Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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editorial

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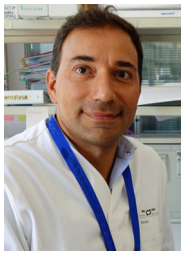

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Boosting the arsenal against COVID-19 through computational drug repurposing

The coronavirus disease 2019 (COVID-19) world health emergency is calling scientists for unprecedented, huge investigation efforts to urgently answer key questions: what is the natural origin of the SARS-CoV-2 virus? What molecular changes account for its aggressiveness and mortality in humans? What immunological responses are specifically activated and how long will acquired immunity last in recovered people? Is there a most susceptible, exposed population based on the genetic background? Are patients treated with angiotensin-converting enzyme (ACE) inhibitors at increased risk for COVID-19 infection? On top of these, what are the best therapeutic options we have ready to help cure COVID-19 patients? With ~15% of patients suffering from severe disease, hospitals being overwhelmed worldwide and a global mortality rate of 5.7% [1], it goes without saying that new efficacious treatments are immediately needed.

New interventional clinical trials for COVID-19 treatment involve the use of an antiviral drug previously used to treat the Ebola virus known as remdesivir or the combination of two antivirals: ritonavir + lopinavir, previously approved to treat the HIV infection. Additional active clinical trials involve the use of drugs approved for different therapeutic indications. This is the case, for example, for: (i) the FDA-approved antimalarial drugs chloroquine and hydroxychloroquine, owing to their ability to interfere with basic cellular pathogenetic mechanisms; and (ii) monoclonal antibodies against interleukin-6 receptor (anti-IL-6R) which might be helpful in reducing abnormal inflammatory response upon cytokine storm, thus improving organ functions in COVID-19 patients. This 'recycling' strategy based on the re-use of approved drugs is commonly referred to as drug repurposing and is largely successful, as demonstrated by examples of repurposing treatments in cancer and other human diseases [2]. Drug repurposing is a modern therapeutic strategy that substantially reduces the risks of drug development and costs. In this emergency, it shortens the time gap between the identification of a potentially useful drug and the treatment of the patient owing to the availability of large amounts of safety, tolerability, pharmacokinetic, pharmacodynamic and clinical data on the existing drug. Indeed, the use of a drug for a different therapeutic indication – also referred to as off-label use – can take advantage of Phase I/II trials for defining the potential maximum tolerated dose and predicting potential side effects or supportive therapies. Thus, in the presence of preliminary clinical efficacy observations or a strong pharmacological rationale, it is possible to immediately test existing drugs for novel therapeutic indication in human patients.

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How can efficacious drug repurposing be reached? Drug repurposing is often the result of serendipity, it might also result from an experimental drug screening or the identification of target similarities among different diseases, or the involvement of common pathogenetic mechanisms among different diseases, similarly to the scientific bases that motivated the above-described repurposing trials ongoing worldwide to cure COVID-19.

Together with the current approaches, there are multiple, incisive investigation steps that can be immediately undertaken in the context of drug repurposing approaches to boost treatment strategies against COVID-19, thanks to the availability of omics data and the implementation of biocomputational drug repurposing approaches. *In silico* drug repurposing is a hypothesis-driven approach that takes advantage of the use of big data to identify drugs to treat disease or disease-related symptoms. The process is based on the collection and coherent integration of disease data generated through omics studies, followed by their combination with pharmacological data. The ultimate goal is to integrate a disease network with a drug's mode of action network [3]. *In silico* drug repurposing has the unique advantage to transform systems biology data of disease phenotypes and targets into a prediction of druggable targets and, ideally, to provide an FDA-approved compound with potential modulatory and/or inhibitory functions for an immediate preclinical or clinical test. Importantly, data relevant to biological clinical features, pharmacological responses, drug targets and even drug off-targets can provide unexpected insights for understanding COVID-19 pathology, symptoms and, possibly, identifying treatments. With these computational tools in hands, theoretically – and with the obvious caution based on the predictive nature of this type of study – it could be possible to generate a hypothesis-driven, computer-aided drug repurposing aimed to: (i) reduce virus infection and its replication; (ii) contrast the infection's adverse symptoms; (iii) understand positive or negative interactions among treatments; (iv) identify mechanisms of the viral infection's susceptibility; and (v) predict potential side effects of treatments against antiviral immune response, a fact that could eventually result in a worse clinical outcome. The possibility to perform drug repurposing for each of the above-mentioned objectives is uniquely limited by the availability of data to generate computational modeling of the diseases relevant to each investigation direction. As a first step for *in silico* drug repurposing against SARS-CoV-2, a computational modeling of viral pathogenesis and disease-related symptoms is necessary. Thanks to the release of the SARS-CoV-2 genome sequence [4] important biological information is already emerging. Phylogenetic studies have suggested the natural origin of SARS-CoV-2 and the highest nucleotide sequence identity (79.7%) with SARS-CoV among the six other known pathogenic HCoVs, revealing the closest evolutionary relationship between SARS-CoV-2 and SARS-CoV [4]. Similarly to SARS-CoV, SARS-CoV-2 also uses the ACE2 protein as a virus receptor [4] and can generate severe lung-associated diseases [5]. These available data can be immediately used in biocomputational drug repurposing studies, especially related to the mechanisms of host–virus interaction and virus replication. Pending additional omics data on COVID-19 pathogenesis, disease modeling can also be generated using molecular data and studies that are already available on SARS-CoV, because they are evolutionarily related viruses. However, the different mortality rates and the divergent molecular evolution clearly show that COVID-19 is a unique, peculiar disease. This key aspect claims for caution about the interpretations of *in silico* drug-repurposing results obtained with the use of SARS-CoV-based studies.

From a methodological point of view, many computational tools can be implemented based on different data types and methodologies. Data types include drug chemical structures, physicochemical properties, known molecular targets and omics data types, such as drug-induced transcriptional responses or metabolic simulations. Methodologies range from classical statistical methods to modern machine learning techniques. Computational drug repurposing tools can be designed to directly attempt drug-repurposing predictions or to help in the process. For example, tools based on drug–disease association networks can immediately suggest novel clinical applications for similar disease phenotypes, whereas chemical structure similarities can be exploited to prioritize alternatives to existing compounds [3]. By contrast, other computational tools can support the drug repurposing process providing biological insights into drug modes of action or discovering unknown molecular targets of existing drugs. Gene expression data can be used to characterize the effects of drug treatments. For this reason, a systematic collection of drug-induced whole-genome expression profiles has been produced in the past through the Connectivity Map (CMap) project, and its latest release within the Library of Integrated Network-Based Cellular Signatures (LINCS) project. A network-based analytical tool is needed to explore drug neighborhoods based on the similarity between induced transcriptional responses. Additional powerful computational tools such as PREDICT, SDTNBI, ChemMapper, SIDER and DrugBank will well-fulfil and implement hypothesis-driven drug repurposing [3].

The number of studies on *in silico* drug repurposing against COVID-19 is growing rapidly – among others, worth citing is an interesting approach generating a systems-pharmacology-based network medicine platform that identified the interplay between the HCoV–host interactome and drug targets in the human protein–protein interaction network and that has identified potential drug repurposing treatments against such interactions [6]. Moreover, a virtual screening approach was used to investigate the FDA-approved LOPAC library and to predict drugs able to minimize the interaction between the viral spike (S)-protein and ACE2 host cell receptor [7]; in an additional report, a novel deep learning platform was used to identify top potential inhibitors of the SARS-CoV-2 main protease by screening 1.3 billion compounds [8]. These types of reports probably represent just a tip of the iceberg of ongoing drug repurposing investigations, the results of which will appear in the coming weeks. Indeed, the computer-aided battle against the virus has just started and it is also engaging the most powerful technological platforms to satisfy demands for massive amounts of computational capacity. To this aim, the recently launched COVID-19 High-Performance Computing Consortium in the USA will aggregate computing capabilities from the world's most powerful and advanced computers to help COVID-19 researchers execute complex computational research programs to help fight the virus [9].

What other directions should researchers on *in silico* drug repurposing boost? Besides identifying novel, hypothesis-driven drugs to treat COVID-19 patients, the computational approaches could also help a further understanding of currently used treatments. For instance, an antiviral inflammatory response network would help to better decipher key mechanisms involved in the response to anti-IL-6R, by taking

advantage of large studies on inflammatory cytokines and available biomarkers. Similarly, the inspection of the drug–drug network and side effects could predict whether a specific drug under or proposed for investigation would exacerbate any of the severe lung disease symptoms. For instance, it would be helpful to predict whether chloroquine, potentially reducing infection efficacy, could, in turn, affect the antiviral immune response or target pathways crucially implicated in chronic diseases of elderly patients. If this is the case, it could draw the attention on possible chloroquine off-targets and side effects, in certain patients, that would limit treatment benefits on patient survival. Finally, in such a pandemic scenario in which medications against COVID-19 become urgently needed in mass quantities and could face a shortage, a computational drug repurposing approach might assist to quickly identify similar drugs with an analogous mode of action or to design alternative synthetic plans of a drug to overcome patented routes and to identify inexpensive and diverse starting materials, once shortages of the commonly used substrates could occur [10].

Although timing for an efficacious vaccine remains uncertain, a vibrant multidisciplinary research operation is already at work to provide immediate and concrete therapeutic options based on drug repurposing. We hope to further inspire targeted, computer-aided drug repurposing studies to boost and tailor effective therapies against the COVID-19 pandemic disease.

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