Drug repurposing in the era of COVID-19: a call for leadership and government investment

Investment is urgently needed in repurposed drugs which could ease the burden of the COVID-19 pandemic

Human coronaviruses, including severe respiratory syndrome coronavirus (SARS-CoV) and the 2019 novel coronavirus (SARS-CoV-2), cause pandemics. There are currently no effective drugs targeting SARS-CoV and SARS-CoV-2, although there is plenty of media coverage regarding potential drugs (such as hydroxychloroquine and azithromycin[1]) or drugs to avoid (such as non-steroidal anti-inflammatories and angiotensin-converting enzyme inhibitors[2]). This advice can be more harmful than using the standard care for people with viral illnesses, and clinical groups have appropriately distanced themselves from such advice until more evidence is available.[3,4] The current COVID-19 epidemic suggests that urgent investment in repurposed drugs is a necessary strategy.[5]

What is drug repurposing?

Drug repurposing involves identifying new uses for approved or investigational drugs that are outside the scope of the original intended or approved medical use.[6,7] It represents an appropriate alternative strategy in the current era, reducing development time and costs compared with de novo drug discovery and development. It is a relatively new term for a process that has been happening for many years. In simple terms, it involves identifying existing compounds through biological plausibility; in vitro, in vivo and in silico studies; or serendipitous clinical observation. Provision of these compounds to patients can be through compassionate use or clinical trials, which in the setting of the current pandemic raises many ethical questions. These include, for example, opportunity cost, where a patient is given a drug with little efficacy that precludes them from taking a more effective one, and selection for a hospital-based clinical trial which then reduces the ability of patients to partake in better trials in the future.

It needs to be clear, however, that a drug repurposing strategy requires time, funding and drug development knowledge to understand how to use the drugs appropriately and prevent toxicity. The required clinical pharmacology and clinical trial knowledge to support use, albeit based on smaller and shorter studies compared with the full dossier needed for a new chemical entity, must still be undertaken before appropriate drug prescribing or registration can occur. Sometimes, however, only bioequivalence studies are required. Registration for clinical use of a new strength, formulation and indication of morphine sulfate pentahydrate required a single randomised controlled trial and a literature review only.[8]

Although the methodology has been around for some time, the profile of drug repurposing has recently risen for three main reasons. Firstly, using existing drugs for new purposes reduces drug development time by utilising what is already known about those drugs, including their pharmacokinetics, pharmacodynamics, common and uncommon toxicities, dosing schedule, and mechanism of action. This means, secondly, that most steps of the pre-clinical and early clinical development phases can be bypassed.[1] As such, drug repurposing presents a significantly faster pathway into phase 2 trials compared with traditional drug discovery and development, where the safety, dosing and toxicity profile of new drugs is not known. Thirdly, as a result, development-related financial investment is substantially reduced.[7]

While the discovery and development of new drugs remains essential, a new drug requires 12–16 years processing time and an investment of US$1–2 billion to achieve regulatory approval. In contrast, repurposing an existing drug for a new therapeutic use takes on average 6.5 years to obtain approval and an investment of US$300 million.[9] A combination of both traditional drug development and drug repurposing is therefore prudent if we are to make timely inroads into treating human coronaviruses more efficiently and deliver a significant impact on human health.

Examples of successful drug repurposing

Drug repurposing has been used successfully in many clinical settings (extensively reviewed by Pushpakom and colleagues[7]). A famous example was the incidental discovery that sildenafil (Viagra; Pfizer), originally used to relieve the symptoms of angina, was also effective for erectile dysfunction, receiving United States Food and Drug Administration approval in 1998.[9] Within the first 3 years of approval, nearly 8 million men were taking sildenafil in the US alone, with annual sales of US$1.5 billion.[10] Similarly, thalidomide was first marketed in 1957 as a sedative

Jennifer H Martin[1,2]

Nikola A Bowden[1]

1 University of Newcastle, Newcastle, NSW.

2 Hunter New England Health, Newcastle, NSW.

jen.martin@newcastle.edu.au

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but withdrawn in 1961 after it caused skeletal defects in more than 15 000 children. Thirty years later, the anti-angiogenic actions of thalidomide were discovered, making it an attractive drug to repurpose for cancer treatment. Within 4 years, thalidomide was approved for the treatment of multiple myeloma.[11] The thalidomide story shows "that no drug is ever understood completely, and repositioning, no matter how unlikely, often remains a possibility".[6]

Relevance of drug repurposing in the COVID-19 era

Time is important as we are in the middle of a pandemic. However, research and development funding is often not available from the pharmaceutical industry; significant government investment is therefore needed for:

- pharmacology scientists;
- drug repurposing groups around Australia to work with the national drug discovery centre led from the Walter and Eliza Hall Institute, and clinicians (immunology, microbiology, infectious diseases and clinical pharmacology) to enable drug options and provide knowledge about clinical trial design; and
- experts in translational drug development, including clinical pharmacologists, pharmacists and clinician trialists in infectious diseases.

Although the media commonly appear willing to portray a development in the laboratory as a miracle drug, it is a long way from rediscovering drugs in the laboratory to understanding their mechanism of action, dose–response relationship, inhibitory and effective concentrations, and efficacy and safety in humans; how these chemicals affect pathophysiology and people with the disease; and what doses to use and their timing. It is very important that new lab discoveries or revisited older work in cell lines, and underpowered poorly designed clinical trials, even if biologically plausible, are not assumed to mean a drug at a certain dose or regimen can be used in patients.

As a recent example in the COVID-19 era, President Donald Trump announced that the antimalarial hydroxychloroquine will be available to patients in the United States as it has shown "very, very encouraging early results" in treating COVID-19.[12] The announcement was followed by a number of letters of concern from clinicians and scientists,[13,14] and the US Food and Drug Administration has clarified that use of the drug in this context still requires a clinical trial before registration[15]— the appropriate method of developing a repurposed drug. While it is of interest to have a US President tweeting about use of a theoretical proposition to a world pandemic, hope must be tempered with clinical and scientific reality, and funding to deliver the translational knowledge. Specifically, we must be cognisant of the fact that use of these drugs may cause toxicity — in this case, fatal arrhythmias at the doses likely to be needed for antiviral efficacy, or toxicity without efficacy at all. Worse still, use of these drugs may reduce opportunities for a patient to receive another more useful therapy or stifle investment in potentially more beneficial options.

As a second similar example, two antivirals used in treating human immunodeficiency virus infection (lopinavir and ritonavir) were also touted as being a potential treatment for COVID-19. A clinical trial has now reported this combination to be ineffective and also cause toxicity;[16] recent media coverage has reported similar toxicity.[17] Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown in vitro activity against SARS-CoV-2 with supportive data from a recent pharmaceutical company funded, peer reviewed study of 61 severe COVID-19-positive patients.[18] Clinical improvement was observed in 36 of 53 patients (68%); further trials are currently underway.

A major issue highlighted by this study,[18] and one we wish to highlight as the drug repurposing field moves forward, is that the study design, including appropriate drug dosage and regimen for the new indication, must be based on sound biology, immunology, pharmacology and clinical pharmacology. The deliberations in the study around choice of dose are not provided. It thus remains unclear whether the lopinavir–ritonavir study[16] was negative because the drugs do not work or the pharmacology knowledge was inadequate, that is, the optimal dose and co-medications were incorrect. In their discussion, the authors state that the 50% effective concentrations (EC_{50}) suggest that there was inadequate dosing for this virus; for example, the EC_{50} of lopinavir in vitro for SARS-CoV ranged from 4.0 to 10.7 μg/mL, although other studies reported that lopinavir was inactive or that higher concentrations (25 μg/mL) were required for inhibition. The authors also question whether the EC_{50} value is an adequate threshold and whether unbound lopinavir concentrations in human plasma at the doses used were sufficient for inhibition of SARS-CoV-2; importantly, lopinavir exposure in this study was not measured. Critically unwell patients have different dose–exposure relationships to chronically unwell patients, owing to the role of third spacing and also effects of inflammation on drug clearance. It is therefore unclear whether the study was negative because the drugs do not work or rather the pharmacology knowledge was inadequate.

So how do we move the field forward rapidly? Firstly, we need an integrative, antiviral drug repurposing methodology. In the US, a systems pharmacology-based network medicine platform has been developed,[19] quantifying the interplay between the human coronavirus–host interactome and drug targets in the human protein–protein interaction network. Potential anti-human coronavirus repurposable drugs (eg, melatonin, mercaptopurine, sirolimus) were further validated by enrichment analyses of drug–gene signatures and human coronavirus-induced transcriptomics data in human cell lines. Three potential drug combinations were then identified (eg, sirolimus–dactinomycin,

mercaptopurine–melatonin, and toremifene–emodin).[19] This is a helpful shortcut to enable the clinical pharmacology platform to be developed for future clinical trials.

There has also been considerable discussion about angiotensin-converting enzyme 2 (ACE2) inhibitors being detrimental in COVID-19 treatment.[4] ACE2, a monocarboxypeptidase, is a homologue of ACE, negatively regulating the renin–angiotensin system by converting angiotensin (Ang) II to Ang-(1-7), thereby reducing Ang II (the primary effector of the renin–angiotensin system), decreasing vasoconstriction and increasing production of the vasodilatory Ang-(1-7). ACE2 is membrane bound, but the role of membrane bound versus soluble ACE2 is unclear. Human pathogenic coronaviruses bind to their target cells through ACE2, expressed by epithelial cells of the lung, intestine, kidney and blood vessels. As ACE2 is substantially increased in patients with type 1 or type 2 diabetes — who, along with patients with hypertension, are often treated with ACE inhibitors and Ang II type 1 (AT_1) receptor blockers — upregulation of ACE2 is common in some patient groups. ACE2 levels can also be increased by ibuprofen. It was therefore hypothesised that increased expression of ACE2, as occurs with treatment of many people with diabetes and hypertension, would facilitate infection with COVID-19.[20] For readers interested in this field, activators of ACE2 such as diminazene and XNT (1-[(2-dimethylamino) ethylamino]-4-(hydroxymethyl)-7-[(4-methylphenyl) sulfonyloxy]-9H-xanthene-9-one) reduce mRNA levels of renin, ACE, angiotensinogen, AT_1 receptor receptors and pro-inflammatory cytokines, and increase levels of the anti-inflammatory cytokine, interleukin-10. What occurs in humans with such chemicals in terms of toxicity, efficacy and dosage is not known.[21] In distinction, using a thorough knowledge of the biology, pharmacology and physiological of the renin–angiotensin system, the outcomes of a US multicentre, double-blind study of patients with COVID-19 requiring inpatient hospital admission randomised 1:1 to a pharmacologically plausible dose of losartan (an angiotensin receptor blocker) or placebo for 7 days (https://clinicaltrials.gov/ct2/show/NCT04312009) will be of significant interest, as these drugs are available now.

It appears that now is the time to focus on health care driven drug repurposing initiatives, with input from the pharmaceutical industry together with experienced scientists, clinicians and medicines regulators. This will enable us to more rapidly assess and test potentially efficacious drugs that will ease the burden of pandemics such as COVID-19.

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