ScienceTalk: Covid-19 treatments and their role in the war against the pandemic

Researchers and clinicians have been working hard to find the right mix of therapeutics to treat patients suffering from the disease. PHOTO: REUTERS

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SINGAPORE – The world is currently focused on the development of Covid-19 vaccines, with the expectation that these will protect the healthy population and allow for a return to normality.

However, it is important to bear in mind not everyone will respond equally well to a vaccine.

In addition, vaccines are not designed to treat a patient who has already been infected.

This is where therapeutics come in, to treat infected patients and restore them to health.

Researchers and clinicians have been working hard to find the right mix of therapeutics to treat patients suffering from the disease.

As Covid-19 is a novel viral infection, one of the quickest routes to treatment is to repurpose existing drugs that have been used to treat similar diseases.

These drugs have already been approved by regulatory bodies for other indications, therefore securing approval to use them against Covid-19 can be achieved faster than developing entirely new drugs.

Take the antiviral drug remdesivir, for example. First created to treat Ebola, it has been used as part of clinical trials for Covid-19 patients in Singapore, and has been granted conditional approval by the Health Sciences Authority (HSA) to be administered to severely-ill Covid-19 patients.

However, repurposed drugs have limitations in terms of specificity and efficacy.

Several drugs initially touted as effective against Covid-19 were eventually found to have minimal efficacy, or even adverse effects.

One approach to get high-quality evidence about the safety and efficacy of the drugs in an accelerated time frame has been multicentre randomised controlled trials involving large numbers of patients. These include the United Kingdom's Recovery trial, WHO (World Health Organization)'s Solidarity trial, and United States' NIH ACCT and ACTIV trials, which have recruited thousands of patients over two to four months.

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Indeed, these trials have shown that remdesivir and dexamethasone are effective therapeutics, while ivermectin, favipiravir and hydroxychloroquine are not.

Clearly, other therapeutic approaches besides repurposed drugs are required.

HARNESSING ANTIBODIES TO HELP THE BODY FIGHT COVID-19

A more effective, but lengthier and more difficult approach to Covid-19 therapeutics is to develop an entirely new antiviral drug. Such a drug would be specific to the Sars-CoV-2 virus that causes the infection, or capable of addressing the body's immune response to infection.

There are two broad categories of antiviral treatments: small molecules and large molecules, referring to the molecular size of the treatment particles.

Small molecule drugs are commonly used today, and are typically chemically based, and taken orally.

Large molecule drugs are a relatively newer approach based on biological protein, and typically administered via injections.

Convalescent plasma samples being tested for Covid-19 antibodies at the Blood Banks Pre-Patient Laboratory in Washington, DC. PHOTO: REUTERS

A potential treatment that offers much hope in the current pandemic is large molecule antibody-based therapy.

Antibodies are the body's soldiers, formed to fight off invaders from bacteria to viruses. They are generated by our immune system and have the potential to be used for both treatment and prevention, and can be mass-produced in the laboratory relatively rapidly.

One way to manufacture antibody treatments is to harness them from the blood of recovered Covid-19 patients, which is also called convalescent plasma.

While convalescent plasma can be used to treat Covid-19 patients, we have yet to see high-quality published evidence to draw definitive conclusions on its relative efficacy and safety.

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Moreover, the extraction and purification of convalescent plasma to produce neutralising antibodies is challenging, and large amounts of plasma are required to produce a uniform product in sufficient quantities, limiting the number of people who can be treated with this approach.

Data from comprehensive access programmes (where treatments which have not been approved yet are given to gravely ill patients) on convalescent plasma in the US also showed variability in the antibody levels that are potentially effective in improving survival in severe Covid-19 cases.

Antibodies can also be mass-produced in the laboratory.

Known as monoclonal antibodies (mAbs), they are identical immunoglobulins produced by a single clone of a white blood cell called the B-cell. They can serve as substitute antibodies that can enervate, enhance or mimic the immune system's attack on disease cells.

Recent advances in antibody engineering have allowed the rapid screening of potent antibodies against Sars-CoV-2 from patient samples.

The main target of Sars-CoV-2 neutralising mAbs is the surface spike glycoprotein that gives the coronavirus its characteristic crown-like spiky appearance. This protein pares the way for the virus's entry into host cells.

All mAbs currently in development for Covid-19 target this protein, and work to block the virus from attaching and entering human cells.

In addition to their use in antiviral therapy, antibodies are also being tried in a new treatment strategy which can help to correct the immune imbalance that is increasingly seen in Covid-19 patients.

The intention is to combine the use of what is called an immunomodulatory mAb, with an antiviral drug to calm the immune system, and target the virus respectively.

This will allow physicians more time to provide supportive treatment for severely-ill Covid-19 patients, and significantly improve clinical outcomes.

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Eli Lilly Covid-19 antibody drug gets emergency FDA clearance

Apart from large molecule antibody treatments, there are several efforts to develop experimental small molecule therapies which could be more effective when targeted at Covid-19.

These drugs work by inhibiting various enzymes or other viral proteins.

Ensoma University in the US, discovered and developed an orally available antiviral compound that could be a potential treatment for Covid-19. The compound has been exclusively licensed to Ridgeback Biotherapeutics which has initiated two clinical trials and is conducting further studies with an industry partner.

Several other groups such as biotechnology companies Asitrive Lifesciences and Selva Therapeutics are working on other targets like proteases (enzymes which break down proteins) but they are still in the pre-clinical stage and have not yet been tested on people, underscoring the difficulty in bringing small molecule drugs to the clinic.

GLOBAL EFFORTS IN DEVELOPING COVID-19 THERAPEUTICS

The pace of mAb development during the current outbreak has been unprecedented.

The standard time from discovery of an antibody to initiation of clinical trials has been reduced by nearly half, and it is possible that further large-scale trials of neutralising antibodies will be started.

Several Sars-CoV-2 mAbs are poised to enter clinical trials in coming months and many companies are joining global efforts to develop antibody therapies to treat Covid-19.

A few Sars-CoV-2 antibody treatments, including those from US pharmaceutical company Eli Lilly, US biotech companies Regeneron and Vir Biotechnology, have already started clinical trials.

The European Commission and the US National Institutes of Health have also started international public-private initiatives like the Antibody Therapy Against Coronavirus (Atac) and the Accelerating Covid-19 Therapeutic Interventions and Vaccines (Activ) respectively to pursue and accelerate Covid-19 therapeutic and vaccine efforts.

Preliminary reports suggest beneficial effects of mAbs.

Eli Lilly has reported initial results of a 12 per cent reduction in hospitalisation risk among patients who received its mAb, compared to those who received a placebo. The US FDA has recently authorised the emergency use of Eli Lilly's experimental Covid-19 antibody treatment for non-hospitalised patients with mild-to-moderate symptoms. South Korean biopharmaceutical company Celltrion reported positive safety data in its Covid-19 antibody phase 1 study.

Similarly, Israel biopharmaceutical company Kmaabs announced that initial interim results for a clinical trial involving its plasma-derived antibody treatment showed improvement of symptoms in Covid-19 patients.

However, these results are early-stage studies, and further large clinical studies will be needed to evaluate the utility of mAbs in clinical development.

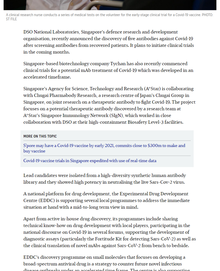
Meanwhile, it is critically important to monitor the emergence of antibody escape mutants – mutations which could elude antibody treatment and lead to reduced efficacy of the mAbs.

Researchers from the Global Initiative on Sharing all Influenza Data (Gisaid), a platform which pioneers the international sharing of all influenza virus sequences, have done pioneering work in this regard.

The CoVtracers mutations app in Gisaid's database allows researchers, clinician scientists and surveillance labs to rapidly screen their sequences for potentially interesting mutations to identify candidates for phenotypic (observable) changes or special epidemiological relevance.

SINGAPORE'S COVID-19 TREATMENT EFFORTS

Several research groups in Singapore are involved in the accelerated development of mAbs and therapeutics against Sars-CoV-2.



A clinical research nurse conducts a series of medical tests on the volunteer for the early-stage clinical trial for a Covid-19 vaccine. PHOTO: REUTERS

DSO National Laboratories, Singapore's defence research and development organisation, recently announced the discovery of five antibodies against Covid-19 after screening antibodies from recovered patients. It plans to initiate clinical trials in the coming months.

Singapore-based biotechnology company Tychan has also recently commenced clinical trials for a potential mAb treatment of Covid-19 which was developed in an accelerated timeframe.

Singapore's Agency for Science, Technology and Research (A*Star) is collaborating with Clingai Pharmabody Research, a research centre of Jiangxi Clingai Group in Singapore, on joint research on a therapeutic antibody to fight Covid-19. The project focuses on a potential therapeutic antibody discovered by a research team at A*Star's Singapore Immunology Network (SIgN), which worked in close collaboration with DSO at their high-containment Biosafety Level-3 facilities.

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Lead candidates were isolated from a high-diversity synthetic human antibody library and they showed high potency in neutralising the live Sars-Cov-2 virus.

A national platform for drug development, the Experimental Drug Development Centre (EDDC) is supporting several local programmes to address the immediate situation at hand with a mid-to-long term view in mind.

Apart from active in-house drug discovery, its programmes include sharing technical know-how on drug development with local players, participating in the national discourse on Covid-19 in several forums, supporting the development of diagnostic assays (particularly the Forttrack Kit for detecting Sars-CoV-2) as well as the clinical translation of novel mAbs against Sars-CoV-2 from bench to bedside.

EDDC's discovery programme on small molecules that focuses on developing a broad-spectrum antiviral drug is a strategy to counter future novel infectious disease outbreaks under an accelerated time frame. The centre is also supporting local biotechnology companies – Adan, Asmi Biosciences, and Rhea Pharmaceutical Sciences to test their compounds as possible treatments for Covid-19.

In addition, EDDC is working with DSO in the pre-clinical and clinical development of a potential Covid-19 therapeutic called ADD65, which is a Sars-CoV-2 neutralising mAb.

The safety and pharmacokinetics of ADD65 will be evaluated in healthy subjects during clinical studies in Singapore, followed by looking at the drug's antiviral activity in Covid-19 patients.

SPEED IS CRITICAL, SO IS SAFETY

Drug discovery and development is a process that takes time.

Despite best efforts, it will be some time before we can establish whether some of the new treatments work for patients.

It is paramount that the drugs themselves do not cause harm.

In spite of all these hurdles, why are so many scientists working tirelessly to develop therapeutics on very accelerated timelines?

It is because we recognise the imperative role that these treatments can play to save lives, alleviate suffering, and ease the burden on healthcare systems.

Infectious disease epidemics have plagued mankind for the longest time, and are not likely to go away anytime soon.

New pathogens continue to be discovered, and existing ones may evolve as well.

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With each battle however, we learn and adapt, and we develop new tools and technologies to enable safe and effective treatments and vaccines.

As the world tries to overcome the Covid-19 pandemic, and as scientists talk about the menacing "Disease X" yet to come, we can draw hope from the scale of cooperation that we are witnessing in Singapore and around the globe to develop therapeutics – for this pandemic and beyond.

About the authors:

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Correction note: The article has been edited for clarity.

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