Review

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Repurposing Molnupiravir as a new opportunity to treat COVID-19

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Abstract

With the emergence of new and re-emerging viral diseases, scientists have been working to produce new medications with novel targets and pathways. The discovery of safe and efficacious antiviral medicines is critical due to the constant introduction of new virus types and short lifetime of protection. Since the outbreak, there have been significant efforts to repurpose existing and licensed medications for rapid human testing and possible emergency use authorizations. The exploration of surviving medications for new restorative motives is known as drug repurposing. It is a successful, rapid, and highly reliable alternative to traditional drug methods. COVID-19 is being treated using a number of repurposed and new medicines. Molnupiravir is a repurposed Covid-19 medicine that was specifically developed to cure influenza and is used to treat mild to moderately ill Covid-19 patients with high risk of becoming seriously ill. The importance of medication repurposing, as well as the regulatory procedure for repurposed pharmaceuticals and Emergency Use Authorization in the United States, are summarized in this article.

Keywords

Drug repurposing, emergency use authorization, Molnupiravir, Covid-19, United States

Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-caused Coronavirus Disease 2019 (COVID-19) has resulted in a significant increase in morbidity and mortality around the world.[1] Finding therapies for COVID-19 has taken a significant amount of time and effort.[2] But besides advancements in technology and increased understanding of human related illness, therapeutic developments have become much slower than anticipated. Drug discovery can take decades and is complex and expensive.[3] To bring a medicine to market, it ends up taking an average of 10 years and at least $1 billion.[4] The COVID-19 pandemic has prompted the researchers and doctors to repurpose antiviral medications to combat SARSCoV-2 infection.[5] Drug repurposing (DR), also known as drug rescuing, drug redirection, drug repositioning, therapeutic switching, drug reprofiling, drug recycling and drug re-tasking, is a method of recognizing novel therapeutic evidence from Investigational/pro-drugs/old/already marketed/existing/FDA approved/failed drugs, and applying the new advanced medicine to the management of diseases other than the ones for which they were originally developed.[6] Regulatory authorities throughout the world have established fast-track methods to speed up the research and approval of COVID-19 therapeutics.[7] Some of the recommended approaches include the use of antiviral medicines or immune function modulators.[8] Many medicines have demonstrated potent activity against COVID-19 in animal/preclinical investigations and have progressed to human clinical trials, among which Molnupiravir being authorized for treatment of COVID-19 in the United States, India, the United Kingdom, and other countries.

Emerging approaches in drug repurposing

De novo identification and development of new molecular entities (NME) is a classic strategy to drug discovery that comprises five phases: discovery and

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preclinical, safety evaluation, clinical trials, FDA clearance, and FDA post-market safety monitoring. Because of the specific characteristics of the medicine for a mechanism, the approach is arduous, time-consuming, and costly, and it comes with a significant risk of failure. Drug repositioning, on the other side, has only four stages: compound recognition, compound procurement, development, and FDA post-market safety monitoring.[6,9] In comparison to the lengthy traditional research and development methods, DR is inexpensive and faster method of bringing effective treatments to patients. Because data about safety, effectiveness, and the proper delivery route is available, less efforts are necessary to bring a repositioned medicine to commercialization.[10] The most challenging component of product repositioning is discovering novel drug responses. A number of ways have been developed to solve this problem, such as computational approaches, biological experimental approaches, and mixed approaches.[11] While the advantages of repurposing are obvious, the majority of accomplishments to yet have been coincidental. Due to the lack of a comprehensive physical drug database, poor quality drug descriptions, and inadequate readouts of therapeutic activity out of which additional conditions might be expected, systematic, large-scale repurposing initiatives have proved impossible. Latest technological advancements have allowed for a significant improvement in the capacity to measure pharmacological actions in their entirety.[12] Indeed, as the number of repositioned pharmaceuticals mounted, it was suggested that a comprehensive screening of all known drugs would reveal new suitable drugs.[13]

Molnupiravir

Molnupiravir, commercialized as Lagevrio, is an orally bioavailable, directly acting antiviral therapeutic medicine that was initially approved to treat influenza.[14] It's a precursor of β-d-N4-hydroxycytidine, a new antiviral nucleoside analogue. SARSCoV-2, seasonal or pandemic influenza, and MERS corona virus are all targets of this broad-spectrum antiviral agent.[15] It was reported to be extremely effective in reducing nasopharyngeal infection rate and had a positive safety and tolerability record in COVID-19 patients who received short-course, 5-day treatment.[16–17] On 23 December 2021, the FDA approved the medicine under an EUA for the treatment of mild-to-moderate COVID-19 in individuals who have a positive consequences of SARS-CoV-2 virus test and are at high risk of developing chronic COVID-19.[18]

Who can take Molnupiravir?

It is granted for patients who have received a positive test from significant SARS-CoV-2 viral testing, or who are at danger of developing severe COVID-19, which could result in hospitalization or death, or for whom other FDA-approved COVID-19 treatment options are not available or efficacious.[19]

Who should not take Molnupiravir?

It is not approved for use in individuals under the age of 18, for the commencement of therapy in patients who require treatment due to COVID-19, for use for more than 5 days, or as a pre-exposure or post-exposure prophylactic for COVID-19 prevention.[20] Molnupiravir is not indicated for usage during pregnancy. During therapy and for 4 days following the final dosage of the medication, breastfeeding is not suggested.[19]

When should Molnupiravir be taken?

For 5 days, four capsules of the medicine must be consumed per 12 h. Even if the patient feels well, it is critical to finish the entire 5-days course of therapy with the medicine.[21]

Mechanism of action

Molnupiravir acts by inhibiting RdRp of SARS-CoV-2 to induce RNA mutagenesis in two steps. Molnupiravir is converted to EIDD-1931 in the body, which on phosphorylation by host kinases provides the EIDD-1931-triphosphate. This triphosphate acts as an alternate/competitive substrate for the RdRp enzyme of SARS-CoV-2. Therefore, RdRp generates mutated RNA copies for SARS-CoV-2. This process causes the inhibition of the normal functions of RdRp. Molnupiravir is a better electron donor than electron acceptor, and hence this reducing property can contribute to the antiviral activity as it affects the conditions required for viral infection.

Discovery and development

Molnupiravir is an isopropyl prodrug of EIDD-1931, which has been shown to suppress the reproduction of a wide range of viruses, including coronaviruses, with potential safety profiles. In laboratory animals, EIDD-1931, on the other hand, had a poor absorption. EIDD-1931 was quickly metabolised in nonhuman monkeys' enterocytes after oral administration. In the papers, there is information on EIDD-1931 uptake and

distribution in mice. EIDD-2801's low bioavailability was addressed with the development of Molnupiravir.

Molnupiravir was created with funding from the US government by scientists at Emory University in Atlanta. Emory University, Ridgeback Biotherapeutics, Wayne and Wendy Holman, and Merck have also agreed to collaborate on the development of Molnupiravir as an oral therapy for non-hospitalized COVID-19 individuals. Molnupiravir was developed to treat infections caused by the alpha virus. It was under preclinical development for seasonal flu at the period of the pandemic's outbreak. Following the dissemination of COVID-19, the Molnupiravir development effort shifted to COVID-19 therapy.

Pre-clinical studies

In mice, ferrets, and nonhuman primates, it showed significant anti-influenza efficacy and high oral absorption. It found a therapeutic window of >1713 (antiviral effectiveness vs. cytotoxic effects) and proposed that Molnupiravir be tested further in clinical trials for influenza therapy. It's oral efficiency against coronaviruses was also demonstrated in preclinical research in an animal study. EIDD-1931 was also shown to be effective against a remdesivir-resistant infection, suggesting that it may be potent against a larger variety of viruses than remdesivir. SARS-CoV-2 propagation is ineffectively controlled by Remdesivir. Molnupiravir, on the other hand, was shown to be efficient in ferrets in reducing SARS-CoV-2 virus and halting dissemination. As a result, Molnupiravir has been proposed as a protective measure to combat SARS-CoV-2 infection in the community.[14]

Clinical studies

Phase 1 studies

Molnupiravir was well tolerated in the first double-blind, randomized-controlled Phase 1 study (NCT04392219) on study participants, with dosage related pharmacokinetics following medication. The prodrug Molnupiravir is quickly degraded to its active component EIDD-1931 after oral ingestion, with an average time of maximum detected concentration of 1–1.75 h. During the absorptive state, there was no decline in absorption, but there was a drop in the absorption rate. A single oral dose of up to 1600 mg and a range of 50–800 mg twice day for 5.5 days were shown to be harmless.

The Royal Liverpool and Broadgreen Clinical Research Facility used a Bayesian technique to undertake an open label randomised controlled but small phase Ib/IIa study called AGILE (NCT04746183). Elderly patients with SARS-CoV-2 illness diagnosed by RT-PCR within 5 days of appearance of symptoms were randomised to standard of care (SOC) or 300, 600, and 800 mg Molnupiravir orally twice for 5 days by oral route daily. Minimal detrimental reactions were detected in all (4/4, 100%) patients who received 300 and 600 mg, 1/4 (25%) patients having 800 mg, and 5/6 patients (83%) taking SOC. This study discovered that the maximum dosage of 800 mg twice daily seemed to have a 0.9% chance of causing 30% more toxic effects than the controls.

Phase 2 studies

The safety and tolerance of COVID-19 in patients admitted with minimal to moderate COVID-19 were analyzed in a double-blind, randomized-controlled, multicentric phase 2a (MK-4482-006) (NCT04405570) study. After allocation, the test group underwent twice daily oral dosages of 200 mg, 400 mg, and 800 mg Molnupiravir for 5 days compared. Placebo. The study's performance, wellbeing, and tolerance were evaluated for 4 weeks after it commenced. When compared to the placebo, the Molnupiravir 800 mg twice day group had a considerably shorter time to elimination. Furthermore, as compared to placebo, the reduction in time to viral RNA clearance was likewise larger and meaningful. On Day 3, viral isolation was considerably lesser in subjects taking 800 mg twice daily versus placebo. Other double-blind phase 2 experiment is now underway to assess the safety of EIDD-2801 and its effect on SARS-CoV-2 infection shedding.

Phase 3 studies

The independent data safety monitoring board recently halted the phase 3 double-blind, randomised trial (MOVe-OUT) that was designed to evaluate the efficacy and safety of the drug in 1850 non-hospitalized participants with COVID-19 (NCT04575597, MK-4482-002) due to the increased advantage in the active therapy group compared to the placebo. A proven SARS-CoV-2 illness with samples taken ≤5 days previous to the day of allocation and negative serum testing in light of recent or earlier exposure were among the study's eligibility criteria. At day 29, the interim results (n ¼ 775) of this phase 3 (NCT04575597) research revealed a 50% reduction in the probability of hospitalization or mortality.

On day 29, 7.3% of Molnupiravir subjects (28/385) had been hospitalised or deceased, compared to 14.1% of placebo individuals. On day 29, no deaths were

recorded in the Molnupiravir population, compared to eight casualties in the placebo arm. Furthermore, the SARS-CoV-2 variant (gamma, delta, or mu), the period of onset of manifestations, and the inherent risks had no influence on the effectiveness of the drug. In both the Molnupiravir and control arms, the prevalence of all side-effects and drug-related side effects was revealed to be similar. However, compared to the placebo arm, fewer patients in the Molnupiravir group stopped taking a medication.

A further phase 3 double-blind, randomised research (MOVe-IN, NCT04575584) that has been set to investigate the effectiveness and safety of Molnupiravir in 304 hospitalised adult COVID-19 (MK-4482-001) subjects was halted after an initial review of the data revealed that a clinical efficacy in hospitalised individuals was improbable. Nonetheless, a huge (*n* 14 1332) phase 3 multicentric, randomised, double-blind, placebo-controlled investigation (NCT04939428) is actively exploring the safety and effectiveness of Molnupiravir for the mitigation of COVID-19 in adults (MOVe-AHEAD) living with a human who has COVID-19, with the assumption that Molnupiravir would be efficacious in blocking laboratory-confirmed COVID-19 infestation through day 14 especially in comparison to placebo. Meanwhile, many Indian pharmaceutical firms confirmed preliminary results from phase 3 studies with Molnupiravir in mild/moderate COVID-19 patient populations in India.[1]

Regulatory pathway for emergency use authorization in United States

Under agency from the Secretary of Department of Health and Human Services (HHS), the Food and Drug Administration (FDA) may issue an Emergency Use Authorization (EUA) approving the urgent use of an unauthorized medicine, unlicensed or uncleared instrument, or unregistered biological component; or a non - authorized use of an effective drug, authorized or approved machine, or registered biological drug.[22] In other texts, when "no appropriate, authorized, and accessible approaches" exist, an EUA can enable healthcare countermeasures (e.g. prescription medications, vaccines) to be included during an announced outbreak "to detect, treat, or avoid potential or life-threatening illnesses" associated with biological as well as other entities.[23] An EUA differs from a marketing authorization in that it is dependent on a higher standard of proof. In order for an EUA to be granted, FDA must determine, based on existing data, that the product is potentially effective for the intended purpose and that the product's known and prospective benefits exceed the product's known and potential dangers.[24]

The role of emergency use authorization within the FDA's mission

The FDA grants EUAs, which represent the agency's goal to safeguard public's health by guaranteeing the safety, effectiveness, and integrity of human and veterinary pharmaceuticals, biologicals, medical instruments, the country's food system, cosmetics, and radiation-emitting goods. The FDA is in charge of the following counterterrorism and evolving threats sectors:

- Ensure that registered medical instruments are safe and secure;
- Developing emergency planning and response skills;
- Establishing a robust and effective food security policy;
- Accelerating the development and supply of healthcare countermeasures;
- Assuring the agency's assets are safe and secure

The emergency use authorization process

The procedure for obtaining an EUA consists of five phases:

1. The identification of an urgent situation;
2. The announcement of an urgent situation;
3. Review of the request for EUA by the FDA;
4. Issuance of the EUA or denial of the request;
5. Termination of the EUA.[25]

The FDA Commissioner must take numerous procedures before issuing an EUA. One of the four criteria listed below must be met:

1. The Secretary of Department of Defense (DoD) declares a combat emergency or a serious possibility of a military urgent situation.
2. The Secretary of the Department of Homeland Security (DHS) declares a domestic emergency or a possibility for a domestic emergency.
3. The Secretary of the Department of Health and Human Services (HHS) announces a public health emergency or a serious risk of a public health emergency.
4. The Secretary of Homeland Security issues a material security decision.

The HHS Secretary can release a notice that situations prevail to support awarding the EUA once one of the four decisions is made. This proclamation is unique to EUAs and has nothing to do with other emergency announcements. EUA will be approved if the conditions are satisfied.[26]

Pre emergency use authorization-activities

Early involvement with FDA regarding possible EUA goods by corporate or government sponsors can promote more thorough EUA proposals and improve FDA's capacity to examine and issue the EUA if needed. Even though an EUA may not be given until the secretary has declared a state of emergency, FDA acknowledges that the time available for the filing and evaluation of an EUA request may be severely constrained in such situations. Discussions with the FDA regarding a prospective EUA product might be part of the pre-EUA process. Such consultations may take place before the HHS Secretary issues an EUA notification or submits an official application for review of an EUA.

Review of the request for emergency use authorization by the FDA

During whole EUA pathway, from pre-EUA filings until final judgment, including the requirement for the EUA declaration, FDA normally works collaboratively with HHS and other respective government entities, and any EUA discussions with government affiliates. A sponsor requesting an EUA should make a formal request in the format of an EUA filing, referencing any necessary pre-EUA filings already examined by FDA and requesting that the EUA be issued through the same procedure.

Issuance of emergency use authorization

The Commissioner will sign a letter to the funder approving the emergency use, that will include a summary of the licensed drug and its usage, any product potential side effects, the factors for approval of the request, the context of the approval, exemption of some specifications, and any restrictions on the approved usages. The signed letter of approval and any supporting permitted documents will make up an accepted EUA. If an EUA is approved, the FDA commissioner must set essential criteria of use targeted at safeguarding patient safety, to the degree practicable given the situation of the emergencies, and may set additional restrictions for human safety. These restrictions, as well as which are necessary, vary based upon whether EUA permits the need for an unauthorized medicine or an FDA-authorized product used off-label.

Termination of the emergency use authorization

These restrictions, as well as which are necessary, vary based upon whether EUA permits the need for an unauthorized medicine or an FDA-authorized product used off-label. Except if the EUA is repealed owing to the proclamation requirements, it will remain in effect for the term specified in the EUA notification. The HHS Secretary's EUA announcement shall expire on the earliest of the HHS Secretary's judgment that the conditions that prompted the statement have expired or a modification in the product's authorized status so that the product's approved uses are no longer unauthorized. An unauthorized medication and its labelling, as well as product description for an unlicensed use of a permitted drug, must be discarded of upon withdrawal of an EUA or its discontinuation as just a result of the cessation of the HHS EUA statement promoting it as shown in Figure 1.[27,28]

Regulatory pathway for drug repurposing in United States

A 505(b)(2) submission is a type of the US New Drug Application (NDA) that includes comprehensive documents of efficacy and safety research, with part of the material required for acceptance lacking a point of reference and relying on previously authorized evidence.[29] Its goal is to boost drug research innovation without necessitating duplicate research of already available data. Dosage form, strengths, method of administration, dosing regimen, and API switch are examples of modifications that support the filing of this application. It permits a pharmaceutical company to use available data in its NDA by referencing it. This saves money on license; the typical 505(b)(2) license costs $3-7 million, significantly less than the predicted $1.3 billion it costs to bring the new medication to market under 505(b)(2) and get FDA clearance in as short as 30 months[30] Furthermore, based on the scope of the modification to the previously existing drug and the kind of clinical evidence included in the NDA, a 505(b)(2) candidate may be eligible for 3, 5, or 7 years of market dominance, rather than the 180 days granted to generic medicines authorized under section 505(j).[31]

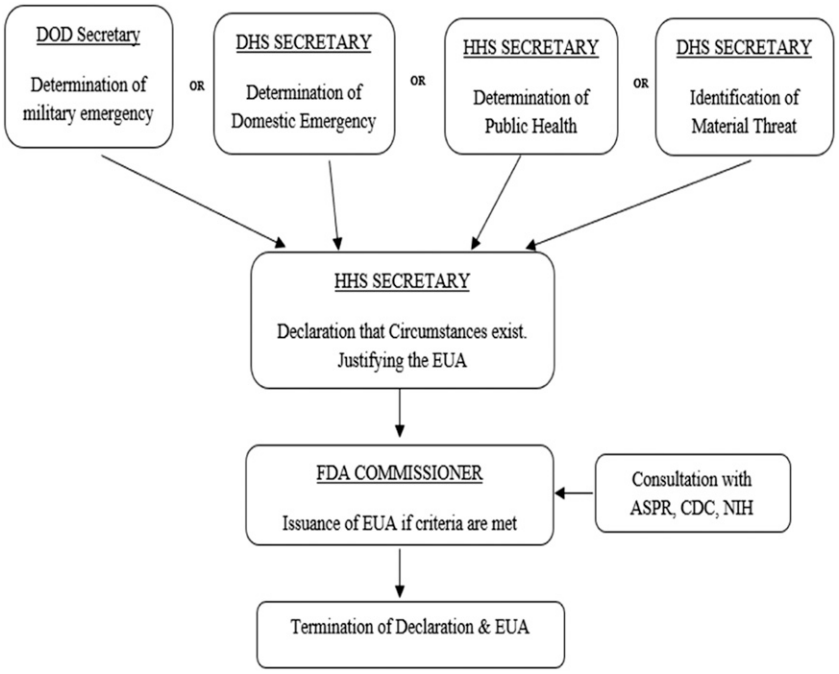

Figure 1. Emergency use authorization process in US.[26]

505(b) (2) approval pathway

Start

While a 505(b)(2) method provides a unique chance for quick approval, success is dependent on discovering goods with established market difference, minimal development threat, and huge revenue potential. Products with novel uses, innovative combination drugs, and prodrugs of an established medicine are all potential 505(b)(2) prospects.

Feasibility

Candidates should be assessed before to development since it is critical to determine the marketing strategy of a product idea for sponsors and to avoid the danger of expensive blunders. Some questions, such as scientific, medical, regulatory, and economic viability, must be explored in order to produce evidence that would validate a drug's potential worth.

Pre-IND

The pre-IND conference with the FDA kicks off the 505(b)(2) procedure, which then proceeds forward to drug formulations (and, if essential, human trials) and later submits the IND proposal. The goal of this conference is to get FDA approval and advice on the studies, the chemistry, manufacturing, and controls (CMC) strategy, and medical research programs in order to reduce the number of new research needed. Certain development projects may undertake bridging research that eliminate the necessity for animal or medical testing, or even both, because the 505(b)(2) route enables the use of online records or the FDA's earlier findings in place of unique trial results. Phase I clinical testing resources (typically used to establish therapeutic bioequivalence) must reflect the industrial production process, along with packing. The three stability sets that will be required for shelf-life assessments are manufactured in generally at this point. As a result, even Phase I trials require a significant amount of CMC research before they can begin.[32]

Following the conclusion of all requisite studies, the applicant submits a 505(b)(2) application for drug commercialization as shown in Figure 2. The FDA's evaluation team determines whether or not an NDA is complete after receiving it. The review board has the right to decline to file the NDA if it is deficient. If everything is in order, the review panel will have 6–10 months to decide whether or not to license the medicine. When the FDA finds that a medicine is safe and efficacious for such intended purpose, it must then collaborate with the applicant to establish and modify prescription documentation. "Labeling" is the term for this. However, before a medicine may be licensed for commercialization, there are many unresolved difficulties and those should be resolved. FDA may ask the manufacturer to respond to queries relying on existing

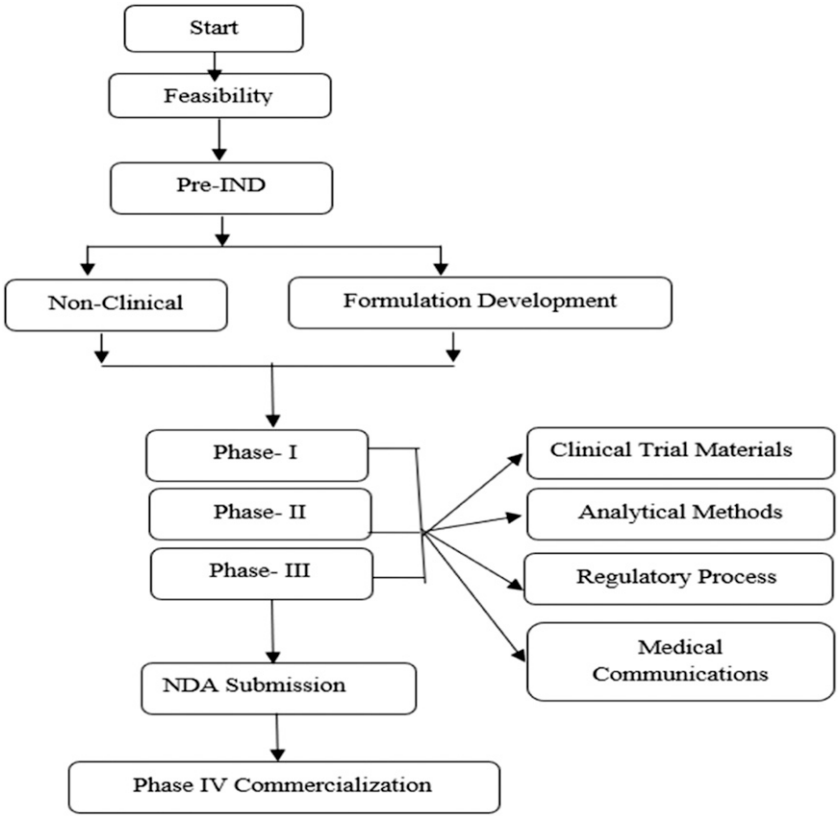

Figure 2. Steps involved in 505(b)(2) approval pathway.[32]

information. In some circumstances, the FDA needs additional research. The manufacturer can now make a decision whether or not continue working on the project. There are pathways for formal application if a manufacturer disagrees with an FDA judgement.[33]

Conclusion

The research community has rallied to discover and assess various medicines and vaccinations as the COVID-19 outbreak spreads throughout the world, from academia and government institutions to minor biotechnology startups and major pharmaceutical enterprises. Repurposing preexisting medications authorized for other uses as antiviral treatments for SARS-CoV-2 is one feasible method. However, there are a few drawbacks to drug repositioning, such as the fact that the recommended dose for the treatment of a novel disease is generally different from that needed for its intended target disease, and if this is the case, the discovery group will have to start from Phase I human development, effectively eliminating drug repositioning's upsides over de novo drug development. Although repurposed medications with acceptable safety records might be beneficial, there are currently no widely marketed COVID-19 preventive or therapy alternatives.

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