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Accelerating Drug Development through Repurposed FDA-Approved Drugs for COVID-19: Speed Is Important, Not Haste

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A life-threatening, emerging respiratory disease, called coronavirus disease 2019 (COVID-19), originated in the city of Wuhan in China's Hubei province in December 2019 and has been classified as an international pandemic by the World Health Organization. As of 30 April 2020, more than 3,249,022 COVID-19 cases caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) have been recorded worldwide, and more than 230,804 people have been reported dead. Upon this outbreak, global collaborations between the public, private, and academic sectors have been coordinated, and as a result of these extraordinary endeavors, SARS-CoV-2 has been identified and characterized (1, 2).

Work continues across the globe to further characterize this virus and the disease it potentiates. For instance, the crystal structure of the SARS-CoV-2 nucleocapsid protein (N) has been determined to be similar to that of the previously described coronavirus N proteins, albeit with distinct surface electrostatic potential characteristics (3). Additionally, emerging novel clinical and basic research data via molecular modeling (MD), docking, and MD simulation-based approaches can be the starting point for generating hypotheses, as it was for Jin et al. in their preprint analysis of the M^{pro} SARS-CoV-2 enzyme (4). Studies such as that one can effectively guide further targeted bench work to accelerate the development of specific drugs to treat SARS-CoV-2.

However, these specifically targeted antiviral therapies will take several years to develop and evaluate; therefore, to date, quarantine and transmission-blocking measures are the only operational treatments for both SARS-CoV strains. Social interventions such as these are efficacious at the population level, but they are not socially or economically sustainable in the long term, and they do not help those who contract the disease (5). In the short term, a range of existing FDA-approved drugs potentially could be repurposed to treat COVID-19 relatively quickly. Recent publications have drawn attention to the possible benefit of antimalarial drugs atovaquone (6), chloroquine (7, 8), and hydroxychloroquine (9, 10); the angiotensin-converting enzyme inhibitor moexipril (6); the cholesterol-lowering rosuvastatin (11); the chemotherapy drugs daunorubicin and mitoxantrone (6); the painkillers baricitinib (12), thalidomide (ClinicalTrials.gov registration no. NCT04273581), metamizole, and nafamostat mesylate (13); the antihistamine bepotastine; the antidiabetic agent metformin; the antischizophrenia drug haloperidol; the interleukin-6 (IL-6) inhibitor sarilumab; and the IL-6 receptor blocker tocilizumab (ClinicalTrials.gov registration no. NCT04322773). Several antiviral drugs are also being tested, including antrafenine (14), darunavir (6, 15), elbasvir (14), favipiravir (15), ledipasvir (14), lopinavir/ritonavir (15), nelfinavir (6), paritaprevir (14), remdesivir (8, 15, 16), ribavirin (17), telbivudine saquinavir (6), umifenovir (15), and

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velpatasvir (14). Vitamins B_{12}, D, and nicotinamide (ClinicalTrials.gov registration no. NCT04334005), as well as traditional Chinese medicine (18), are also under study. While results have yet to be published, it has been reported that Gilead's clinical trial of remdesivir is showing 31% improvement in patient recovery time over placebo (19), highlighting the potential of this approach.

We consider this broad list of agents to have two distinct subgroups: (i) pathogen directed, i.e., providing direct antiviral activity alone or in combination with other medications, and (ii) host directed, i.e., those that enhance the protective antiviral immune response by interfering with host cell factors or dampening the inflammatory response, preventing lung damage (20, 21). Identifying preclinical endpoints for progression into clinical trials is warranted for a greater understanding of the impact of treatment with repurposed FDA-approved drugs. This process will be accelerated by delivering the data just in time for optimizing key go/no-go decision points for investigating the potential efficacy, combination therapy (10), pharmacokinetics (22), pharmacodynamics, or toxicity of the treatments in cell culture as well as in animal models (23–25). It will be important to, in parallel, elucidate the exact molecular and immunological mechanisms of action of these drugs against SARS-Cov-2.

Reports by Li et al. (26) and Martinez (27) offer important and timely insights relevant to potential therapeutic approaches and a summary of therapeutic compounds against SARS-CoV-2, respectively. Many of these drugs are safe, inexpensive, and readily available and have been previously explored against infectious pathogens. Continuing to screen and test drug libraries for efficacy against SARS-CoV-2 remains an essential endeavor until a universal treatment or vaccine is available. Most important will be the rapid and clear communication of findings so that economic, social, political, and clinical decisions will be based on scientific merit and not desperation: speed but not haste.

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