Repurposing existing drugs for COVID-19 a more rapid alternative to a vaccine, say researchers

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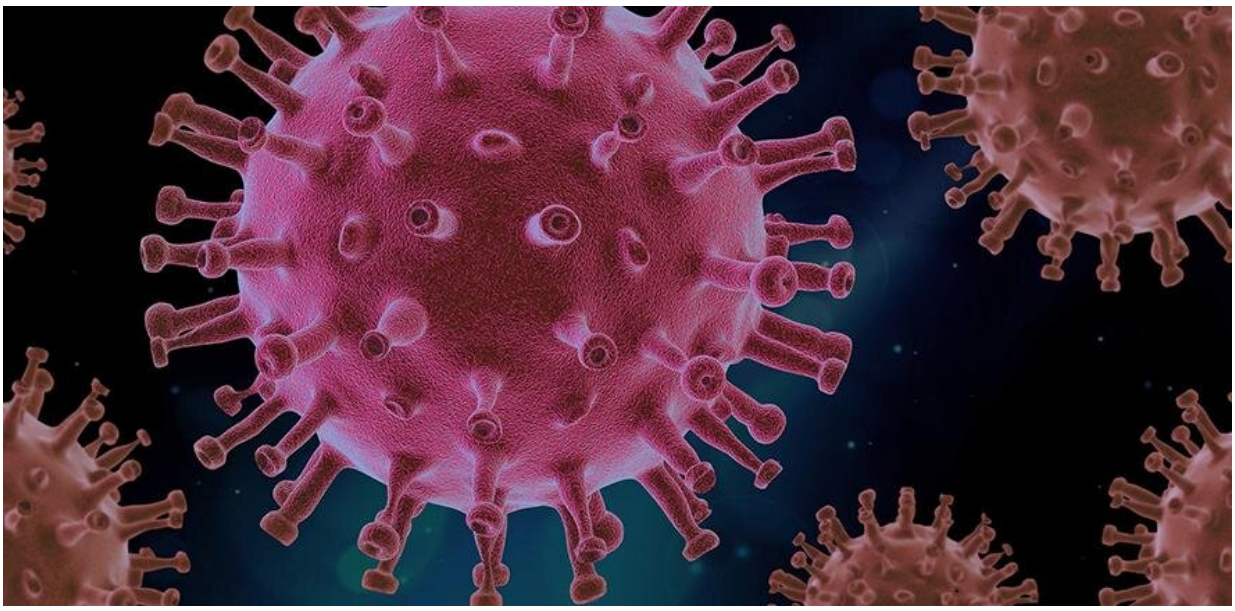

Coronavirus. Credit: PIRO4D

Repurposing existing medicines focused on known drug targets is likely to offer a more rapid hope of tackling COVID-19 than developing and manufacturing a vaccine, argue an international team of scientists in the *British Journal of Pharmacology*.

Since the emergence of the SARS-CoV-2 virus in late 2019, more than

3.5 million people are known to have been infected, leading to over 240,000 deaths worldwide from COVID-19, the disease caused by the novel coronavirus. The race is on to find new drugs to treat COVID-19 patients and to develop a vaccine to prevent infection in the first place.

A team of researchers representing the International Union of Basic and Clinical Pharmacology today say there will be no 'magic bullet' to treat the disease and argue that a multi-pronged approach is needed to find new drugs. They caution that an effective and scalable vaccine is likely to take over a year before it can used to tackle the global pandemic.

When a virus enters our body, unless we have already developed immunity from previous infection or vaccination, it will break into our cells, hijacking their machinery and using it to replicate and spread throughout the body. Often, the symptoms we see are a result of our immune system fighting back in an attempt to clear the infection. In severe cases, this immune response can become overactive, potentially leading to a so-called cytokine storm, causing collateral damage to organs along the way.

"Any drug to treat COVID-19 will need to focus on the three key stages of infection: preventing the virus entering our cells in the first place, stopping it replicating if it gets inside the cells, and reducing the damage that occurs to our tissues, in this case, the lungs and heart," said Professor Anthony Davenport from the University of Cambridge, one of the authors of the review.

The review looks at potential therapeutic drug targets—the chinks in the virus's own armour or weak spots in the body's defences. Two key targets appear to be proteins on the surface of our cells, to which SARS-CoV-2 binds allowing it entry—ACE2 and TMPRSS2. TMPRSS2 appears to be very common on cells, whereas ACE2 is usually present at low levels that increase depending on sex, age, and smoking history.

"As we know these two proteins play a role in this coronavirus infection, we can focus on repurposing drugs that already have regulatory approval or are in the late stages of clinical trials," said Professor Davenport. "These treatments will have already been shown to be safe and so, if they can now be shown to be effective in COVID-19, they could be brought to clinical use relatively quickly."

One promising candidate is remdesivir, a drug originally developed for Ebola. Although clinical trials found it to be insufficiently effective at treating Ebola, clinical trials in the U.S. have suggested the drug may be beneficial for treating patients hospitalised with COVID-19, and the FDA has now approved it for emergency use. There have also been promising findings from studies of monoclonal antibodies, but this type of drug is expensive to produce and therefore less likely to be scalable.

"While we're waiting for a vaccine, drugs currently being used to treat other illnesses can be investigated as treatments for COVID-19—in other words repurposed," said Dr. Steve Alexander from the University of Nottingham.

"There's unlikely to be a single magic bullet—we will probably need several drugs in our armoury, some that will need be used in combination with others. The important thing is that these drugs are cheap to produce and easy to manufacture. That way, we can ensure access to affordable drugs across the globe, not just for wealthier nations."

The team say that we need to move quickly to identify existing drugs that are effective in clinical trials so that we can begin treating patients as rapidly as possible, but also because cases are likely to fall during the summer meaning there will be fewer people who can be recruited to clinical trials ahead of an anticipated second wave of the disease in autumn. They estimate there are currently more than 300 clinical trials taking place worldwide, though many of these investigational drugs are

unlikely to be effective for widespread use because either it is not clear which part of the disease pathway they are targeting or they cause unpleasant side-effects.

They also advise patience for the promise of developing an effective vaccine against the virus anytime soon. Even after a new vaccine candidate has been shown to offer immunity against the coronavirus in humans, it needs to be tested in larger numbers of people to ensure it is safe to use. Manufacturing and distributing a vaccine at the scale needed to tackle this pandemic will also present significant challenges.

"Although there are a lot of vaccines being developed around the world, which we hope will be successful, it's still going to take a long time before those vaccines are shown to be effective and can be manufactured at the scale needed to make an impact," said Dr. Steve Alexander.

"Some of the vaccines may not work, so the more drugs that can be tested and the more we know about the targets, the more likely we are to get something which is effective. The very specificity of vaccines means they are limited in which viruses they can neutralise. The lessons we learn and the drugs we generate will hopefully provide a greater degree of protection, not just against the COVID-19 virus, but also against the next viral threat."

More information: S.P.H. Alexander et al. A rational roadmap for SARS-CoV-2/COVID-19 pharmacotherapeutic research and development. IUPHAR review "XXX", *British Journal of Pharmacology* (2020). DOI: 10.1111/bph.15094

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