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Expert Opinion on Drug Discovery

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iedc20

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To cite this article: Carolina L. Bellera , Manuel Llanos , Melisa E. Gantner , Santiago Rodriguez , Luciana Gavernet , Marcelo Comini & Alan Talevi (2020): Can drug repurposing strategies be the solution to the COVID-19 crisis?, Expert Opinion on Drug Discovery, DOI: 10.1080/17460441.2021.1863943

To link to this article: https://doi.org/10.1080/17460441.2021.1863943

Accepted author version posted online: 19 Dec 2020.

Publisher: Taylor & Francis & Informa UK Limited, trading as Taylor & Francis Group

Journal: *Expert Opinion on Drug Discovery*

DOI: 10.1080/17460441.2021.1863943

Can drug repurposing strategies be the solution to the COVID-19 crisis?

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Keywords: COVID-19, COVID, SARS-CoV-2, Drug repurposing, Drug repositioning, Virtual screening, Collaborative drug discovery, Open source drug discovery, Open innovation, Drug discovery

Abstract:

Introduction: The COVID-19 pandemic resulted in disastrous human and economic costs, mainly due to the initial lack of specific treatments. Complementary to immunotherapies, drug repurposing is possibly the best option to arrive at COVID-19 treatments in the short-term.

Areas covered: Repurposing prospects undergoing clinical trials or with some level of evidence emerging from clinical studies are overviewed. The authors discuss some possible intellectual property and commercial barriers to drug repurposing, and strategies to facilitate equitable access to incoming therapeutic solutions, highlighting the importance of collaborative drug discovery models. Based on a critical analysis of the available literature about in silico screens against SARS-CoV-2 main protease, the authors illustrate how frequently overconfident conclusions are being drawn in COVID-19 related literature.

Expert opinion: Most of the current clinical trials on potential COVID-19 treatments are, in fact, drug repurposing examples. In October 2020, the FDA approved a repurposed antiviral, remdesivir, as the first treatment for COVID-19. Considering the high expectations invested in approaching therapeutic

solutions, the scientific community must be careful not to raise unrealistic expectations. Today more than ever, the conclusions drawn in scientific reports have to be fully supported by the level of evidence, avoiding any sort of unfounded speculation.

Article Highlights

- Drug repurposing has already provided treatments for COVID-19 in an expedited manner.
- A substantial fraction of ongoing COVID-19-related clinical trials focuses on drug repurposing.
- Current remdesivir pricing suggests the alleged cost- and time-efficiency of drug repurposing do not necessarily translate into equitable access.
- Several collaborative initiatives to fight COVID-19 have emerged globally; many of them have drug repurposing among their goals.
- It is possible that affordable COVID-19 medications will be available as new therapeutic options enter the market.

- Screening campaigns for COVID-19 treatments frequently arrived at biased conclusions, unsupported by available evidence.

1. Introduction

The outbreak of the novel coronavirus disease, COVID-19, caused by the new and highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), represents a pandemic threat to global health, with so far more than 65 million confirmed cases and 1.5 million deaths worldwide, resulting in unprecedented human and economic losses [1, 2].

The international political and scientific communities have responded energetically to provide new diagnostic and therapeutic solutions. Regulatory agencies worldwide have implemented fast-track procedures to expedite the development and marketing authorization of therapeutic solutions against COVID-19. For instance, the US Food and Drug Administration (FDA) has launched a special emergency program to expedite the development of coronavirus therapies, the Coronavirus Treatment Acceleration Program (CTAP) [3]. To date, the CTAP website lists above 560 drug development programs in the planning stage, more than 370 trials reviewed by the agency, five COVID-19 treatments authorized for emergency use (including, very recently, the anti-arthritis drug baricitinib) and one treatment (remdesivir) currently approved by FDA against COVID-19. Several international collaborative drug development initiatives have arisen to provide rapid responses to the current crisis, including crowdsourcing, open innovation and

public-private consortiums, among other models [4, 5]. An overview of these projects will be presented later in this article.

Among emerging treatments against COVID-19 we may mention small molecules and immunotherapies, including convalescent plasma transfusion, hyperimmune globulin and monoclonal antibodies [6-7]. Naturally, significant focus has been placed on therapeutic interventions that may provide a solution in the short or mid-term, such as vaccines. It is hence not surprising that the so far only approved drug therapy and most of the candidates that underwent or are undergoing clinical trials are repurposed drugs.

Drug repurposing consists in establishing new medical uses for existing drugs, which comprise approved, shelved, withdrawn and investigational drugs. The strategy has gained substantial momentum lately: approximately one out of three approvals in recent years correspond to drug repurposing, and repurposed therapeutics presently generate about 25% of the pharmaceutical industry revenue [8]. The approach has been progressively integrated into the life cycle management of pharmaceutical products and numerous small repurposing-focused companies have been created [8, 9].

Prior knowledge on the repurposed candidates, such as pharmacokinetic and manufacturing data, helps shorten the commonly long drug development timeline, and the cost of development is also diminished. The key advantage of drug repurposing is the proven safety of the repurposing candidates, which are much less likely to fail at early clinical trials and might even bypass Phase I trials if dose-compatibility with the original indication is met [10, 11].

World Health Organization's document on Draft Target Product Profiles (TPP) for treatment of COVID-19, emphasizes preferred profiles which are more likely to be immediately fulfilled by repurposed drugs [12], such as:

1. pregnant women and small children are included in the target population;
2. safety profile similar or superior to available therapeutic agents;
3. absence of adverse events that require monitoring;
4. capability to rapid scaling up at costs per dose that allow broad use.

It should be pointed out, however, that "proven safety" is not synonym for "adequate benefit-risk profile" [13], as the latter is influenced by the level of efficacy in relation to a particular indication, the existence (or not) of therapeutic alternatives, the severity of the targeted disease, and the target population (e.g. age, comorbidities).

All things considered, the relative advantages of drug repurposing (compared with *de novo* drug discovery) explain why so much ongoing COVID-19-related projects and clinical trials focus on repurposed matter: it is a natural choice to address urgent therapeutic needs for orphan diseases in a time- and cost-efficient manner. Here, we will overview such efforts, discriminating virus-focused treatments from host-based treatments. Next, as intellectual property and commercial matters frequently pose an obstacle to drug repurposing [14, 15], and considering that a definite solution to the current pandemic will necessarily require broad access to therapeutic solutions, we will summarize some of the *ad hoc* initiatives of

collaborative drug discovery. At last, having in mind the flood of original articles that focus on potential therapeutic solutions against COVID-19, we will use a literature survey from the field of computer-guided drug repurposing to highlight the renewed need of balanced, evidence-based scientific conclusions.

2. Virus- and host-focused drug repurposing

Priming for activation of host immune response against specific pathogens, or the so called immunoprophylaxis (vaccines), has rendered a successful and, to a large extent, safe approach to control or even eradicate several viral diseases (e.g. measles, influenza virus, papilloma virus, hepatitis B virus). However, emerging viral diseases presenting massive transmission potential (infectivity), high morbidity, antigenic drift potential and other immune escape mechanisms pose a challenge for the rapid and sustained development and implementation of effective vaccines. So far, the only vaccines available to prevent viral respiratory infections are those targeting the influenza virus, which due to virus mutability need to be

reformulated on an annual basis. For such challenging pathogens, antiviral drugs and biologicals, either repurposed or not, show promise for disease control and/or as palliative agents. Interestingly, it was a “global epidemic”, caused by the human immunodeficiency virus (HIV), which boosted modern antiviral drug development in the early 80s´. Since then, the development of antiviral therapies has been mostly centered on chronic viral diseases such as HIV and Hepatitis C virus (HCV), which account for 68% of the FDA antiviral drug approvals [16]. In contrast, up to date, only a few drugs have been marketed for the treatment of acute respiratory infections caused by influenza (four drugs) and respiratory syncytial virus (one drug), despite both viral pneumonias being among the most lethal for the elderly and childhood populations [17]. In this respect, the ongoing COVID-19 pandemic calls for reconsidering not to neglect acute viral diseases within the list of targets for drug development/repositioning.

Current drug repositioning against SARS-CoV-2 is focused in exploring the cross-reactivity of chemical and biological entities interfering with the activity of specific viral molecules or immunomodulating agents [18, 19]. For instance, the first actions, including clinical trials, were oriented to test the therapeutic efficacy of antiviral drugs targeting viral ARN replication (e.g. remdesivir [20]) and proteases (e.g. ritonavir, liponavir [21]), as well as interferons and immunoglobulins [22, 23]). Adjunctive treatments based on monoclonal antibodies (e.g. tocilizumab [24]) or drugs (e.g. chloroquine, dexamethasone [25, 26]), and aimed to diminish the exacerbated inflammatory (“cytokine storm”) response have also been assayed in COVID-19 patients. Another example of a host-directed agent explored for its

potential for hampering SARS-CoV-2 replication is ivermectin [27]. This macrocyclic lactone is a broad-spectrum, FDA-approved drug used for the treatment of several (neglected) parasitic diseases [28]. Its antiviral activity has been associated with the inhibition of the host nuclear transport importin α/β1 heterodimer that is hijacked by viruses to suppress the antiviral response or to translocate viral proteins required for replication [29]. However, the pharmacological dose of ivermectin that may exert anti-SARS-CoV-2 activity *in vivo* has been estimated to be 50- to 100- fold higher (single-dose basis) than the highest regulatory approved dose of this drug [30]. Many of these drug candidates, alone or in combination, were or are still subjected to clinical evaluation on larger and randomized cohorts. Among them, the world´s largest trials of COVID-19 therapies (WHO SOLIDARITY trial: 11,000 patients in 400 hospitals around the globe) has recently released an interim report [31]. The results were highly disappointing, since none of the four drugs tested, namely remdesivir, lopinavir/ritonavir combination, hydroxychloroquine and interferon-β 1, reduced overall mortality, initiation of ventilation and duration of hospitalization of COVID-19 patients. On the other hand, an almost parallel and small scale placebo-controlled study for remdesivir suggested that the clinical benefits of the treatment, measured as the time to recovery in COVID-19 hospitalized adults, is largely determined by the time chemotherapy is initiated [32]. Last October, the FDA approved intravenous remdesivir for the treatment of COVID-19 in adult and pediatric patients 12 years of age and older. 1,062 hospitalized patients with mild, moderate and severe COVID-19 participated in a randomized, double-blind, placebo-controlled clinical trial (ACTT-1). They received remdesivir or placebo plus

standard of care showed that the median time to recovery was significantly reduced for the remdesivir group (10 versus 15 days for the placebo group). The odds of improvement at day 15 were also statistically higher in the remdesivir group [33]. A second randomized, open-label multi-center trial of hospitalized adults with moderate COVID-19 compared 5-day and 10-day treatment with remdesivir with standard of care. The odds of improving were statistically significantly higher in the 5-day cohort, compared with placebo.

A recent retrospective study evaluating IFNα in COVID-19 patients correlated early administration of the cytokine with decreased mortality and its late use with increased mortality and delayed recovery [34]). So far, the glucocorticoid dexamethasone, which reduces inflammation-mediated lung injury and thereby progression to respiratory failure, is the only success case of repurposed drug that lowered COVID-19 mortality in severe patients (i.e. receiving invasive mechanical ventilation or oxygen [35]). Worth noting, almost all the trials quoted above were conducted in patients diagnosed several days to weeks before the initiation of the clinical tests, and with advanced disease signs and symptoms. Such experimental design provides valuable information about the curative or infection control effect of the chemotherapies. In contrast, clinical studies in cohorts at the very early onset and/or at high risk of SARS-CoV-2 infection are missing, despite they would allow assessing the impact of early intervention and the prophylactic, respectively, potential of the repurposed drugs. In this regard, and given its affordability, clinical trials evaluating ivermectin potential as preventive (IVERCAR: *IVER*mectin + *CAR*rageenan nasal administration) or therapeutic (IDEA: *I*vermectin,

*D*examethasone, *E*noxaparin and *A*spirin, systemic administration) anti-COVID-19 agent, in combination with adjunctive drugs or molecules, have been launched [36].

It is important that drug repositioning research against COVID-19 keeps pace with the novel and steady findings on the pathophysiology of SARS-CoV-2 infection. The discovery of new disease-related molecules and/or mechanisms may disclose novel potential candidates or therapeutic strategies for drug intervention. For instance, the deubiquitinating and deISGylating activities of the viral papain-like protease has been shown to contribute to subverting the host immune system by downregulating the interferon and NF-κβ pathways [37]. Another example is the recent finding that, in addition to angiotensin-converting enzyme 2 (ACE2) [38]), SARS-CoV-2 uses neuropilin-1 as host´s receptor to colonize airway epithelium and penetrate tissues [39]. Thus, clinical drugs with the potential to counteract or interfere with these immune evading and viral entry mechanisms should be further explored.

Figure 1 summarizes the state of art of repurposed small-molecule drugs in clinical trials as inhibitors of SARS-CoV-2. Antimalarial and antiviral compounds are by far the most explored drug classes both as single and combination therapies. There are 23 trials for hydroxychloroquine in different phases (from early I to IV) and 3 trials for the related antimalarial chloroquine. As mentioned before the antiviral compound remsedevir is already approved for the treatment of severe COVID-19, and two other antiviral drugs are recruiting for phase IV trials. Antibiotics, antihypertensives and a serine protease inhibitor are also in the race. The

individualization of the drugs, the trial sponsors and the trial code are given as supporting information (Table S1).

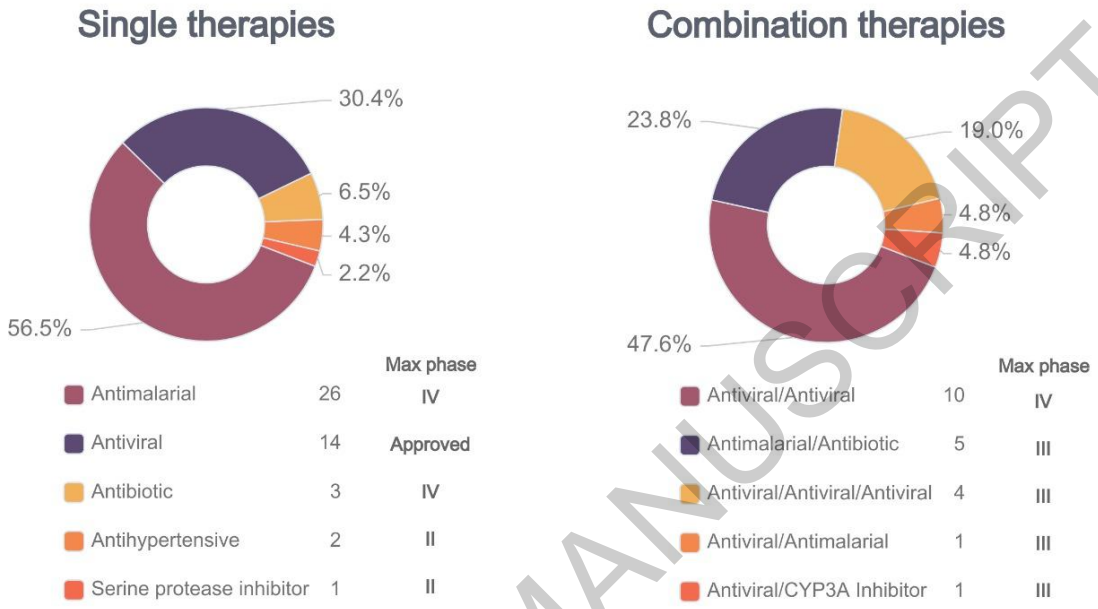

Figure 1. Distribution of repurposed compounds (either as single or combination therapies) according to their drug classes. The number of trials and the maximal phase reached are also included. The phase shown corresponds to the one consigned in www.clinicaltrials.gov. Most of the phase IV trials are either recruiting or not yet recruiting. One combination therapy has completed the recruiting stage for phase IV studies.

3. Intellectual and commercial barriers and collaborative models

Despite promising preliminary evidence of a potential indication shift, there are several commercial, legal and intellectual property barriers that occasionally disincentivize the development and commercial exploitation of new therapeutic indications of known drugs [15, 40]. Whereas it is possible to protect a new medical use in most of the major pharmaceutical markets, the new patent application may collide with previous patents, or the novelty of the second medical use could be endangered by knowledge available in the public domain. Even If the repurposing candidate is off-patent and a new patent is obtained, enforcing patent rights could be an issue; the need of novel formulations or potencies to exploit the new indication can help to overcome prior art [40].

However, the current global crisis has forced us to rethink common practices and assumptions. Intellectual property is generally regarded (not without detractors) as a driver for innovation. But concerns have been raised about the possibility of it becoming a barrier to innovation in the present context, if equitable access to the incoming therapeutic interventions is not granted, or if a patent battle delays the production of therapeutic solutions [41-45]. Far ahead of the clinical trials, AbbVie was the first pharmaceutical company to surrender IP for lopinavir/ritonavir as potential COVID-19 therapies. It has been noted that intellectual property laws provide flexibilities to allow access to medical technology in times of sanitary crisis [41, 42, 44], such as compulsory licenses or regulatory exceptions. Declining patent rights allow manufacturing generic drugs, which concomitantly increases supply capacity. In fact, AbbVie's decision was likely influenced by the compulsory license of Israel for these medicines. Compulsory licences are usually, however,

time-bound targeted exceptions which might not constitute enough incentive for a pharmaceutical company to invest in a repurposed candidate for COVID-19 that does not present freedom to operate.

Major players worldwide have tilted towards collaborative and open innovation models, where multiple organizations share data and resources towards a common goal, a practice that has progressively gained adherents in the drug discovery sector [46, 47] but certainly grew in the present scenario. These initiatives could help to overcome the usual barriers for the realization of drug repurposing. Some outstanding collaborative projects are summarized in Box 1.

Box 1. A summary of some of the most relevant collaborative and open innovation initiatives launched during the COVI-19 crisis.

- *Access to COVID-19 Tools Accelerator*: a joint effort by organizations such as the World Health Organization, the World Bank, the Global Fund, Wellcome and the Bill and Melinda Gates Foundation to support the development and equitable distribution of diagnostic tests, treatments and vaccines (https://www.who.int/initiatives/act-accelerator).
- *Corona Accelerated R&D in Europe (CARE)*: a consortium of 37 renowned academic institutions, pharmaceutical companies and non-profit organizations that has, among its main goals, to provide an emergency response towards the current pandemic by drug repositioning (https://cordis.europa.eu/project/id/101005077/es).
- *EXSCALATE4COV (E4C)*, a public-private consortium supported by the European Commission's Horizon 2020, which will used a supercomputing

platform for large-scale virtual screening (https://www.exscalate4cov.eu/index.html).

- *opnMe*, a proprietary library by Boehringer Ingelheim available to scientists to encourage open innovation during the pandemic (https://opnme.com/home).
- *The Covid BOX*: 160 compounds with known or predicted activity against SARS-COV2 and other coronaviruses, gathered by Medicines for Malaria Venture and available free of charge (https://www.mmv.org/mmv-open/covid-box).
- *The Medicine Patent Pool* (MPP, https://medicinespatentpool.org/what-we-do/disease-areas#pills-COVID-19/): a United Nations-backed public organisation engaged in facilitating equitable access to medicine and technology against COVID-19 in low- and middle-income countries through its voluntary licensing mechanism to patented products and technologies.

4. *Balanced expectations: an example of COVID-related structure-based virtual screens*

In accordance with the rapid response from policy makers and the international scientific community, an impressive volume of SARS-CoV-2 literature was published during 2020, encompassing a diversity of fields, from economics to molecular biology, from immunology to drug discovery, which includes preprints

that have still not undergone peer review. Possibly due to the short timeframe, many published papers, despite peer review, contained substantial flaws or reached overoptimistic conclusions. A quick search in the Retraction Watch Database with a focus on retracted articles with the term “SARS-CoV-2” in the title, reveals that, so far, more than 30 items fulfilling the search criteria have been retracted. The reasons are diverse, from clinical studies lacking informed consent to plagiarism. The most frequent causes of retraction are, however, concerns about data, results and/or conclusions.

We performed a literature survey in Scopus up to August 26th, 2020, focused on original articles describing applications of structure-based virtual screening to identify novel inhibitors of SARS-CoV-2 main protease [48]. The search criteria (“covid” AND “docking” AND “main protease”) resulted in 104 original articles, out of which 96 actually reported the use of molecular docking to identify potential compounds against SARS-CoV-2 main protease. 31,2% of these focused on drug repurposing. *None of the 96 analyzed studies reported any level of experimental validation of the in-silico predictions*. We later assessed the level of *in silico* validation of the utilized docking protocols (presence/absence of validation procedures, and type/s of validation performed, if any). Shockingly, 40.6% of the articles described no validation procedure at all (Figure 2). Among the studies that did perform some level of validation (57 articles), 28,1% only validated the docking power (i.e. the ability of the docking protocol to reproduce the ligand pose observed in an experimental complex). This is a curious choice. The goal of a virtual screen is to rank a chemical library to prioritize, on the basis of the docking

scores, which compounds will be submitted to experimental testing. 40,3% of the reviewed studies did not validate the docking power, but performed some level of validation of the scoring power (they informed the predicted binding energy of one or more known ligands, or, in the best case, they assessed the discriminating power by using a test set or retrospective screen). Only 31,6% among the 57 studies with validation included both types of validation. The preceding figures are surprising, considering the known fact that the performance of docking studies is highly dependent on the system under study, and the high false positive rate associated to docking-based virtual screening [49-53].

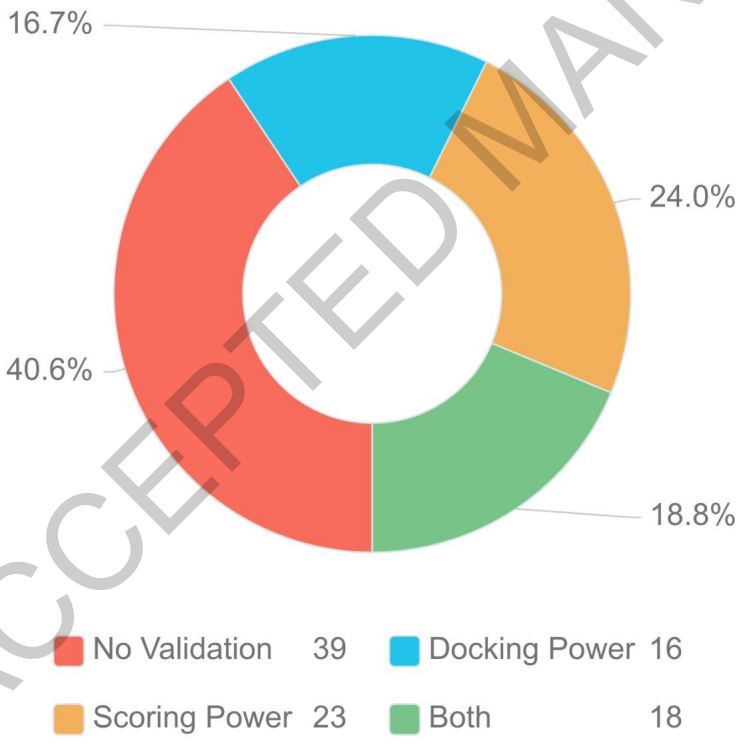

Figure 2. Distribution of validated and non-validated structured-based in silico screening reports with a focus on the SARS-CoV-2 main protease.

Some of the reviewed papers arrive at assertive conclusions despite that no proper (either *in silico* or experimental) validation was performed [54-56]: *"the docking simulation results also indicate the synergistic interactions of 10 substances in the Melaleuca cajuputi essential oil exhibit the significant inhibition into the ACE2 and PDB6LU7 proteins. This prevents protein maturation of the virus…"*; *"the present study revealed that saquinavir is able to bind with the catalytic dyad, and is thereby anticipated to interrupt 3CLpro activity. So, we recommend saquinavir as the potent protease-inhibitor for drug-repurposing against COVID-19"*; "*This study identified a single drug – paromomycin – with activity against two targets of SARS-CoV-2 i.e., spike protein (S1) and protease domain. Paromomycin was found to have strong binding affinity for both targets of coronavirus"*.

Conclusions

In less than one year since the COVID-19 outbreak, drug repurposing has already provided approved therapeutic solutions. In October, FDA has approved remdesivir (originally developed to treat Ebola and Marburg virus), and, soon later, it approved the anti-arthritis drug baricitinib for emergency use (remdesivir approval has however been controversial, owing to its seemingly modest effects and the disappointing outcome in the Solidarity trial [57]). More repurposed drugs are expected to arrive soon as Phase III studies get concluded and their results scrutinized by national health authorities. With no doubt, repurposing candidates are, together with immunotherapies, among the most advanced prospects to fight SARS-CoV-2.

An aspect sometimes overlooked in drug repurposing strategies, is the rationalization of the *in vivo* antiviral activity (i.e. dose, and treatment regimen) in the context of the pharmacodynamic performance of the drug. This information is available for approved drugs and performing such analysis deems essential to estimate whether the pharmacological window and biodistribution of the *to-be* repurposed drug match the safety range and infection foci. In consequence, more rational medical expectations will be raised for the candidates.

Despite the possibility of delivering “new” therapeutic agents in an expedited manner, drug repurposing can also deliver low-cost medications, as the novel therapeutic indication is built on prior (already financed) knowledge. Thus, it may provide equitable access to COVID-19 therapies. The current pricing of remdesivir, however, is not in line with such optimistic expectations (especially considering that the development was partially financed by public funds). Collaborative initiatives raised by the current global emergency suggests, however, that affordable solutions can still be achieved, especially when public, philanthropic and non-for profit organizations have a leading role in the development process.

Although drug repurposing potential has once and again been demonstrated (with around one third of drug approvals in recent years resulting from this strategy), its virtues should not be exaggerated. Our literature survey on computational screens on COVID-19 main protease inhibitors shows that one third of the studies focused on drug repurposing, but in many cases bold conclusions have been drawn from, at most, weak evidence. Accordingly, the potential of repurposing prospects should be weighted and communicated in an unbiased manner.

Expert opinion

Together with immunotherapies (e.g. vaccines, convalescent plasma), repurposed drugs are possibly our best opportunity to arrive at therapeutic solutions to the current pandemic in the short- or mid-term. In fact, remdesivir, a repurposed antiviral agent, has become the very first approved medication for COVID-19 (it was also the first approval for emergency use, back in May). The anti-arthritis drug baricitinib got FDA-approval for emergency use last November. Most potential treatments that have undergone or are undergoing clinical trials, or those that have been empirically tried (off-label) to manage severe COVID-19 cases, are, also, repurposed drugs.

The primary matter of initial repurposing projects has, naturally, been on-target repositioning candidates (perspectives of indication expansion for antivirals or, at most, other anti-infective agents). However, other repurposing opportunities have arisen from the systematic exploration of less obvious, off-target drug repositioning. For instance Riva et al. developed a high-throughput screen on about 12K clinical-stage or FDA-approved small molecules from the ReFRAME library, identifying 100 molecules that inhibited viral replication of SARS-CoV-2, among them 21 drugs that display dose–response relationships [58]. 13 of these have effective concentrations that are probably achievable with the therapeutic doses used for the original indications. As the universe of potential repurposing candidates is finite and sustained chemotherapeutic control of infectious agents tends to be evasive, the development of repurposing projects is naturally paralleled by the investigation

of *de novo* therapeutic agents, which was out of the scope of this review. For example, FDA has recently approved the emergency use of the antibody combination of casirivimab and imdevimab.

After an historically unprecedented short time from development to clinical implementation. in a few weeks, the first SARS-CoV-2 vaccines will begin to be applied massively to a significant fraction of the world population, Although most of the vaccine candidates displayed a significant degree of protection [59], it is yet unknown how long this effect will last and whether the phenomenon of "vaccine-enhaced disease", commonly observed in animals [60-62], will arise in humans. On the other hand, for several reasons (e.g. non-risk groups, lack of logistic/infrastructure, immunological disorders/diseases, ongoing anti-cancer treatment, economically unaffordable or anti-vaccine movement, etc), the majority of the people will not have immediate access or will never receive immunoprophylactic treatment against COVID-19. Altogether, this highlights the relevance for having chemotherapy as either first-line, complementary or backup option to combat SARS-CoV-2 infections and reach those groups having intrinsic difficulties or prejudgment for vaccines.

Understandably, concerns have been raised about the need of providing equitable access to the incoming therapeutic tools for COVID-19. Drug repurposing offers the possibility of finding therapeutic solutions in an expedited manner and with a substantially reduced investment. This improves the chances of finding affordable solutions. However, the current price of remdesivir (more than USD 3,000 for a course, in the US, for private insurers) seemingly shatters any optimistic

expectation on universal access, and refutes some of the alleged advantages of drug repurposing. The development has been undeniable fast, but far from cost-efficient, as Gilead has reportedly invested one billion US dollars on the drug. The projected prices of incoming vaccines, which range from 3-4 to 40 US dollars per dose, suggest that accessibility to therapeutics will benefit as competing alternatives enter the market, especially if such options have been developed with central participation of public and non-for-profit organizations. Hopefully, open innovation models will emerge strengthened from this pandemic. In the worst scenario, if intellectual property becomes an obstacle for equal access to therapeutic solutions, national authorities do have tools within patent legislation to temporarily make intellectual property rights more flexible in a sanitary crisis scenario. In any case, commitment from the public sector and corporate social responsibility practices are to be expected, or at least demanded by civil society.

The energic and concerted response of the scientific community has been paralleled by a flood of COVID-19-related scientific articles in a noticeably short period. As exemplified by our brief analysis of *in silico* screening reports focused on SARS-CoV-2 main protease, overconfident statements / conclusions are frequently found that are not fully supported by the level of experimental evidence. Similar excessively firm conclusions were observed in some small-scale clinical studies. On the other hand, a high number of COVID-related articles have been promptly retracted due to a number of reasons, usually data concerns. As society as a whole is placing high (and comprehensively eager) expectations on scientific advances, we believe that today more than ever it is important that the conclusions

in scientific reports are clearly and fully supported by the level of evidence provided by experimental results.

All in all, we believe that drug repurposing will provide therapeutic solutions to the COVID emergency in the short to midterm (it already is), as well as starting points for specific, *de novo* drugs. Based on the present experience, future efforts of the global political and scientific communities should focus on providing therapeutic solutions for emerging infectious diseases in advance, in order to avoid, as much as possible the loss of human lives and the inherent social cost of epidemics.

Funding:

The authors are funded by the Agencia Nacional de Promoción de la Investigación, el Desarrollo Tecnológico y la Innovación via grants PICT 2017-0643 and PICT 2016-0165. This work was also supported by the URGENCE nouveau coronavirus fundraising campaign of the Institut Pasteur.

Declaration of Interest:

CL Bellera, ME Gantner, M Llanos, S Rodriguez; L Gavernet and A Talevi are members of and are supported by the Argentinean National Council of Scientific and Technical Research Council (CONICET) and/or the National University of La Plata (UNLP). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial

conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer Disclosures:

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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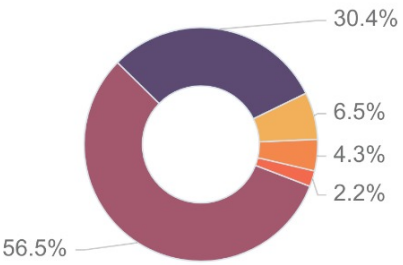
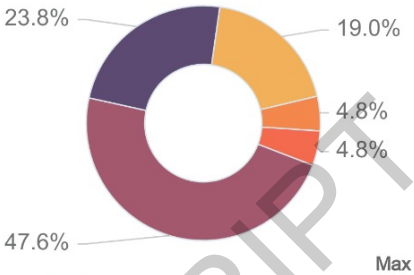
Single therapies



		Max phase
Antimalarial	26	IV
Antiviral	14	Approved
Antibiotic	3	IV
Antihypertensive	2	II
Serine protease inhibitor	1	II

Combination therapies



		Max phase
Antiviral/Antiviral	10	IV
Antimalarial/Antibiotic	5	III
Antiviral/Antiviral/Antiviral	4	III
Antiviral/Antimalarial	1	III
Antiviral/CYP3A Inhibitor	1	III

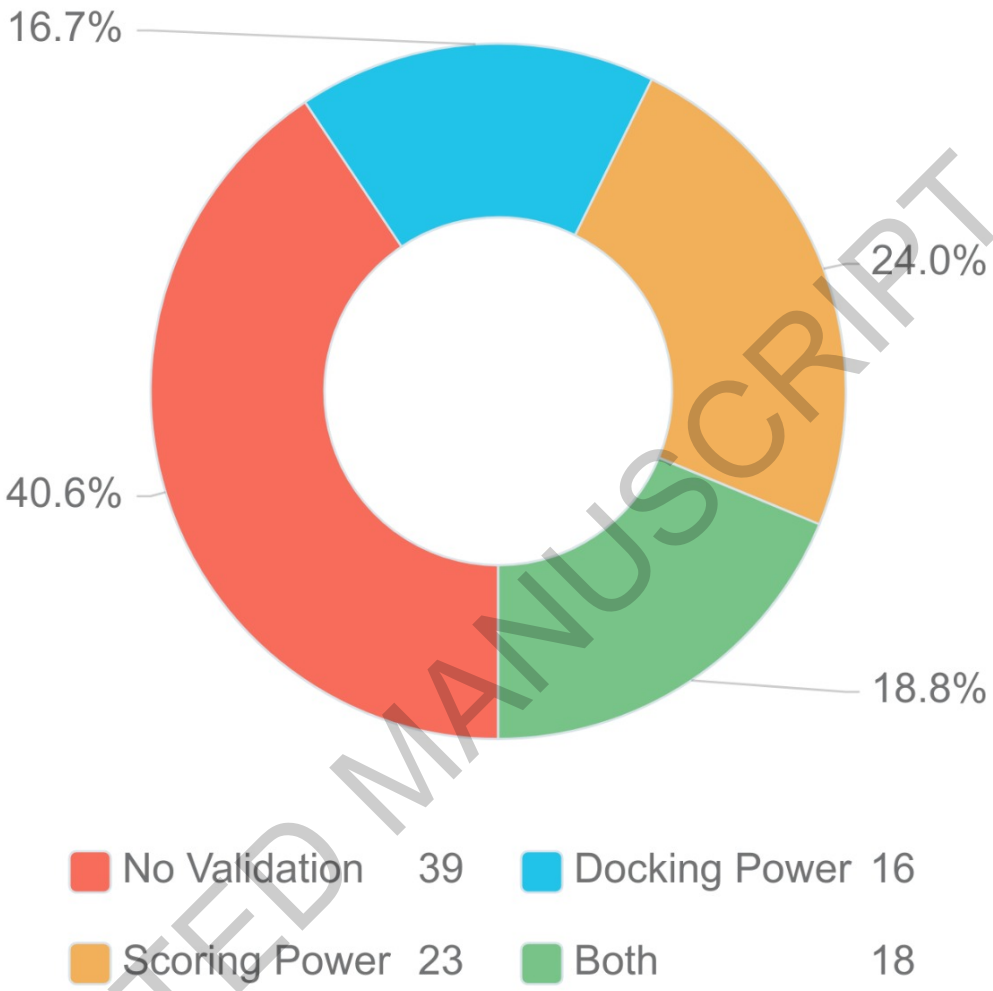


Table S1. Repurposed drug candidates undergoing clinical trials against COVID-19. The trial codes were mainly retrieved from [63] and were verified in the NIH clinical trials database (https://clinicaltrials.gov/).

Drug name	Drug class (original indication)	Stage of development (Phase)	Sponsor	Clinical trial identifier
Single therapies				
Losartan	Antihypertensive	2	University of Minnesota	NCT04311177
		3	Bassett Healthcare	NCT04328012
Arbidol (Umifenovir)	Antiviral	4 (Not yet recruiting)	Ruijin Hospital	NCT04260594
		4 (Recruiting)	Tongji Hospital	NCT04254874
		4 (Recruiting)	Tongji Hospital	NCT04255017
Carrimycin	Antibiotic	4 (Not yet recruiting)	Beijing YouAn Hospital	NCT04286503
Molnupiravir	Antiviral	2	Ridgeback Biotherapeutics, LP	NCT04405570
		2		NCT04405739
Hydroxychloroquine	Antimalarial	4 (Not yet recruiting)	Instituto de Investigación Marqués de Valdecilla	NCT04330495
		3	Massachusetts General Hospital	NCT04332991
		2, 3	University of Washington	NCT04328961
		2	Asan Medical Center	NCT04307693
		2, 3	Oslo University Hospital	NCT04321616
		3	Shanghai Public Health Clinical Center	NCT04261517
		3	Hospital do Coração	NCT04322123
		3	University Hospital, Angers	NCT04325893

		3	University of Minnesota	NCT04308668
		1	Sanofi	NCT04333654
		3	Institut National de la Santé Et de la Recherche Médicale, France	NCT04315948
		3	Hospital Israelita Albert Einstein	NCT04321278
		2, 3	Columbia University	NCT04318444
		3	National Institute of Respiratory Diseases, Mexico	NCT04318015
		2	University of Pennsylvania	NCT04329923
		early 1	Rambam Health Care Campus	NCT04323631
		3	Barcelona Institute for Global Health	NCT04331834
		3	Gangnam Severance Hospital	NCT04330144
		3	National Institute of Respiratory Diseases, Mexico	NCT04315896
		3	Centre Hospitalier Universitaire de Saint Etienne	NCT04328285
		2	Intermountain Health Care, Inc.	NCT04329832
		3	University of Calgary	NCT04329611
		3	Ayub Medical College, Abbottabad	NCT04328272
Chloroquine	Antimalarial	4 (Recruiting)	Wroclaw Medical	NCT04331600

			University	
		2	Fundação de Medicina Tropical Dr. Heitor Vieira Dourado	NCT04323527
		2	Oxford University Clinical Research Unit, Vietnam	NCT04328493
Remdesivir	Antiviral	2, 3	Oslo University Hospital	NCT04321616
		3	Institut National de la Santé et de la Recherche Médicale, France	NCT04315948
		2	Sunnybrook Health Sciences Centre	NCT04330690
		3	China-Japan Friendship Hospital	NCT04257656
		3	China-Japan Friendship Hospital	NCT04252664
		3	Gilead Sciences	NCT04292730
		3	Gilead Sciences	NCT04292899
		3	National Institute of Allergy and Infectious Diseases (NIAID)	NCT04280705
		Approved for marketing	Gilead Sciences	NCT04323761
Azithromycin	Antibiotic	2	Intermountain Health Care, Inc.	NCT04329832
		3	Ayub Medical College, Abbottabad	NCT04328272
Oseltamivir	Antiviral	4 (Recruiting)	Tongji Hospital	NCT04255017
		3	Tongji Hospital	NCT04261270

Camostat	Serine protease inhibitor	1, 2	University of Aarhus	NCT04321096
Combination therapies				
Lopinavir/ritonavir	Antiviral/Antiviral	2	Bassett Healthcare	NCT04328012
		2	Asan Medical Center	NCT04307693
		3	Institut National de la Santé et de la Recherche Médicale, France	NCT04315948
		3	Centre Hospitalier Universitaire de Saint Etienne	NCT04328285
		4 (Recruiting)	Tongji Hospital	NCT04255017
		3	St. Michael's Hospital, Toronto	NCT04321174
		2	The University of Hong Kong	NCT04276688
Oseltamivir/Chloroquine	Antiviral/Antimalarial	3	Rajavithi Hospital	NCT04303299
ASC09F/Oseltamivir	Antiviral/Antiviral	3	Tongji Hospital	NCT04261270
Ritonavir/Oseltamivir	Antiviral/Antiviral	3	Tongji Hospital	NCT04261270
Danoprevir/Ritonavir	Antiviral/Antiviral	4 (Recruitment Status Completed)	The Ninth Hospital of Nanchang	NCT04291729
Darunavir/Cobicistat	Antiviral/CYP3A Inhibitor	3	Shanghai Public Health Clinical Center	NCT04252274
Hydroxychloroquine/Azithromycin	Antimalarial/Antibiotic	3	Hospital do Coração	NCT04322123
		2	Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau	NCT04332094
		3	Hospital Israelita Albert Einstein	NCT04321278
		2	Chronic Obstructive	NCT04322396

			Pulmonary Disease Trial Network, Denmark	
		early 1	Azidus Brasil	NCT04329572
Darunavir/Ritonavir/Oseltamivir	Antiviral/Antiviral/Antiviral	3	Rajavithi Hospital	NCT04303299
Lopinavir/Ritonavir/Oseltamivir	Antiviral/Antiviral/Antiviral	3	Rajavithi Hospital	NCT04303299
Favipiravir/Lopinavir/Ritonavir	Antiviral/Antiviral/Antiviral	3	Rajavithi Hospital	NCT04303299
Darunavir/Ritonavir/Favipiravir	Antiviral/Antiviral/Antiviral	3	Rajavithi Hospital	NCT04303299