Source: *The Straits Times,* pB6
Date: 2 June 2022

NUS researchers tap AI to improve effectiveness of Covid-19 drugs

It can determine optimal combination of antiviral drugs and correct dosage

Cheryl Tan

Researchers in Singapore are hoping artificial intelligence (AI) can help better fight Covid-19 infections, with AI determining the optimal combination of antiviral drugs and the correct dosage.

A recent study led by Professor Dean Ho, director of the Institute for Digital Medicine at the NUS Yong Loo Lin School of Medicine, has shown some promise.

He found that when antiviral drugs molnupiravir and Paxlovid were each combined with the protease-inhibiting drug YH-53, the mix was effective against the Omicron variant of the coronavirus in laboratory settings.

Prof Ho used his AI platform, known as IDentif.AI, to determine the combination and dosage.

The study involved two antiviral drugs that have been used to fight Covid-19 infections.

Currently, Paxlovid is about 90 per cent effective in preventing the need for hospitalisation or infection progression, when given within five days of symptoms appearing.

Molnupiravir is around 30 per cent effective, said Associate Professor David Allen, who was involved in the study.

He is the associate vice-president of health innovation and translation at the National University of Singapore (NUS).

Paxlovid comprises two drugs – nirmatrelvir, an antiviral medicine that targets the Sars-CoV-2 virus' 3CL enzyme, which the coronavirus needs to replicate; and ritonavir.

Ritonavir helps keep the antiviral active in the body at higher concentrations for a longer time to combat the virus.

Molnupiravir works by targeting an enzyme that the virus needs to make copies of itself, by introducing errors into its genetic code.

Prof Allen noted that while each drug has not shown diminished efficacy, some patients in Singapore and abroad have had an infection relapse after a course of Paxlovid, despite an initial response to the drug.

This suggests the Sars-CoV-2 virus was not completely eradicated by the drug, nor by the infected person's immune defences.

Prof Allen said virus resistance to the drugs has not been identified as the cause of relapses thus far, but it remains a looming concern.

He added that trials are under way to clarify if the course of Paxlovid should be taken for a longer period to prevent relapses.

Such drug resistance – caused by viral mutations – could undermine a drug's effectiveness when used to treat patients.

Professor Dean Ho and fellow researcher Agata Blasiak with their artificial intelligence platform IDentif.AI. ST PHOTO: GAVIN FOO

The team then asked if a combination of drugs could potentially decrease the chances of Sars-CoV-2 viral resistance.

Prof Ho and his team used IDentif.AI and explored different combinations and the most precise dosing needed, to amplify the effects of both molnupiravir and Paxlovid against Omicron.

Each drug combination was then validated against the Sars-CoV-2 virus in lab tests, before it could be considered for further clinical evaluation.

One of the combinations involved adding YH-53, a protease-inhibiting drug from Japan.

Protease-inhibiting drugs also aim to block the coronavirus from replicating.

The results so far have shown that both Paxlovid and molnupiravir, when combined with YH-53, had dose-dependent synergy.

This means that when used together at the right dosing, the drugs were jointly more effective against Omicron, said Prof Ho.

The team is further exploring broader dose configurations for these combinations to determine the most effective one against Omicron, with minimal toxic effects.

Prof Ho said another combination involved trialling molnupiravir with a cheap influenza drug known as favipiravir.

"Many clinicians had requested that we trial favipiravir, one reason being that the drug has been stockpiled in many countries for treating flu, as it is relatively inexpensive and well tolerated," he added.

There have been mixed results in clinical trials done in Russia and Japan on favipiravir's efficacy when used alone, but there were "interesting results" when mixed with molnupiravir in lab tests, Prof Ho noted.

The team's results corresponded with another study done in Paris in November last year.

That study showed that both molnupiravir and favipiravir worked synergistically, but favipiravir had to be given at "fairly high" doses, said Prof Ho.

The team had previously used the AI platform to determine the best drug cocktail against the Beta and Delta variants.

It saw molnupiravir combined with baricitinib, an anti-inflammatory drug.

Prof Ho and his team are currently in discussions with clinicians here on possibly conducting a pilot for a drug combination to improve its efficacy on immunosuppressed patients.

He said it would benefit these patients as they have weakened immune systems and may not be able to mount a strong defence against a Covid-19 infection even when they are fully vaccinated.

Further studies will also look at a potential Covid-19 pill, known as Shionogi, which is also a protease inhibitor that is currently in phase three clinical trials.

The studies will also examine the potential of Plitidepsin, a cancer therapeutic that could be effective against Covid-19.

tansuwen@sph.com.sg