of these combinations could be found in Table 1.

Table 1: Binary drug combinations selected for experimental testing.

Drug 1	Drug 2
Emetine	Favipiravir
Dehydroemetine	Ritonavir*
Lopinavir*	Hydroxychloroquine
Ritonavir*	Alisporivir
Rupintrivir	Camostat
Triazavirin	Saquinavir
Hydroxychloroquine	Favipiravir
Camostat	Remdesivir
Indinavir	Remdesivir
Favipiravir	Oseltamivir
Emetine	Lopinavir*
Dehydroemetine	Alisporivir
Lopinavir*	Umifenovir
Ritonavir*	Triazavirin
Alisporivir	Indinavir
Hydroxychloroquine	Remdesivir
Camostat	Favipiravir
Camostat	Oseltamivir
Saquinavir	Favipiravir
Remdesivir	Griffithsin

Note: * Kaletra (Lopinavir/Ritonavir combination) may be used in this case.

To go further, we have also identified twenty promising combinations of three (in some cases four, if to count Kaletra as two drugs) drugs for testing in vivo (see Table 2). These drug combinations will be tested as soon as necessary infrastructure for testing treble combinations

will be developed. Both binary and treble combinations are subjects of availability – the priority is given to combinations of drugs that are physically available in our collection.

Table 2: Treble drug combinations selected for future experimental testing.

Drug 1	Drug 2	Drug 3
Emetine	Favipiravir	Camostat
Dehydroemetine	Ritonavir*	Primaquine
Lopinavir*	Hydroxychloroquine	Atovaquone
Ritonavir*	Alisporivir	Umifenovir
Rupintrivir	Camostat	Griffithsin
Triazavirin	Saquinavir	Remdesivir
Hydroxychloroquine	Favipiravir	Ritonavir*
Camostat	Remdesivir	Ritonavir*
Indinavir	Remdesivir	Rupintrivir
Favipiravir	Oseltamivir	Primaquine
Emetine	Lopinavir*	Atovaquone
Dehydroemetine	Alisporivir	Favipiravir
Lopinavir*	Umifenovir	Doxycycline
Ritonavir*	Triazavirin	Remdesivir
Alisporivir	Indinavir	Griffithsin
Hydroxychloroquine	Remdesivir	Saquinavir
Camostat	Favipiravir	Rupintrivir
Camostat	Oseltamivir	Ritonavir*
Saquinavir	Favipiravir	Ritonavir*
Remdesivir	Griffithsin	Primaquine

Note: * Kaletra (Lopinavir/Ritonavir combination) may be used in this case

Conclusions

The opportunities that may be provided by synergistic antiviral action of drugs for battling SARS-CoV2 are currently underestimated. The history of anti-HIV and anticancer research inspired us to suggest combination therapy as a potential solution for COVID-19. Moreover, modern AI technologies realized as text, data, and knowledge mining and analytics tools provide the researchers with unprecedented opportunities for “smart” design of drug combinations with synergistic antiviral activities. To the best of our knowledge, we are the first

who applied the combination of data, text, and knowledge mining and modeling towards identification of drug combinations against SARS-CoV2. Using these AI tools and our expertise, we identified 281 combinations of 38 drugs that may serve as potential treatment for COVID-19. Among them, we have identified twenty binary combinations that were submitted to experimental testing and twenty treble drug combinations that will be submitted for experimental testing as soon as necessary infrastructure will be developed. We hope that both the ideas and data presented in this study will stimulate the scientific community to consider combination therapy as an efficient treatment for COVID-19.

Acknowledgments

In general, we do not support the idea of publishing computational study with no experimental validation (if this is ever possible). We initiated this study in the end of February and originally wanted to wait for the results of experiments before publishing the paper. However, given the emerging situation with COVID-19, increasing number of people getting infected daily, and absence of successful treatment, we decided to share our ideas with scientific community as soon as possible. We would like to thank the ChemRxive for the opportunity of publishing our viewpoint instantaneously and apologize for any cases of poor language in the paper caused by the haste in writing. We are going to extend, update, and improve the text of this paper with the ultimate goal of including the results of ongoing experiments with binary combinations and future experiments with treble combinations.

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Conflicts of interest

The authors declare no conflicts of interest.

Supplementary information

Supplementary information includes the Excel file with all the drug combinations suggested in this work.

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