CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.6488806

Available online at: http://www.iajps.com *Review Article*

DRUG REPURPOSING (DR) APPROACHES AND CHALLENGES IN CURRENT PANDEMIC: A REVIEW

Aditi Gupta[1], Aakib Ali[2], Abhijeet K. Lodhi[3], Abhishal Awasthi[4], Sonika Jain[5], Dr. Vivek Jain[6]

[1]Adina Institute of Pharmaceutical Sciences, Sagar, (M.P.)

Article Received: March 2022 **Accepted:** March 2022 **Published:** April 2022

Abstract:

Traditional drug development and discovery has not kept pace with threats from emerging and re-emerging diseases such as Ebola virus, MERS-CoV and more recently, SARS-CoV-2. Among other reasons, the exorbitant costs, high attrition rate and extensive periods of time from research to market approval are the primary contributing factors to the lag in recent traditional drug developmental activities. The improving knowledge of the virology and clinical presentation of COVID-19 is leading to a broadening pool of potential pharmacological targets. The aim of this review is to describe regulatory and pharmacological aspects of drug repurposing and to identify drugs proposed for repurposing in COVID-19 based on registered clinical trials, Model-informed drug repurposing, Drug repurposing, Drug repurposing for COVID-19 , Proposed AI techniques for drug Repurposing . The challenges of the correct interpretation of existing pre-clinical/clinical evidence as well as the Proposed AI techniques for drug Repurposing will also be discussed.

Key words: *Drug repurposing, COVID-19, Challenges, Approaches*

Corresponding author:
Dr. Vivek Jain
vivek.adina@gmail.com

QR code

Please cite this article in press Vivek Jain et al, ***Drug Repurposing (Dr) Approaches And Challenges In Current Pandemic: A Review.,*** *Indo Am. J. P. Sci, 2022; 09(04)*

INTRODUCTION:

Novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread aggressively. With a mortality rate of about 7%, 213 countries and territories around the world have reported a total of 7,817,195 confirmed cases with a death toll of about 430,397. It started with patients reporting pneumonia-like symptoms of unknown etiology, in the Wuhan district of China (Hubei Province), and was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. SARS-CoV-2 is a class of enveloped viruses with a positive-sense RNA genome. They come under the Betacoronavirus group, having the same phylogenetic similarity with the previous severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Thus it is the 3rd coronavirus epidemic, and as a result of evolution of the virus, the spread of COVID19 is more severe than that of the previous SARS-CoV and the MERS-CoV [1].

The SARS-CoV-2 pandemic has forced researchers to invent new strategies for rapid antiviral treatment. Host-based antiviral agents target host cellular machinery essential for viral infections or innate immune responses to interfere with viral pathogenesis. It can be augmented by employing well-validated drug discovery approaches. There are two basic strategies in drug discovery, conventional drug development and drug repositioning. Besides the success rate being very low, the conventional way typically takes 10–15 years, is very expensive and needs high investments. Drug repositioning, instead reuses old drugs for exploring new therapeutics, making it more efficient, economical, and riskless [2].

More than 80 pioneering clinical trials have been instigated at present to test coronavirus treatment, including potential old drugs and investigational new drugs. Recycling and reusing old drugs, recovering shelved drugs and increasing patients' lives makes drug repositioning an appealing system of drug discovery. It requires a thorough in-depth knowledge of present practices acquired by assessing both biological and pharmaceutical learning and interpreted mechanism-of-action of drugs.

In this regard, the pharmaceutical industry is also looking for novel leading-edge technologies to track, monitor and restrict the dissemination of COVID-19 disease. AI is one such parallel technology that can provide support against this virus by population screening, medical help, notification, and suggestions about infection control. AI is also implemented in the field design through inception of learning prediction model and performs a swift virtual screening to accurately display the congruent outputs. With a drug repositioning strategy, AI can briefly screen drugs that have potential to fight minacious diseases such as COVID-19. Being an evidence based medical tool, this technology has the potential to improve the drug discovery, planning, design treatment and outline follow-ups of the COVID-19 patients. This review describes the current application of AI in Drug Repurposing for treating COVID-19 pandemic.

MODEL-INFORMED DRUG REPURPOSING:

At the start of a pandemic there is very little information about the NP. Information on mechanism of infectivity and site of action (SOA) of infection are obtained, followed by testing in vitro potency of compounds that have shown efficacy against similar pathogens with the clinical isolates of the NP. in vitro potency information is compared against reported clinically achievable exposures, providing estimation of probability of achieving clinically effective concentrations . While the translatability of the in vitro systems to clinical outcome might be questionable, these data define the extent of actionable information. For RDs that appear promising, clinical pharmacokinetics (PK) could be explored in order to develop recommendations on optimal posology as there is no reason, a priori, to believe that a posology developed for a labelled indication will be optimal for treatment of an NP. In such cases, the suitability of the available safety data may need to be reassessed prior to progressing to clinical trials.

The passage of time yields data: information about NP viral kinetics becomes available. These data are used to build a viral kinetic (VK) model that links events in the viral life cycle to PK of the RD , guiding clinical trial design.

Later in the pandemic, greater experience with RD interventions allows comparison, contrast and synthesis. As clinical response data emerge, exposure–response (E-R) analysis can be used to assess adequate exposure in the patient population and to understand factors that drive response . This data can loop back to the early in vitro data, and questions around dose and regimen specific to the NP can be addressed.

A complementary arrangement of this MIDR strategy is made by considering what can be done in preparation for a pandemic, what must be done during the pandemic, and what should be done after the pandemic . In each step of the MIDR process,

particular data are needed, and specific assumptions must be made. Below is a discussion of each of the MIDR steps described .

Step 1. Repurposed drug product label and in vitro data
RD information from the product label and publications is mined and compared to in vitro data generated for the NP, providing initial assessment of potential for use of the RD against the NP.

The suitability of the labelled posology is considered by two quantitative methods (Step 1) using a readily available in vitro parameter such as IC50: [3]comparing the ratios of in vitro IC50 of the RD for approved marketed indication(s) relative to that of the NP and [4]comparing the ratio of the average, maximum and minimum steady-state RD free concentration at the approved clinical regimen to the NP IC50. [5] Both steps offer initial assessments of whether concentrations near or above the NP IC50 can be achieved. For most antivirals, exposures higher than IC50 are likely to be required to eradicate the infection.

Step 2. Repurposed drug clinical PK and in vitro data
Once initial assessment that the RD has the potential to reach effective concentrations has been achieved, the potential for the RD to be optimized can be further evaluated. Investigations at this stage include determining (or predicting) NP exposure at the SOA, considering the predicted RD concentration within its therapeutic window (including safety margins), adjustments of posology to account for the acute nature of the NP, and making assumptions about the interaction between NP and RD at the SOA.

This step considers the potential for differences in the SOA between the indication with marketing approval and the NP. Free drug concentration can be a useful surrogate for tissue concentration. If available, PK studies that directly measure RD concentration in target tissues are ideal. If not, mathematical modelling such as physiologically-based pharmacokinetic models (PBPK) may be utilized to account for altered partitioning, transporter utilization and tissue metabolism. [5]

Step 3. Repurposed drug PK and novel pathogen kinetic data
With the PK of the RD determined and initial NP viral kinetic (VK) data emerging, efforts should focus on understanding the effect of RDs on the viral kinetics of the NP. Once an NP is identified, integrating VK models with PopPK/PBPK models is crucial to understanding where and when an RD could have the largest impact. A critical prerequisite for understanding viral kinetics is the development of a new, reliable, sensitive assay to measure the NP across the time course of the infection[6].

Viral kinetic data provide an understanding of the infection characteristics, which differ by virus: latency period, virus generation time and duration of infectiousness. [7] For influenza and respiratory syncytial virus (RSV), the time between clinical symptom onset (1 and 3 days, respectively) and peak viral load is short relative to the start of infection [8] In contrast, symptom appearance and corresponding diagnosis is considerably longer (range 5–24 days) [9] following SARS-CoV-2 infection, and may occur just prior to or near the time of maximal viral load[10]

Consideration of the time window between infection at the SOA and symptom onset is crucial to developing effective therapies and the optimal timing of their administration. Most antiviral drugs are designed to inhibit infectivity or free virion production, and are only active prior to peak viral load . If diagnostic tools are available and the time between infection and symptom onset is short (<3–5 days), drug repurposing using established replication inhibitors may be effective for treatment and prophylaxis.

Step 4. Repurposed drug PK and novel pathogen clinical outcome data
Once the kinetics of the RD and the NP have been considered and evaluated, information gained from the aforementioned steps can be used to inform robust clinical trial designs that follow sound clinical pharmacology and model-informed principles. Furthermore, dose– and/or exposure–response analyses from these robust clinical trials can then be used to feed back into the previous steps. For this to occur effectively, informative virologic and clinical outcome measures need to be collected and rapidly returned for analysis and incorporation into the previously built models .

Improving patients' morbidity and mortality is the key component of clinical efficacy when evaluating candidate therapeutics. For respiratory virus infections, a broad range of clinical endpoints may be considered. For example, in mild respiratory viral illnesses in ambulatory patients, endpoints could include individual symptom scores, temperature, tissue weight for nasal discharge or even oxygen saturation at room air, [11]whilst in more severely ill patients endpoints could include time in ICU, need for mechanical ventilation and survival[12]. Composite symptom scores for an NP may also be developed

and validated during clinical development leading to a diversity of endpoints in clinical trials. See the recent publication by Dodd et al. on the statistical power for trial endpoints for COVID-19 [13] and in the Supplementary Materials

Step 5. MBMA and clinical outcome data
As a pandemic progresses, clinical trials that evaluate drug interventions against the NP appear, and model-based meta-analysis (MBMA) approaches can be employed to maximize the information which emerges from them . Initially, trials will focus on RDs, with trials of de novo anti-NP treatments (e.g., vaccines, novel antibody therapies, convalescent plasma) appearing later. Earlier trials are likely to be small, uncontrolled proof-of-concept studies in well specified populations, with larger, confirmatory studies occurring later.

This variability in patient demographics and study conduct will further increase as the pandemic spreads. Moreover, the standard-of-care (SoC) will be geographically diverse and will evolve over time. The NP itself may also change (mutations, changes in virulence factors, differential effects by geography).

This creates a huge potential to obtain insights into the impact of drug treatment on the course of disease, vital signs and biomarkers. These insights help identify the likelihood of success of RD interventions and will also provide directions to increase the efficiency of future clinical trials. It may identify enriched populations for initial proof-of-concept trials, before embarking on larger studies in allcomer populations.

Drug Repurposing:
Drug discovery is a high-risk, lengthy and expensive process . According to a report by the Eastern Research Group (ERG), while it takes 10-15 years to develop a new molecular entity, the success rate is only 2.01% . The concept of drug repurposing reuses old drugs for the treatment of a never-considered therapeutic indication. It is an experimental approach of identifying the pre-approved, discontinued, shelved and investigational drugs for authorized restatement for the treatment of other diseases. Conventional drug development usually includes five stages:

(i) discovery and development,
(ii) pre-clinical research,
(iii) clinical research
(iv) FDA review and
(v) FDA post-market safety monitoring and development.

However, there are only four steps in drug repurposing:

(i) compound identification
(ii) compound acquisition
(iii) clinical research and
(iv) FDA post-market safety monitoring and development [2].

A repositioned drug goes directly to preclinical testing and clinical trials omitting the initial steps, thus narrowing down the risks and lowering the costs. Fundamental principle in drug repurposing is that a common molecular pathway is associated and accountable for numerable diseases and a multitude of explicit information that is accessible on the formulation, dose, toxicity, pharmacology and clinical trial data of the authorized, approved, shelved or discontinued drugs [14].

Drug repurposing for COVID-19:
Drug "repurposing" in this article refers to the use of existing approved drugs for the treatment of a never-considered therapeutic indication - in this case, COVID-19. The discovery and development of new molecular entities being lengthy, time-killing and high-priced for clinical trials to earn regulatory authorizations or sanctions, the momentary passage thus to potential treatments is the repurposing (repositioning) of prevailing approved drugs for the treatment of COVID-19. In this context, Chloroquine (CQ) and it's Hydroxyl analogue Hydroxychloroquine (HCQ) have been reported in the treatment of viral infection. These drugs have antimalarial activity and also showed in vitro treatment against COVID -19 [15].

Similarly, an antiviral drug Remdesivir primarily used in the treatment of Ebola virus clinical studies exposed new successful effects against COVID-19 in vitro. It is an adenosine analogue, basically integrates into nascent viral RNA chains and shows in early termination. Lopinavir and Ritonavir were used in the ministration of COVID-19 patients. These two antiviral agents mainly affect proteolysis in coronavirus replication cycle. Ribavirin is an analog of ribonucleic and inhibitor of RNA polymerization. This drug has shown in vitro activity against SARS-CoV-2 in preclinical studies [15].

Furthermore, Tocilizumab, an immunosuppressive drug, was also used in the treatment of COVID-19 patients in vivo in China. This is chiefly employed to aid rheumatoid arthritis tested in COVID-19 patients. The drug successfully mitigates the clinical symptoms of viral infection, but the numbers of patients investigated in the study were very few . The

Anti-flu drug of Japan is revealed significant results in clinical trials over 340 patients . In China, this drug is accepted for the treatment of Influenza and also shown to be efficient against a different type of viruses including SARS-CoV-2. Similarly, Ascorbic acid (Vitamin C) combination with other antiviral drug has shown to be supportive in the treatment of COVID-19 patients. In this context, more studies are suggested for a future drug against COVID-19 [16].

Proposed AI techniques for drug Repurposing:

The main hindrance in drug repositioning is diagnosing and identifying the unique drug-disease relationship. To address this issue, a variety of approaches have been developed including computational approaches (such as AI), biological experimental approaches, and mixed approaches. Thus there are chances that the application of the AI approach in drug discovery is feasible [17]. Researchers have found many similarities between the COVID-19 virus and the 2003 SARS Virus and based on the existing data that caused SARS, AI learning models can be created to predict drug structures that could potentially treat COVID -19 [18]. Notwithstanding effectively affirmed repurposed drugs, there is a requirement for recognizing more repurposed drugs.

AI and machine learning (ML) can support this procedure by rapidly recognizing drugs having adequacy against COVID-19 and thus overcome any barrier between a large number of repurposed drugs, laboratory /clinical testing, and final drug authorization. A good amount of information, discharged by different health agencies and organizations is accessible on open stages [18]. AI likewise contains a subfield called ML, which utilizes factual strategies with the capacity to learn with or without being modified by an external user. Machine learning is divided into supervised, unsupervised, and reinforcement learning [19].

Supervised learning contains characterization and relapse strategies where the prescient model is created dependent on the information from information and yield sources i.e output. Unsupervised learning includes bunching strategies by gathering and deciphering information dependent on input information only. Another field of ML is deep learning. It uses AI neural network with multiple hidden layers apart from the input and output layer. Deep learning permits machines to take care of complex issues in any event, when utilizing an informational index that is exceptionally differing and unstructured. The more Deep learning calculations learn, the better they perform.

The development of DL was seen with the expanding measure of information and the nonstop development of computer power. The striking distinction that DL makes is the adaptability in the design of neural systems such as repetitive neural networks (RNN), convolutional neural networks (CNN), deep belief networks (DBN), and completely associated feed-forward systems. The whole explanation will be better understood. It presents the AI-empowered drug repurposing strategy. We need a Repurposed Drug Database, Open Chemical/Drug Database as an input to the model. Then different algorithms could be applied to the input and the required drug could be obtained [20].

The best and the truly necessary technique during circumstances is to order this unique medication information with the goal that AI scientists can apply their calculations to determine noteworthy bits of knowledge. For this, the world offices and policymakers need to step up to push huge pharma organizations and exploration labs to unite with littler examination associations and pool information sources. To foresee increasingly exact outcomes, specialists need arrangements of good information which is as of now not accessible and are therefore constrained by lack of data or too much noisy data. Associations over the globe are taking vital activities to utilize AI for testing which is empowering, be that as it may, there is a requirement for progressively symptomatic testing .

A few associations have begun to use these advancements to quicken COVID-19 medication disclosure and better fathom how the resistant framework battles the infection. Toward the beginning of April, pharmaceutical organizations GlaxoSmithKline (GSK) and Vir Biotechnology joined forces to progress coronavirus treatment advancement utilizing computerized reasoning and CRISPR.

Furthermore, in the scholarly area, the Harvard T. Chan School of Public Health as of late united with the Human Vaccines Project to dispatch the Human Immunomics Initiative, which uses man-made reasoning models to quicken antibodies for a scope of infections, including COVID-19 [21].

A group from Southern Illinois University (SIU) as of late built up an information representation device that uses GPS data to show users the locations of known COVID-19 cases. Google and Apple have likewise collaborated to build up a contact following application powered by Bluetooth innovation. These

methods may prove effective in the data collection in a great and accurate amount [21].

Organizations are running experimentation explores different avenues regarding effectively approved drugs, having built up wellbeing profiles in people, based on fundamental comprehension of the infection. With regards to COVID-19, hydroxychloroquine (endorsed to treat Malaria) and remdesivir (for Ebola) are the two most popular instances of this up until now [22]. So, the data set of the effectiveness of these medicines may be a good input for an AI model. The organizations which are utilizing AI for repurposing existing medications for COVID19 .

Experimental approaches:

Target-based:

In a target-based screening, the efficacy of the drugs is evaluated based on how well the drug is able to inhibit a single target crucial for the disease progression, typically a protein or a gene [23]In this case, the mechanism of action is already known. Targetbased drug screening typically consists of a few steps. The first step is target identification where pathways or cellular processes crucial for disease progression are first identified, followed by target validation to verify the importance of the target to the disease. The next step is assay development, where the target-disease interaction is captured in a model, typically utilising cell-free binding assay, to enable screening of the drugs. Subsequently, hit identification is carried out where various drugs are tested and evaluated based on their efficacy in inhibiting the said target. The last step is to optimize the hits by chemically modifying the hits to improve their efficacy, safety, and stability.

Animal models for SARS-CoV-2 drug repurposing:

While not exactly an approach to drug repurposing, animal models has been proven to be invaluable in the quest of finding potential therapeutic agents for SARS-CoV-2. Among many, ferrets, Syrian hamster, mice and non-human primates are routinely used as clinically relevant animal models to capture the disease progression in vivo. In this section, we will focus primarily on transgenic mice and non-human primate (NHP) model. Bao and co-workers reported the use of hACE2 transgenic mice as a clinically relevant mouse model of SARS-CoV-2 infection [24]. hACE2 transgenic mice was developed from ICR mice which express human ACE2 receptors, therefore enabling accurate recapitulation of SARS-CoV-2 spike glycoprotein interaction with human ACE2 receptor in vivo. The study reported that unlike the mock-infected hACE2 mice or the wild-type mice, SARS-CoV-2-infected hACE2 mice displayed weight loss and slightly bristled fur. Moreover, viral load was successfully detected by RT-qPCR in the lungs of the hACE2 mice. Following this, infectious SARS-CoV-2 was successfully isolated from the lungs of the infected hACE2 mice (and not from mock-infected or wild-type infected mice), suggesting that ACE2 receptor is crucial for SARS-CoV-2 viral entry into the host cell. In addition, this study also fulfils Koch's Postulate, establishing that SARS-CoV-2 is indeed the causative agent of COVID-19. Following the success of this model, Zheng and colleagues utilised K18-hACE2 transgenic mice, which expresses human ACE2 receptor under the cytokeratin 18 (K18) promoters to establish a mouse model with more severe symptoms [25].

Originally developed in 2006 as a mouse model for the original SARS-CoV, this mouse model displays more severe symptoms upon inoculation with SARS-CoV-2, including severe disease in the lungs and on some cases, the brain. The mice also display severe thrombosis and vasculitis after the onset of severe pneumonia. This mouse model proves to be invaluable in studying the pathological aspects of severe SARS-CoV-2 infection, as well as to test various therapeutic agents.

REFERENCES:

1. Wang L, Wang Y, Ye D, Liu Q. A review of the 2019 Novel Coronavirus (COVID-19) based on current evidence. International journal of antimicrobial agents 2020;55 (6):105948
2. Xue H, Li J, Xie H, Wang Y. Review of drug repositioning approaches and resources. International journal of biological sciences 2018;14(10):1232-44
3. Pushpakom S, Iorio F, Eyers PA, et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov. 2019;18(1): 41-58.
4. Morgan P, Van Der Graaf PH, Arrowsmith J, et al. Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival. Drug Discov Today. 2012;17(9–10):419-424
5. Baker EH, Gnjidic D, Kirkpatrick CMJ, Pirmohamed M, Wright DFB, Zecharia AY. A call for the appropriate application of clinical pharmacological principles in the search for safe and efficacious COVID-19 (SARS-COV-2) treatments. Br J Clin Pharmacol. 2020.

6. Canini L, Carrat F. Population modeling of influenza A/H1N1 virus kinetics and symptom dynamics. J Virol. 2011;85(6):2764-2770.
7. Ferguson N, Cummings D, Cauchemez S, et al. Strategies for containing an emerging influenza pandemic in Southeast Asia. Nature. 2005;437:209-214.
8. El Saleeby CM, Bush AJ, Harrison LM, Aitken JA, DeVincenzo JP. Respiratory syncytial virus load, viral dynamics, and disease severity in previously healthy naturally infected children. J Infect Dis. 2011; 204(7):996-1002.
9. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-1062.
10. Zhou B, She J, Wang Y, Ma X. Duration of viral shedding of discharged patients with severe COVID-19. Clin Infect Dis. 2020;71 (16):2240-2242.
11. Nicholson KG, Aoki FY, Osterhaus A, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Lancet. 2000;355(9218):1845-1850.
12. DeVincenzo JP, McClure MW, Symons JA, et al. Activity of oral ALS-008176 in a respiratory syncytial virus challenge study. N Engl J Med. 2015;373(21):2048-2058.
13. Dodd LE, Follmann D, Wang J, et al. Endpoints for randomized controlled clinical trials for COVID-19 treatments. Clin Trials. 2020;17(5): 472-482.
14. Ngo H, Garneau T, Sylvie G, D. K. A complex game of hide and seek: the search for new antifungals. MedChemComm 2016;7(7):1285-306.
15. Rolain J, Colson P, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. International journal of antimicrobial agents 2007;30(4):297-308.
16. Chan J, Yao Y, Yeung M, Deng W, Bao L, Jia L. Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. The Journal of infectious diseases 2015;212(12):1904-13.
17. Mohs R, Greig N. Drug discovery and development: Role of basic biological research. Alzheimer's Dementia: Translational Research Clinical Interventions 2017;3(4):651-7.
18. GNS H, Saraswathy G, Murahari M, Krishnamurthy M. An update on drug repurposing: re-written saga of the drug's fate. Biomedicine Pharmacotherapy 2019;110(2):700-16.
19. Mak K, Pichika M. Artificial intelligence in drug development: present status and future prospects. Drug discovery today 2019;24(3):773-80.
20. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. Cell Discov 2020;6(14):1-18.
21. J K. How Will Big Data Analytics Factor into the Next Phase of COVID-19? Health it analytics 2020:https://healthitanalytics.com/news/how-will-big-dataanalytics-factor-into-the-next-phase-of-covid-19.
22. A S. How AI is fighting COVID-19: the companies using intelligent tech to find new drugs,. Pharmaphorum 2020:https://pharmaphorum.com/views-analysisdigital/how-ai-is-fighting-covid-19-the-companies-using-intelligent-tech-to-findnew-drugs.
23. 23.Sams-Dodd, F. (2005). Target-based drug discovery: Is something wrong? Drug Discovery Today 10, 139–147.
24. Bao, L., Deng, W., Huang, B., Gao, H., Liu, J., Ren, L., ... Qin, C. (2020). The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice. Nature 583, 830–833
25. Zheng, J., Wong, L. R., Li, K., Verma, A. K., Ortiz, M. E., Wohlford-Lenane, C., ... Perlman, S. (2021). COVID-19 treatments and pathogenesis including anosmia in K18-hACE2 mice. Nature 589, 603–607