Shotgun drug repurposing biotechnology to tackle epidemics and pandemics

COVID-19 is the disease caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) that originated from Wuhan, China in late 2019. It was classified as a global pandemic in March, 2020 by the World Health Organization (WHO). Finding effective, affordable treatments to this pandemic is of utmost importance.

Biotechnology platforms for the rapid high-throughput identification and prioritization of effective therapeutic candidates for multiple indications have the potential to significantly strengthen our response to pathogenic outbreaks and save countless lives [1–4]. In response to the current COVID-19 outbreak, numerous technologies, including those based on high throughput protein-protein complex pulldowns and network biology, have been applied to
quickly screen and identify drug repurposing candidates that may be rapidly deployed to treat infected individuals without the need for full regulatory approval [1,2,5,6].

We developed the Computational Analysis of Novel Drug Repurposing Opportunities (CANDO) platform for shotgun multitarget drug discovery, repurposing, and design [1,2,7], funded in part by a 2010 NIH Director’s Pioneer Award and previously described in Drug Discovery Today in 2014 [1], for precisely this type of pandemic scenario. The platform screens and ranks every existing human use drug for every disease/indication through large scale modelling and analysis of interactions between comprehensive libraries of drugs/compounds and protein structures. The interaction may be determined by any screening or docking method but the built-in ones using a fast bioinformatic docking protocol and the hierarchical fragment-based docking with dynamics protocol CANDOCK [8] are prioritized. The drug-proteome signature comparison and ranking approach used by the CANDO platform yields benchmarking accuracies of 20–40% for ~1500 indications relative to random control accuracies of 2–15%. Across twelve prospective in vitro validation studies, 58/163 (35%) top ranking predictions made using the CANDO platform had comparable or better activity relative to existing drugs across ten indications, and represent potential novel repurposed therapies for indications such as dengue, dental caries, diabetes, herpes, lupus, malaria, and tuberculosis [1,2].

We used the CANDO platform to generate putative drug repurposing candidates against SARS-CoV-2 (Fig. 1). The platform ranks
a number of clinical trial candidates listed in Table 1 of Harrison [9] in the top 1% of predictions and provides relevant target and off-target interaction information for them. We are currently in the process of undertaking in vitro validation of top ranked candidates as well as using EHR data to corroborate or negate predictions made by the platform. This pandemic highlights the importance of developing such robust shotgun repurposing platforms that not only make drug discovery more efficient by systematically evaluating multiple uses of a human ingestible drug but may also be rapidly deployed every time a new disease arises.

Three coronavirus outbreaks in two decades, including the current pandemic, indicates a necessity of preparation for the next one that may be more deadly and costly. The CANDO drug repurposing platform was originally funded and implemented for predicting drug leads for epidemics and pandemics. Sustained funding for shotgun drug repurposing biotechnology that have been benchmarked extensively to identify potential drugs for all diseases, such as CANDO, will prepare us for this eventuality while also providing us with an array of therapeutic solutions to help improve human health and quality of life.

**Author contributions**

WM, ZF, and RS conceived and implemented all data analysis. WM, ZF, and RS wrote the manuscript. ZF generated the docking images. TM directed the prodrug analysis and provided expert opinion on antiviral drugs. GC substantially edited the manuscript and conceived ideas for data analysis.

**Conflicts of interest**

The authors declare no conflicts of interest.

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