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Chapter 11

Drug repurposing for SARS-CoV-2 (COVID-19) treatment

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Chapter outline

11.1 Introduction

Drug repurposing encompasses the process of investigating already existing drugs with an intention to use them for new therapeutic purposes, different from the initially intended use [1,2]. This approach is known by several names, such as drug repositioning, indication shift, indication expansion, and drug reprofiling [3]. With the increasing need for drugs against various diseases, pharmaceutical companies usually fall short to meet the demand by the production of new drugs from scratch from simple molecules (de novo) due to

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various challenges associated with the drug discovery and development process [2]. The same is true for the search against antiviral drugs including drugs that can be used to cure, control, or manage COVID-19. The realization that drugs can be repurposed to work against other indications came as a breakthrough to many drug developers as it helped to bring hope for many manufacturers to find a way of increasing productivity with much less cost and shorter duration among other benefits. By the year 2015, it was reported that repositioned drugs produced about a quarter of revenue annually for the pharmaceutical industry [4]. In order to understand drug repositioning in the perspective of COVID-19, it is important to appreciate the long and costly journey of developing a drug de novo which may not be suitable and preferable for such diseases as COVID-19 which are causing high mortality and demands urgent interventions. Developing drugs de novo is a long process that demands huge investments. However, libraries serve by providing starting materials for some drugs, which somehow shortens the time. Studies toward COVID-19 cure and/or management using drugs have been ongoing for some time now. Several agents were reported by Hodgson [5] which included drug and vaccine agents. The drug agents included those from recombinant proteins and monoclonal antibodies. During the course of the studies, some in vitro work on the efficacy of hydroxychloroquine and antiviral drugs such as remdesivir against SARS-CoV-2 virus showed some positive results to some considerable extents. Despite starting from stages within the discovery pipeline, the work usually takes a long time such that there were still no confirmed drugs or vaccines against COVID-19 [6] by the end of June 2020. Apart from synthetic drugs, many other natural plant products [7–11] were and are still being studied for phytoconstituents that can be used to control, cure, and/or manage COVID-19, which include cannabinoids from *Cannabis sativa* [12–19].

Studying plants in their nonstandardized extract forms is not easy as they are usually not uniform from one location to another which makes it difficult to optimize for drug development; as such, extracts need to be further purified and pure compounds isolated for in-depth studies [16]. This way, there is almost a clear way of reducing risks as the tens or hundreds of compounds found naturally in the extract matrices get narrowed down to a manageable few. It is important to always note that among the tens or hundreds of compounds found in extracts, some are naturally toxic [20,21] to humans and their effects may manifest quickly or too slowly to be linked to the consumption of the extracts later on. A reliable drug agent is supposed to strike an acceptable balance among all the pharmacokinetic parameters such as absorption, distribution, metabolism, clearance, and toxicity (ADMET) [22–24].

11.2 Comparison of drug repurposing and de novo drug development processes

Drug repurposing is generally shorter than the development of drugs from scratch. In as short as 3 years, a repurposed drug can successfully secure a license while a new drug would normally take a minimum of 10 years. Fig. 11.1 shows a comparison between the two approaches.

With this in mind, it is clear why emerging diseases such as COVID-19 would be best addressed with drug repurposing than with de novo synthesis in order to make significant cuts to the time of waiting as the disease demands urgent interventions.

11.3 Selected COVID-19 drugs under repurposing considerations

Table 11.1 presents some of the drugs that are under consideration for repurposing against COVID-19. These drugs come from a wide range of categories from antibiotics to antivirals spanning over different durations of use and mechanisms of action. The activities of the drugs that saw them be considered for potential repurposing included their ability to stop or at least delay the progression of pneumonia and its associated conditions, prevent septic shock induced by acute respiratory distress, inhibiting inflammations and viral entry into cells and decreasing the levels of a number of cytokines among other activities.

Looking at the data in Table 11.1, there is a need to further investigate the antiviral effects of Teicoplanin on SARS-CoV-2 through well-designed randomized controlled trials. In the meantime, Teicoplanin could also serve as a potential alternative treatment for COVID-19.

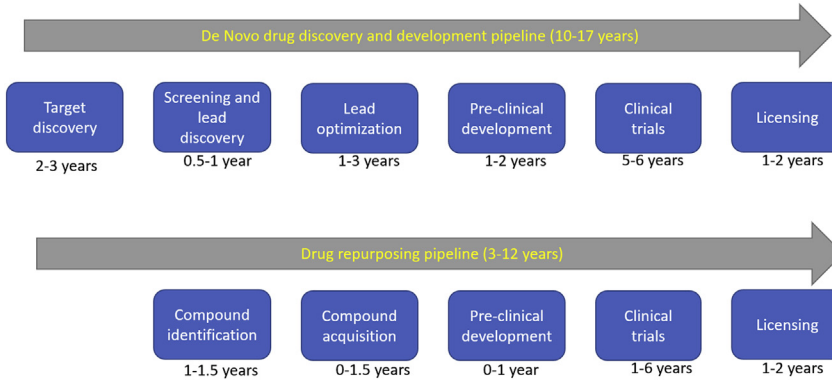

FIGURE 11.1 Drug repurposing and de novo discovery pipelines.

TABLE 11.1 Selected drugs being studied for repurposing considerations against COVID-19.

Drug/chemical	Mechanism	Other uses of the drug/chemical	Dosing	Reference
Teicoplanin (glycopeptide antibiotic)	**Coronaviruses**: Teicoplanin inhibits low-pH cleavage of the viral spike protein by cathepsin L in the late endosomes, which prevents the release of genomic viral RNA and continuation of the virus replication cycle. This also implies that Teicoplanin acts at early stages of the viral life cycle. Furthermore, this activity was conserved against SARS-CoV-2 since the target sequence that serves as the cleavage site for cathepsin L is conserved among SARS-CoV spike protein.	Active against SARS-CoV (in vitro). Gram-positive bacterial infections, i.e., staphylococcal infections coronaviruses, i.e., Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV. Other viruses, i.e., ebola, influenza, flavi, hepatitis C, and HIV.	The concentration reached in human blood for a daily dose of 400 mg is 8.78 μM, yet the concentration of Teicoplanin required to inhibit 50% of viruses (IC_{50}) in vitro is 1.66 μM.	[25–27]
Metronidazole [1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole]	Metronidazole is a redox-active prodrug and acts as a biocidal agent by its interaction with a nitroreductase homolog.	Contrary to the increase in cytokines noted with COVID-19 infection, metronidazole decreases the levels of several cytokines, for example, IL-8, IL-6, IL-1B, TNF-α, IL-12, and IFNγ, levels of CRP, and neutrophil count. Increases the number of circulatory lymphocytes and has lymphoproliferative properties. Decreases neutrophil-generated reactive oxygen species during inflammation.		[28–33]

Tetracyclines	These highly lipophilic antibiotics are known to chelate zinc compounds on matrix metalloproteinases (MMPs); thus, the use of tetracyclines can limit replication of coronaviruses within the host through these zinc-chelating properties. Coronaviruses are known to rely heavily on host MMPs which also contain zinc as part of their MMP complex for several processes, e.g., survival, cell infiltration, cell-to-cell adhesion, and replication. There is a possibility that tetracyclines can also inhibit RNA replication on positive-sense, single-stranded RNA and thus could be beneficial against COVID-19 virus. Independent of their already known antibiotic mechanism, tetracyclines could also be beneficial in COVID-19 infection through their antiinflammatory capabilities and downregulation of the nuclear factor-κB pathway, decrease in levels of inflammatory cytokines, such as TNF-α, IL-1β, and IL-6. Decrease in levels of circulating inflammatory agents with the use of chemically modified tetracyclines could be due to induction of apoptosis of mast cells and activation of protein kinase C.	Treatment of dengue virus by use of doxycycline. Used in treatment of other viral infections, i.e., HIV virus, West Nile virus, and viral encephalitis. Chemically modified tetracyclines can prevent septic shock induced by acute respiratory distress syndrome, one of the significant effects of COVID-19 virus infection in the patients.		[34–39]

Continued

TABLE 11.1 Selected drugs being studied for repurposing considerations against COVID-19.—cont'd

Drug/chemical	Mechanism	Other uses of the drug/chemical	Dosing	Reference
Tocilizumab	Tocilizumab is an IL-6 blocking antibody that acts through targeting IL-6 receptors.	Rheumatoid arthritis. Can be effectively used in patients with extensive bilateral lung lesions opacity or in severe or critical patients, who have elevated laboratory detected IL-6 levels. Tocilizumab can be used in case of persistent fever for more than 3 days and further, the chemiluminescence detection of serum IL-6 content being greater than 20 pg/mL. Tocilizumab treatment is recommended to reduce both mortality and inflammatory storm in severe COVID-19 patients.	**First dose**: 4–8 mg/kg (the recommended dose is 400 mg, diluted to 100 mL with 0.9% normal saline). The infusion time is more than 1 h. **Additional dose**: Possible after 12 h at the same dose as before. The additional dose can be administered in case of patients with poor initial efficacy. A single dose should not exceed 800 mg (maximum dose). The drug should not be administered more than twice, i.e., maximum number of times of administration.	[40, 41]

Baricitinib	Viruses are known to mostly enter cells through receptor-mediated endocytosis. A cell surface protein ACE2 that is present on cells in the blood vessels, heart, kidney, and the lung AT2 alveolar epithelial cells (particularly prone to viral infection) could possibly be the receptor used by the 2019 novel coronavirus to infect the lung cells. It is possible to interrupt the passage of the viruses into cells and the intracellular assembly of virus particles through the disruption of AAK1 (AP2-associated protein kinase 1). Several drugs are already available; for example, sunitinib, erlotinib, exhibit high affinity for AAK1 and inhibit it, but most of these drugs use is limited by their serious side effects and requirement of high doses to inhibit AAK1 effectively. Baricitinib is one of the high affinity AAK1-binding drugs that not only binds to the cyclin G-associated kinase, one of the regulators of endocytosis, but also is a janus kinase inhibitor.	Could be useful in treatment of an appropriate population of COVID-19 affected patients by inhibiting viral entry into cells and inflammation.	At therapeutic dosing of either 2 mg or 4 mg once daily, it is possible to attain the plasma concentrations sufficient to inhibit AAK1.	[42–44]

Continued

TABLE 11.1 Selected drugs being studied for repurposing considerations against COVID-19.—cont'd

Drug/chemical	Mechanism	Other uses of the drug/chemical	Dosing	Reference
Ivermectin	There are several pathways through which ivermectin acts; for example, in invertebrates, the drug acts as an anthelmintic through the opening of glutamate-gated and gamma aminobutyric acid (GABA)—gated chloride channels which leads to increased conductance of chloride ions and causes subsequent motor paralysis in parasites. In vitro ivermectin inhibits replication of flavivirus by targeting the activity of nonstructural 3 helicase (NS3 helicase). Ivermectin acts as a broad-spectrum antiviral against several RNA viruses by specifically inhibiting importin α/β-mediated nuclear transport and eventually inhibiting the nuclear trafficking of viral proteins. It is possible that this drug also acts against SARS-CoV-2 (an RNA virus) by binding to the Impα/β1 heterodimer, thus destabilizing it and eventually preventing Impα/β1 binding to the viral proteins. This whole process prevents viral proteins from entering the nucleus, thereby leading to an efficient antiviral response.	Broad endo/ectoparasiticide activity, antibacterial, anticancer, antiviral (both in RNA viruses and DNA viruses).	The use of ivermectin in critically ill SARS-CoV-2 patients at a dose of 150 μg/kg was found to be associated with a lower mortality rate and reduced healthcare resource use. Further in-depth and well-designed studies, for example, randomized controlled trials, are required to understand the possibility of its wide use in treatment of COVID-19 patients since ivermectin use is hampered by its pharmacokinetic problems, i.e., low solubility and high cytotoxicity.	[45—52]

	Since there are several other pathways that could be involved in achieving the antiviral effects of this drug against the novel COVID-19 virus, further in-depth investigation is required to understand the exact mechanism involved. Synergistic inhibitory effect against SARS-CoV-2 could possibly be attained through combing hydroxychloroquine which would act by inhibiting the entry of SARS-CoV-2 into the host cells and ivermectin would enhance the antiviral activity by inhibiting viral replication.			
Favipiravir	Favipiravir (prodrug) is a novel RNA-dependent RNA polymerase (RdRp) inhibitor.	Treatment of influenza and ebola viruses. Reduction in SARS-CoV-2 infection in vitro.	In a pilot nonrandomized study, favipiravir that was administered orally at a dose of 1600 mg twice daily on day 1 and thereafter at a dose of 600 mg twice daily on days 2−14 showed that FPV had significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance despite the study limitations as compared with LPV/RTV that was administered orally at dose of LPV 400 mg/RTV 100 mg twice daily until the virus cleared/until 14 days had passed.	[53−57]

Continued

TABLE 11.1 Selected drugs being studied for repurposing considerations against COVID-19.—cont'd

Drug/chemical	Mechanism	Other uses of the drug/chemical	Dosing	Reference
Pioglitazone	Inflammatory laboratory markers are elevated especially the ICU COVID-19 patients; thus, pioglitazone administration could produce an antiinflammatory effect as has been assayed through high-sensitive C-reactive protein within short-term intervals after the starting therapy.	Useful in treating insulin resistance. Useful in psychiatric and neurological conditions, for example, in Alzheimer's disease, depression, among others. Could be a potential agent for treatment of COVID-19 patients.	A significant reduction in IL-6 and TNF-α with pioglitazone administration in insulin-resistant individuals at a dose of 30–45 mg/day for 3 months was noted. Reduction in monocyte gene and protein expression of IL-1b, IL-6, IL-8, lymphocyte IL-2, IL-6, and IL-8 was noted with pioglitazone use at a dose of 45 mg/day for 4 months. In astrocytes stimulated with lipopolysaccharide, pioglitazone inhibits the secretion of the proinflammatory cytokines but it increases the antiinflammatory ones. Decrease in ferritin has also been noted with administration of pioglitazone in a rat model. In a mice cecal ligation puncture model, 7-day pioglitazone administration significantly reduced TNF-α and IL-6 mRNA expression in the peritoneal lavage fluid of this model, thus attenuating lung injury in this model.	[29, 59–68]

Methylprednisolone		Stops/delays the progression of pneumonia. Proved to be effective for the treatment of acute respiratory distress syndrome. The early, low-dose, and short-term administration of methylprednisolone along with the other standard treatment prescribed in severe patients with COVID-19 pneumonia leads to overall better clinical outcomes, i.e., a faster improvement of SpO2, significantly shorter interval of using supplemental oxygen therapy, a faster decrease in C-reactive protein and interleukin-6, significantly shorter hospitalization of ICU, and the length of hospitalization.	The critically ill COVID-19 pneumonia patients were treated with methylprednisolone at a low dose of 1−2 mg/kg/day for 5−7 days via intravenous injection along with the standard treatment prescribed for the patient treatment.	[69−71]
Soluble angiotensin-converting enzyme 2	The full-length ACE2 (a monocarboxypeptidase) contains a structural transmembrane domain which anchors its extracellular domain to the plasma membrane, thus acting as a receptor for several viruses inclusive of SARS-CoV-2. The soluble form of ACE2 lacks the membrane anchor and thus may act as a competitive interceptor of several viruses like SARS-CoV-2 and this would prevent binding of the viral particle to the surface-bound, full-length ACE2.	Administration of soluble recombinant human ACE2 protein could be beneficial in combating or limiting infection progression caused by coronaviruses especially the ones that utilize ACE2 as a receptor. Animal models have demonstrated its benefit in treatment of kidney diseases also. There are limited animals or human studies designed to test the therapeutic potential of soluble recombinant ACE2, thus limiting evidence to support its use in COVID-19 patients too.		[72−78]

Continued

TABLE 11.1 Selected drugs being studied for repurposing considerations against COVID-19.—cont'd

Drug/chemical	Mechanism	Other uses of the drug/chemical	Dosing	Reference
Human umbilical cord Wharton's jelly-derived mesenchymal stem cells (hWJCs)	Mesenchymal stem cells (MSCs) demonstrate immunomodulatory effects either by secreting many types of cytokines by paracrine secretion or through direct interaction with immune cells. **COVID-19 patient (as reported in one patient)**: A significant improvement in inflammation and immune situation along with no obvious side effects has been reported in a severe COVID-19 patient treated with MSCs injection of hWJCs. A gradual reduction in serum CRP and inflammatory factors, i.e., IL-6, TNF-α, along with the improvement in some other vital signs was recorded in this patient. Furthermore, increase in the counts of CD3+, CD4+, and CD8+ T cell was also recorded after intravenous injection of hWJC. There is need to determine how hWJCs can counteract cell death and promote cell regeneration especially in COVID-19 patients.	MSCs' good safety profile has supported its use in treating several diseases over the years, for example, autoimmune diseases and graft-versus-host disease, among others. Significant immunomodulation and tissue repair effects with low immunogenicity have been reported with hWJCs use; thus, this could be a potential candidate for treatment of COVID-19 patients possibly by preventing or attenuating the cytokine storm. Several beneficial effects were reported following the MSCs accumulation in the lungs after intravenous infusion, i.e., improvement in the pulmonary microenvironment, protection of the alveolar epithelial cells, prevention of pulmonary fibrosis, and the overall improvement in lung function. Under unfavorable conditions, MSCs are known to improve cell survival, prevent apoptosis, necroptosis, and pyroptosis from occurring in not only various parenchymal or nonparenchymal cells but also immune cells.	Prior to administration of the intravenous infusion of hWJC, dexamethasone 2 mg is to be administered. Fresh culture of the hWJCs is to be prepared before injecting the patient(s) and the hWJCs are to be suspended in 100 mL of normal saline. The total number of transplanted cells to be calculated by 1×10^6 cells per kilogram of weight and injection to be performed about 40 min with a speed of 40 drops per minute. This treatment is administered along with other conventional therapies prescribed for treating the COVID-19 patient(s).	[79–87]

Ciclesonide (inhaled steroid)	The COVID-19 virus could replicate in alveolar epithelial cells, causing lung damage/injury and simultaneously infecting alveolar macrophages as reported with other viruses, for example, SARS and MERS. The virus may also cause local inflammation and it is expected that the antiviral and antiinflammatory effects of ciclesonide could be effective in treating the lung injury caused by the COVID-19 infection. On administration, this inhaled prodrug stays on the lung surface with only minor increases in blood levels.	Ciclesonide has also shown strong antiviral activity against SARS-CoV-2 though these data are not yet published/ preliminary. It has demonstrated antiviral activity against MERS virus. It is a steroid that is both safely and effectively used in controlling chronic inflammation of the respiratory tract in a diverse group, i.e., from premature babies and newborns to the elderly. Used in pneumonia patients to rapidly improve the patient symptoms and prevent progression of the disease to the severe form.	Although the standard dose in adult is 400 mg once a day and the maximum dose is 800 mg/ day or 400 mg, twice a day, the dose prescribed for viral treatment is proposed to be higher since the viral replication time is approximately 6–8 h and a higher dose than standard is required to achieve the desired effect in the alveoli. It is also desirable to inhale the drug deeply and continue treatment for about 14 days or longer after starting it to avoid the reactivation of residual virus or appearance of resistant virus. **Treatment of pneumonia in confirmed COVID-19 positives**: A dose of ciclesonide (Alvesco) 200 mg inhaler (56 puffs/kit), 2 times a day, 2 inhalations each time or ciclesonide (Alvesco) 200 mg inhaler (56 puffs/kit), 3 times a day, 2 inhalations each time (to be used in severe cases and cases where the effect is not sufficient) is the proposed treatment for these patients. For the case of long-term positive asymptomatic patients, further in-depth and well-designed studies are needed.	[88–90]

Continued

TABLE 11.1 Selected drugs being studied for repurposing considerations against COVID-19.—cont'd

Drug/chemical	Mechanism	Other uses of the drug/chemical	Dosing	Reference
Interferon beta-1b		Could be useful in treatment of COVID-19 patients.	**Triple combination regimen dose for COVID-19 patients (as used in an open label, randomized, phase 2 trial):** Interferon beta-1b 8 million international units (0·25 mg) on alternate days, lopinavir 400 mg plus ritonavir 100 mg every 12 h, and ribavirin 400 mg every 12 h. The above dose was used to treat patients who showed mild to moderate disease at the time of enrollment in the study (reference provided in next column). Significant benefits were reported with the use of the above triple combination treatment, i.e., reduction in the duration of viral shedding, symptom alleviation, and reduction in duration of hospital stay, among others as compared to using lopinavir 400 mg plus ritonavir 100 mg every 12 h alone. There is need for further studies to support the use of this drug in sever patients of COVID-19 along with other patients (mild-moderate symptoms).	[91]

11.4 Pros and cons of drug repurposing

Drug repurposing comes with some advantages as it reduces the risks of attrition rates associated with early drug discovery and stages thereafter [92]. Drugs that are considered for repurposing are those that have already undergone all necessary checks and balances in terms of optimization for druggability. This means that compounds that would not make it into drugs have already been removed from the pipeline remaining with only those compounds that favorably met ADMET specifications. The other factor that is circumvented is the long duration associated with the drug discovery process [92]. Instead of starting from the beginning, researchers will only begin from somewhere in the middle as Fig. 11.1 showed. This cuts short the time required for appropriate interventions to be made on a particular disease burden that requires urgent remediation such as COVID-19. In the same understanding of cutting through the process, huge financial costs are saved from the early discovery research process. Repurposing of a drug is also advantageous as it reduces the number of steps required for clinical trials which is beneficial for efficient timelines.

Despite the advantages stated, drug repurposing possesses several challenges including regulatory hurdles [92]. These challenges include technological demands as usual, the biological targets are different for the originally intended purpose of the drug and the new disease toward which the drug is to be repositioned. This means a research group should have enough skills and equipment to optimize and validate the drug for the new target. Repositioning drugs may have a disadvantage in that it may have a new mechanism of action with biological targets which would require an entire study beyond just clinical trials which would still demand financial investments. Another downside of this approach is dosage formulation which would not be the same as the originally intended disease. Reformulation may go overboard and cause various side effects which would not be in the original case, as this time, increased concentration subjected to biological targets and the pathway has been disturbed. On the part of administration and regulation, intellectual property transfers may become another challenge particularly in cases where there are no or little legal framework backing up the repositioning.

11.5 Political antagonism that COVID-19 drug repurposing faced

Political sentiments took a very significant place in the process of drug repurposing against COVID-19 to the point that it became very hard for both scientists and the general public to take home facts. This happened probably due to the failure to strike a balance between economic gains that would be realized in coming up with the repurposed drugs on one side and the urgency for action that the fatality and other effects of the disease demanded. One most

discussed drug repurposing project involved hydroxychloroquine an antimalarial that had shown promise to alleviate some conditions in COVID-19 patients as a potential antiviral drug [93,94]. Various countries and hospitals made huge orders of the drug to help in combating the disease. Various research groups took on the project and proceeded to determining various stages of repurposing. Some researchers believed in the process to get to the end but others thought it was a political hype. Politicians took it to top various podia supporting the drug until a paper by Mehra and others [95] in May 2020 published in the Lancet convinced many that the drug would not just work as earlier hyped. At this moment, most countries halted any use of the drug in experiments, research groups including the WHO halted any further studies, and focus was put on other projects. With mounting evidence of significant flaws in the integrity of the data in the famous Mehra's paper, it was discovered that the conclusion was in err and researchers including the WHO reverted to the various repurposing experiments with the drug. The Lancet had the paper immediately retracted [95]. Political influence remains a significant challenge to drug discovery and repurposing and needs to be put to check as it has a significant potential to deny patients their right to life and/or may push for agents that are not fully studied and cause many adverse events in the long term.

11.6 Future perspectives

The future of the fight against diseases including emerging ones such as COVID-19 looks promising with the contribution of drug repositioning research projects. The good thing with this approach is that it does not require huge investment technology, provided enough and relevant literature and standard operating procedures are available. This work can therefore be undertaken in both developed and developing countries, which is good for inclusive research and collaboration worldwide. This field provides a reliable platform for drug developers in the developing world to contribute to the discovery pipeline by developing local databases of drugs that can be potentially repurposed against emerging diseases. This demands the use of chemi- and bioinformatic approaches, medicinal chemistry, chemical biology and computational chemistry among many others. Natural product-based libraries, both from plants and animal matrices can also be considered as a way of designing potential substrates that can work imitating already existing drugs. If these are known, understood and availed early, it will turn out to be relatively cheaper and less time demanding than other approaches of drug discovery. Drug repositioning appears to be the next breakthrough intervention in disease management with lower costs and shorter duration of the discovery pipeline. It is imperative that drug discovery research be put in motion without significant political influence which has a strong bearing on the possibility of denying many the right to life.

11.7 Conclusion

Drug repositioning is very essential particularly if it is found to work against emerging diseases such as the COVID-19 pandemic which requires urgent attention and interventions. This is so as the drugs being considered are already derisked and well studied over a lengthy period of time while ensuring their success and safety to a relatively higher degree. Despite the advantages, it is important to keep parallel de novo drug discovery projects running to offset any challenges that may occur in the pipeline potentially causing the discontinuation of the repurposing. In regard to what the chapter has discussed and presented, drug repurposing presents a good platform from which COVID-19 can be well controlled, managed, and/or completely cured upon successful controlled randomized trials.

List of Abbreviations

AAK1 Adaptor-associated protein kinase 1
ACE-2 Angiotensin-converting enzyme 2
ADMET Absorption, distribution, metabolism, excretion, and toxicity
AP Adaptor protein
ARDS Acute respiratory distress syndrome
CD Cluster of differentiation
COVID-19 Coronavirus disease 2019
CRP c-reactive protein
hWJCs Human umbilical cord Wharton's jelly-derived MSCs
ICU Intensive care unit
IL Interleukin
MERS-CoV Middle East respiratory syndrome-related coronavirus
mRNA Messenger ribonucleic acid
MSCs Mesenchymal stem cells
SARS-COV-2 Severe acute respiratory syndrome coronavirus 2
TNF-α Tumor necrosis factor α

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