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Drug Repurposing in the era of COVID – a market failure needing leadership and Government investment.

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ABSTRACT

"***The lesson from the thalidomide story is that no drug is ever understood completely, and repositioning, no matter how unlikely, often remains a possibility"*** [1]. The current COVID epidemic suggests urgent investment into repurposed drugs is timely [2].

Introduction

Human coronaviruses (HCoVs), including severe respiratory syndrome coronavirus (SARS-CoV) and 2019 novel coronavirus (2019-nCoV), cause pandemics. There are currently no effective drugs targeting 2019-nCoV/SARS-CoV, although there is plenty of media regarding potential drugs (such as hydroxychloroquine and azithromycin [3]) or drugs to avoid (such as non-steroidal anti-inflammatories and angiotensin converting enzyme inhibitors [4]). This advice can be more harmful than using the standard care for people with viral illnesses. Clinical groups have appropriately distanced themselves from such advice until more evidence is available [5] [6].

What is 'drug repurposing'?

Drug repurposing, a method for identifying new uses for approved or investigational drugs that are outside the scope of the original intended or approved medical use [1, 7], represents an appropriate alternate drug development strategy in the current era where it shortens the time and reduces the cost compared to de novo drug discovery. However it needs to be clear that a drug repurposing strategy requires time, funding and drug development knowledge, to understand how to use the drugs appropriately and prevent toxicity. Specifically, the required clinical pharmacology and clinical trial knowledge to support use, albeit smaller and shorter studies as compared to the full dossier needed for a new chemical entity (NCE), still need to be undertaken before appropriate drug prescribing or registration can occur. Sometimes however, only requiring bioequivalence studies are required. Registration for clinical use of a new strength, formulation and indication of Kapanol® required a single randomised controlled trial and a literature review only [8].

Although the methodology has been around for a while, the profile of drug repurposing has recently risen for 3 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 preclinical and early clinical development phases can be bypassed [1]. As such, drug repurposing presents a significantly faster pathway into Phase 2 trials in comparison to 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 approximately 12-16 years processing time and an investment of US$1-2 billion to achieve regulatory approval. In contrast, repurposing an 'old' 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 HCoVs 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 in [7]). A famous example was the incidental discovery that sildenafil (Viagra), originally used to relieve the symptoms of angina, was also effective for erectile dysfunction, receiving US Food and Drug Administration (USFDA) approval in 1998 [9]. Within the first 3 years of approval, nearly 8 million men were taking sildenafil in the USA alone with annual sales of US$1.5 billion [10]. Similarly, thalidomide first marketed in 1957 as a sedative 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 re-purpose for cancer treatment. Within four years, thalidomide was approved under the trade name Thalomid® for the treatment of multiple myeloma [11].

Relevance of Drug Repurposing in COVID era

Time is clearly the pressing need here. However, the elephant in the room is that research and development funding is often not available from the pharmaceutical industry, therefore significant Government investment is needed. The following is required to be supported by Government:

1. Pharmacology scientists
2. 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, ID and clinical pharmacology) to enable drug options, knowledge about clinical trial design.
3. Experts in translational drug development. These include clinical pharmacologists, pharmacists and clinician trialists in infectious diseases.

Although the media commonly appear willing to portray a development in the laboratory (lab) as a miracle drug, there is a long way from rediscovering drugs in the lab, to understanding mechanism of action, dose response, IC, EC and ED50, their efficacy and safety in humans, how these chemicals affect pathophysiology and people with the disease, and further - 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 recent examples in the COVID19 era, Trump announced the hydroxychloroquine will be available to patients as "*it has shown very very encouraging early results"* [12] followed less than a week later a number of letters of concern from clinicians and scientists [13, 14].

The FDA Chief has clarified that this hope still requires a clinical trial before registration, the appropriate method of developing a repurposed drug. Whilst it is of interest to have a US President tweeting about use of a theoretical proposition to a world pandemic, hope has to be tempered with clinical and scientific reality, and funding to deliver the translational knowledge. Specifically, we have to 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 be on another potentially more useful therapy or stifle investment into potentially more useful options.

As a second similar example, two antivirals used in HIV - lopinavir and ritonavir (Kaletra) were also touted as being a potential treatment for 2019-nCoV. A clinical trial has now reported this combination to be ineffective and also cause toxicity [15], recent media has reported similar toxicity [18].

One of the major issues highlighted by this study and one we wish to highlight as the drug repurposing field goes forward, is that the design of the study 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 if the Kaletra study was negative because the drugs do not work or the pharmacology knowledge was inadequate i.e. the optimal dose and comedications were incorrect. The discussion (summarised in [15]) states that the 50% effective concentrations (EC_{50}) suggests there was inadequate dosing for this virus e.g. EC50 of lopinavir in vitro for SARS-CoV has ranged from 4.0 to 10.7 μg per millilitre, although other studies reported that lopinavir was inactive or that higher concentrations (25 μg per milliliter) were required for inhibition. It also questions if 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. As critically unwell patients have different dose-exposure relationships to chronically unwell, due to the role of third spacing and also effects of inflammation on drug clearance. Therefore, in summary, we remain unclear if 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 drug discovery aspect, Cleveland (US) have implemented a systems pharmacology-based network medicine platform, quantifying the interplay between the HCoV– host interactome and drug targets in the human protein– protein interaction network. Here potential anti-HCoV repurposable drugs (e.g., melatonin, mercaptopurine, and sirolimus) were further validated by enrichment analyses of drug-gene signatures and HCoV-induced transcriptomics data in human cell lines. Three potential drug combinations were then identified (e.g. sirolimus plus dactinomycin, mercaptopurine plus melatonin, and

toremifene plus emodin) [16]. This is a helpful short-cut to enable the clinical pharmacology platform to be developed for future clinical trials.

There has also been a lot of media and other discussion about angiotensin-converting enzyme 2 (ACE2) inhibitors being detrimental in COVID treatment [4]. ACE2, a mono-carboxy-peptidase, is a homolog of ACE, negatively regulating the renin angiotensin system (RAS) by converting Ang II to Ang 1-7, reducing the primary effector of the RAS - Ang II, 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 angiotensin II type-I receptor blockers (ARBs), upregulation of ACE2 is common in some patient groups. ACE2 can also be increased by ibuprofen. It was hypothesised therefore that increased expression of ACE2 as occurs with treatment of many people with diabetes and hypertension would facilitate infection with COVID-19. For people interested in this field, activators of ACE2 such as diminazene and XNT (1-[(2-dimethylamino) ethylamino]-4-(hydroxymethyl)-7-[(4-methylphenyl) sulfonyl oxy]-9H-xanthene-9-one), reduces mRNA levels of renin, ACE, angiotensinogen, AT1 receptors, and proinflammatory cytokines and increase in the anti-inflammatory cytokine, IL-10. What happens in humans with such chemicals in terms of toxicity or any efficacy and different doses is not published [17]. In distinction, and using a thorough knowledge of the biology, pharmacology and physiological of the renin angiotensin system, the outcomes of a US multi-center, double-blinded study of COVID-19 infected patients requiring inpatient hospital admission randomized 1:1 to a pharmacologically plausible dose of losartan, an angiotensin receptor blocker or placebo for 7 days (Trial Registration number NCT04312009) is awaited with excitement.

It appears now is the time to focus on healthcare driven drug repurposing initiatives, including input from drug development and the pharmaceutical industry, together with experienced scientists, clinicians and medicines regulatory people to work together. This will enable us to more rapidly assess and test potentially efficacious drugs that will ease the burden of the pandemics such as the 2019-nCoV pandemic.

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