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Editorial

Computational Drug Screening in COVID-19 Drug Repurposing Research: Encouraging Findings and Limitations

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The ongoing pandemic caused by the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a devastating effect on global public health and economy.[1] At the beginning of the outbreak, in early 2020, our lack of knowledge regarding even basic aspects of the biology of this virus and its effects on the human body has kickstarted a race for clinicians, epidemiologists, immunologists, pharmacologists, regulatory bodies and the pharmaceutical industry in order to deliver accurate diagnostic tests, safe vaccines and effective therapeutic strategies in a timely manner. This push has led to impressive biomedical accomplishments in a very short period of time.[1,2] Amongst the strategies considered in order to identify effective therapeutic compounds against the coronavirus disease 2019 (COVID-19), that of drug repurposing has been at the top of the list.[3,4] The wealth of information generated so far by the undertaking of COVID-19-focused drug repurposing research is impressive.[3] This type of drug development research has been systematically conducted on three levels: (i) that of *in vitro* protein-binding experimentation, (ii) that of computational drug screening, and (iii) that of clinical trials.[4] To date, drugs that have been considered through the drug repositioning pipeline as promising for use against COVID-19 act either through virus-related targets or through host-related pathways.[3]

In this journal, Tang *et al*.[5] of the University of California, San Diego have recently proposed a pharmacophore model based on a recent structural characterization of the SARS-CoV-2 nonstructural protein 15 (Nsp15) uridine-specific endoribonuclease.[6] The Nsp15 is a critical enzyme for the evasion of the host immune response to SARS-CoV-2 and, thus, is a very promising drug target for the treatment of COVID-19.[7] By utilizing the structural information regarding potential functional centres of Nsp15 that form part of the enzyme's inhibitor-binding pocket, Tang *et al*.[5] delivered a pharmacophore search that identified 803 matches after data-mining a conformational database of drugs that have already been approved for clinical use by the US Food and Drug Administration (FDA). After filtering these compounds based on their chemical structure and potential chemical interactions at the best docking pose, 170 of them were selected, clustered and submitted to *in silico* docking, while the three compounds (namely, cefmenoxime, cefotiam and ceforanide) demonstrating the highest docking energies were also further analysed in order to assess the stability of their interactions with Nsp15.[5]

This wonderfully executed computational study (Fig. 1) has identified 170 compounds that can act as Nsp15 inhibitors and include–but are not limited to–pyrimidine analogues (that interestingly correspond to established viral inhibitors), cephalosporin antibiotics, diuretics,

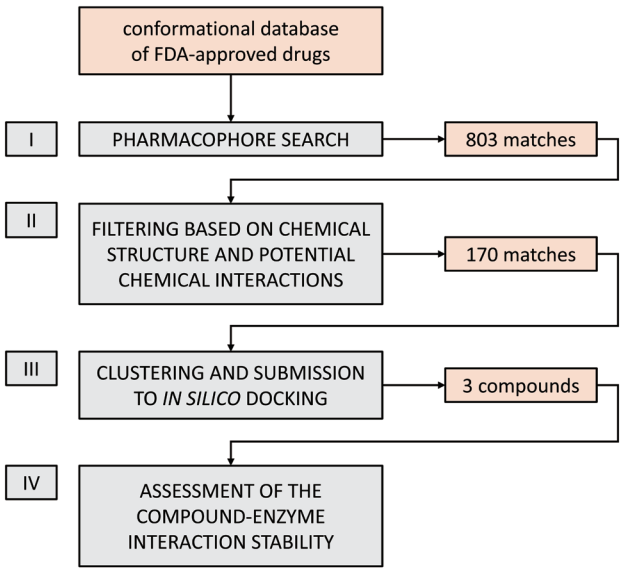

Fig. 1. Schematic summary of the methodological process followed by Tang *et al*.[5] in order to identify potential inhibitors of the SARS-CoV-2 Nsp15 enzyme amongst FDA-approved drugs. The computational process followed can be organised into four phases (I-IV). All hits (matches) identified after the conclusion of phase II are particularly interesting. FDA, US Food and Drug Administration; Nsp15, nonstructural protein 15; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Abbreviations: COVID-19, coronavirus disease 2019; FDA, US Food and Drug Administration; Nsp15, nonstructural protein 15; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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angiotensin-converting enzyme inhibitors, carbapenem antibiotics, beta-blockers, nonsteroidal anti-inflammatory drugs, tyrosine-kinase inhibitors, fluoroquinolones, saccharide-like compounds as well as prostaglandin-like compounds. Although the inhibitory effect of these compounds on Nsp15 requires confirmation through the undertaking of biochemical and cellular assays, Tang *et al*.[5] describe with clarity the necessary next steps in their drug repurposing approach to the targeting of SARS-CoV-2. However, this study is only a tessera in the mosaic of the global COVID-19 drug repurposing effort. Studies have also focused on other parts of the SARS-CoV-2 biology (e.g., the endocytic pathways available for the entry of the virus in the human lung epithelium),[8] with a hallmark study in the field having identified 332 high-confidence protein-protein interactions between the virus and human proteins.[9] In fact, the latter study was published only a few months after the outbreak of the COVID-19 pandemic, and it also managed to identify 66 druggable human proteins/host factors that could potentially be targeted by a total of 69 compounds: 29 already approved by FDA, 12 in the clinical trial stage, and 28 in the preclinical stage.[9]

Drug repurposing strategies offer several advantages, all of which are linked to our understanding of the safety of the candidate compounds and the consequent requirement of fewer steps in order to bring forward well-characterized compounds into a clinical trial or FDA-approved compounds into a different clinical use. In most cases, as the data regarding the preclinical screening, toxicity, optimization, pharmacokinetics, formulation and manufacturing of these compounds are readily available, several critical stages of the drug development pipeline can be shortened or even bypassed.[10] This is, of course, not only a time-saving advantage, but also a cost-effective one. However, reality usually serves generous portions of disappointment as: (i) rarely do repurposed drugs establish therapeutic dosages against a new condition within the already approved therapeutic windows, (ii) the repurposed drugs' physicochemical properties (e.g., permeability) and biodistribution might render their intended applicability impossible, while (iii) the drug repurposing approval processes and intellectual property protection frameworks are still underregulated and complex, respectively.[10] The unprecedented global health challenge imposed to us by the COVID-19 pandemic might offer a unique opportunity for the regulating authorities, the scientific societies and the industry to devise and enforce a more encouraging framework for the undertaking of drug repurposing research.

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Conflict of interest

Dr Apostolos Zarros has been an editorial board member of the *Journal of Exploratory Research in Pharmacology* since August 2021. The author has no other conflicts of interest related to this publication.

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