

# Coronavirus: TCS uses AI for drug discovery

The researchers have identified 31 candidate molecules to target the main protease which helps the virus replicate

SHUBASHREE DESIKAN

Scientists from TCS Innovation Labs in Hyderabad are harnessing the power of artificial intelligence (AI) to identify new molecules which might have the potential to target specific parts of the novel coronavirus (SARS-CoV-2). Using new methods, they have identified 31 candidate small molecules, which may serve as inhibitors of the chymotrypsin-like protease, one of the key drug targets in the fight against COVID-19.

The results have been posted in a preprint repository *ChemRxiv*. Preprints are yet to be peer-reviewed and published in scientific journals.

## Target proteins

The genome of the novel coronavirus codes for several proteins that have crucial roles in entry of the virus into the host cell, its replication, assembly and host-pathogen interactions. Some of these proteins that help the virus perform its functions are common targets for drug developers. Among these

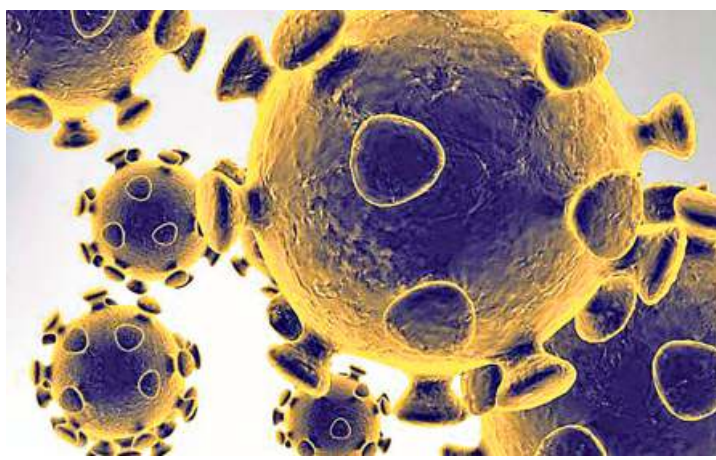
drug targets are the spike protein, which helps the virus attach itself to the host cell and enter it, and viral proteases which help it replicate.

## Role of viral protease

"The viral RNA synthesises two long polyproteins when it infects human cells via a human cell surface protein. The role of the protease protein is to cut the polyproteins to individual proteins, so that new viruses can be assembled. This is important for its replication and survival," explains Arijit Roy from the Life Sciences Division of TCS Innovation Labs, Hyderabad, in an email to *The Hindu*.

The chymotrypsin-like protease or the main protease primarily does the function of cleaving the polyprotein into proteins and the papain-like protease also aids in this process. The former was chosen as the drug target by the group for their research.

First, using a database of approximately 1.6 million drug-like small molecules from the ChEMBL database, the researchers trained



**Line of attack:** Prime drug targets are viral proteases which help the virus replicate and the spike protein. ■ AFP

the generative deep neural network model. As a second step, the network was re-trained with protease inhibitor molecules. This was done with a view to narrow the focus of the neural network on to a smaller subset of the chemical space. "We trained the system with all available protease inhibitors and asked the pre-trained model to produce more new molecules that

possess the characteristics of protease inhibitors," says Dr. Roy, who is an author of the preprint. "Finally, we checked how well these newly produced molecules can bind to the target protein – chymotrypsin-like protease of the virus."

Starting from a space of nearly 50,000 molecules, the team has made a short list of 31 candidates. Two of the designed molecules had

a high degree of similarity to Auranitamide, a naturally occurring antiviral-compound.

"Our aim was to create new molecules which possess the characteristics of protease inhibitors. We checked, whether these molecules retain all the drug-like properties. We also checked how easily they can be synthesised. All these were part of the AI-based model," says Dr. Roy.

Drug discovery is a complex process, needing several layers of validation before the drug may come in use. In this work, the researchers have brought down the time taken for the initial step of designing suitable candidate molecules for testing from years to just a week, reinforcing the power of AI in handling huge datasets.

## Clinical trials

"TCS has signed a MoU for collaboration with CSIR. The clinical trials will take time. The first step is the chemical synthesis and biological testing *in vitro*, followed by pre-clinical testing on laboratory animals," he says.

# Update on India's war against COVID-19

This involves detection, protection, prevention, prescription and, not the least, participation



## SPEAKING OF SCIENCE

D. BALASUBRAMANIAN

Since early March, our war against COVID-19 has been making steady progress in India. This has involved detection, protection, prevention, prescription and participation. Purposefully, private groups, industries, medical fraternity, scientists and technologists have joined hands together with the government in this war, both through financial contributions and participation by involving their R&D expertise. Government agencies such as DST, DBT (and its BIRAC), SERB, CSIR, ICMR, DMR, MHFW, DRDO, and others have announced several grants focusing on specific aspects related to this war, while the Tata Trust, WIPRO, Mahindra, the Wellcome Trust India Alliance and several multinational pharma companies have come forward in this joint effort.

## Detection, prevention, protection

The first thing is to detect whether a person has been infected by the virus. Since COVID-19 spreads within the moist part of the inner nose and throat, one measures the temperature of the individual around his nose and face, using a thermo-screening device (as used with arriving passengers in airports, or entering buildings and factories). Better devices of greater speed, detail and accuracy, such as whole-body scanners which depict body temperatures with colour codes on a computer monitor have come about from abroad. The National Disaster Management Authority (NDMA) has been offered 1,000 digital thermometers for screening, and 100 full-body scanners.

Clearly India needs these by the thousands. This need has triggered some computer industry people in India to make such body scanners here at home, a positive step. We hope these can come about at the soonest.

Once an individual is tested positive this way, it needs to be confirmed by doing a biological test to make sure that it is coronavirus infection. Until a month ago, we needed to import kits to do this. Today, more than a dozen Indian companies (most notably by the MyLab-Serum Inst.duo which can make several lakhs of these kits a week) have made them, each certified by the national body. This has rapidly expanded the scale of reliable testing rapidly across the country. Once tested positive, the patient has to be isolated and quarantined in appropriate centres. This has been done with remarkable speed and reliability, as mentioned below.

An important way to protect oneself against the invasion by the virus is to wear a mask. We constantly hear about how these are not available or sold at exorbitant cost. The notion that it is not always necessary is wrong. As the well known infection expert Dr. Jacob John of Vellore clarifies (*The Hindu*, April 2), it is vital that we mask ourselves as we move about in streets, since the virus is also airborne. Towards this, even as many entrepreneurs and firms across India have started making these at affordable costs, social media such as WhatsApp show the typical jaggaad way of using a baby diaper (unused!), male banian (unused!), the pallu of a saari, or dupatta and such. Happily enough, after the government clarifications and advice on this matter, more and more people are now seen to mask themselves. TV channels are also doing a useful service by inviting experts and asking them to offer relevant advice to people who have specific questions and doubts about protection in specific individual instances.

In this connection, a very recent piece of advice on protection has been given to people wearing glasses, (and also to eye doctors whom they consult) by my colleague Dr. Muralidhar Ramappa of the L V Prasad Eye Institute, Hyderabad. He says: (1) If you wear contact lenses, switch to glasses for a while. (2) Wearing glasses may provide a layer of protection. (3) Do not skip your eye exam, but take precautions. (4) Your eye doctor may recommend some more precautions. (5) Stock up your prescribed eye medicines, if you can and (6) avoid rubbing your eyes.

In addition to what the Central and State governments and notable private hospitals (for example, Apollo, Medanta and others) have set up as isolation and quarantine centres, several private agencies have helped set up these in Hyderabad, Bengaluru, Haryana, West Bengal, and helped equip them (for example, Infosys Foundation, Cyient, Skoda, Mercedes Benz, and Mahindra). These are some examples of how governments and private agencies have joined hands – as they say: We are all in this together.

Another exciting advance towards protection (and prevention of spread) has been the large scale production of incubators, ventilators and devices to monitor the individuals who have been placed in such quarantine centres. Mahindra has successfully made ventilators in large scale at affordable prices, and DRDO has come up with a special kind of tape in order to make patient protection gowns for clinicians, nurses and paramedics.

## Can India offer drugs?

While the possibility of a preventive vaccine for large scale use in India is at least a year away, we need to turn to molecular and drug-based approaches, in which India has great internal expertise and teams of excellent organic and biological scientists. Rightly, the government and some drug companies have turned to them to locally prepare and use several drugs (favilavir, remdesavir, avigen and such), and also modify them using well-known methods. Indeed, the CSIR has already roped in organic chemists and bioinformatics experts who can predict the 3D structures of proteins, so as to look for potential areas on their surface to which molecules can fit (lock and key approach). I have every hope that with such team efforts, India will come out with 'made in India' drug molecules to overcome this killing virus. Yes, we can.

Despite their full knowledge that millions of people have settled in cities and large towns, as daily wage labourers, far away from their families in villages, State and Central governments did not plan ahead for them, nor did they plan to reimburse their wages during the lockdown which blocked their getting back home. This led to a toss of social distancing and possible community spread. Social distancing is, alas, not in Indian culture, while herd mentality is. This could have been thought of by the social scientist advisors to the governments, and could have been avoided.

(Disclosure: it is important to note that I have chosen to highlight only some examples here. There are several more 'unsung heroes' across the states and the nation. I hope they will not be offended that I have ignored them.)

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# Novel coronavirus can be transmitted even before symptoms show up

The existence of presymptomatic or asymptomatic transmission makes contact tracing more challenging

R. PRASAD

A study of seven clusters in Singapore by Vernon J. Lee and others from the Ministry of Health, Singapore, provides some evidence that virus transmission to others (resulting in infection) can happen from one to three days before a person shows symptoms. But the World Health Organization maintains that the risk of getting infected with the novel coronavirus (SARS-CoV-2) from someone with no symptoms at all of Covid19 is "very low". And it says that it is assessing ongoing research on the period of transmission of the virus.

The transmission one to three days prior to onset of symptoms was seen in four clusters, while in three clusters the precise timing of transmission could not be established as the index case and the contacts lived together. The results were published in the *Morbidity and Mortality Weekly Report*.

Early detection and isolation of patients and contact tracing are important to contain the spread the virus. However, the existence of presymptomatic or asymptomatic transmission adds a new layer of complexity and challenge in tracing contacts.

The first cases in Singa-

pore was confirmed on January 23, and during the period from January 23 to March 16, 243 cases were reported of which 157 were locally transmitted. Of the 157 cases of local transmission, 10 (6.4%) cases have been during the period before the person who spread the virus to others showed any symptoms and hence were presymptomatic.

According to *Los Angeles Times*, a choir practice for 150 minutes in Washington on March 10 where 60 people participated left 45 people infected with the virus; two died from COVID-19. The county health officials concluded that the "virus was transmitted through the air from one or more people without symptoms".

## Evidence from China

This is not the first case where presymptomatic transmission has been seen.

Looking at the serial intervals (the number of days between symptoms onsets in a primary case and a second

ary case) in China, researchers had in a study suggested that 12.6% of transmission was presymptomatic.

Similarly, presymptomatic transmission of the virus has been documented in a nursing facility in Kind County, Washington. The re-

sults were published in the *Morbidity and Mortality Weekly Report*. In this case, a healthcare provider, who showed symptoms since February 26, tested positive on March 1 and seven others, too, tested positive for the virus by March 6. An investigation by the Atlanta-based Centers for Disease Control and Prevention (CDC) found that 23 of the 76 residents tested positive for the virus on March 13. Of the 23, 13 did not have any symptoms on the date of testing. Ten of the 13 asymptomatic residents developed symptoms seven days later and hence were presymptomatic at the time of testing.

Some cases in Singapore and other countries suggest that viral shedding can occur in the absence of symptoms and before symptom onset.

## Avoidance of grouping

"These findings suggest that to control the pandemic it might not be enough for only persons with symptoms to limit their contact with others because persons without symptoms might transmit infection. Finally, these findings underscore the importance of physical distancing in the public health response to the COVID-19 pandemic, including the avoidance of congregate settings," the authors write.

# 'Shutdown alone is not enough to break the chain'

R. PRASAD

In an unprecedented measure, India on March 25 began a country-wide shutdown for 21 days to cut the transmission chain of the novel coronavirus (SARS-CoV-2). Till Wednesday, India had adopted the containment measures of screening, testing, isolating and tracing contacts.

On March 25, *The WHO Director-General Tedros Adhanom Ghebreyesus* said: "Shutting down population movement is buying time and reducing the pressure on health systems. But on their own, these measures will not extinguish the epidemic. The point of these actions is to enable the more precise and targeted measures that are needed to stop transmission and save lives." Among other measures every country should take, the WHO chief said the production, capacity and availability of testing has to be ramped up, and a system to "find every suspected case at community level" has to be implemented.

**Giridhara Babu**, Head of the *Lifecourse Epidemiology at the Public Health Foundation of India, Bengaluru*, in an email to *The Hindu* explains how the shutdown along with testing can help flatten the curve.

Prime Minister Narendra Modi said 21 days of lockdown will help cut the transmission chain. Is that true?

Yes, it is the bare minimum period we require to be sure. Prime Minister Narendra Modi's call for a 21-day nationwide shutdown is an effort to break the chain



Giridhara Babu ■ SPECIAL ARRANGEMENT

of transmission. India's COVID-19 fight could make or break the global war. The "incubation period" means the time between catching the virus and beginning to have symptoms of the disease. Most estimates of the incubation period for COVID-19 range from 1-14 days.

A lockdown for 21 days would be a great social experiment which allows physical distancing. If followed strictly, it will contribute to delayed peak and to an extent, in flattening of the curve. Lockdowns may have to get extended in the areas with high transmission. It is important to identify such areas.

India has imposed the lockdown much earlier than many countries, including China, which failed to contain the initial spread of the virus. Although it started late, the Wuhan shutdown slowed the dispersal of infection to other cities by an estimated 2.91 days, delaying epidemic growth elsewhere in China. Other cities that

implemented control measures pre-emptively reported 33.3% fewer cases in the first week of their outbreaks compared with cities that started control later.

## Why were Wuhan and other cities under lockdown for two months?

In Wuhan, the measures started much later as compared to what India is doing. It takes that much longer when you start late. The initial outbreak of COVID-19 started in China and it was spread across before diagnoses and preventive measures could be established. Not just China, by then the virus had spread to other countries as well.

As a result, longer lockdowns of nearly two months were required in some regions. Before the interventions, scientists estimated that each infected person passed on the coronavirus to more than two others, giving it the potential to spread rapidly. But between January

16 and 30, a period that included the first seven days of the lockdown, the virus reproduction decreased from 2.35 to 1.05. The number of new daily infections in China seems to have peaked on January 25 just two days after Wuhan was locked down.

Epidemiologists say that measures implemented during this time did work. But China's mammoth response had one glaring flaw: it started too late. This delayed the measures to contain it.

In China, implementing the measures three weeks earlier, from the beginning of January, would have cut the number of infections to 5% of the total.

## Will complete shutdown for 21 days alone be enough to break the chain? Is it right to say that shutdown only buys time?

It is right to say that shutdown not only buys time but also decreases the overall burden and delays the outbreaks in most places. Stronger containment measures done together with these mitigation measures will ensure flattening the epidemic.

Mitigation measures or shutdown alone are not enough to break the chain of emerging COVID-19 pandemic. The containment strategies include identifying all cases which are positive and identifying their contacts, too. Once identified, cases will have to be isolated, and contacts will have to be placed under quarantine.

Mitigation is a precursory measure and if containment is also not done, it is not going to help. Both need to go hand-in-hand. Also, reviewing of States

where any single case is confirmed is need of the hour. Contact tracing of all those people who might have got the infection is highly needed. Only then will India succeed in current strategies to combat COVID-19.

## What then should be done during the lockdown?

Aggressive testing alone without mitigation doesn't help in breaking the chain of transmission. Without mitigation, the spread of the infection from one person to another will happen at a faster rate. We may find a certain number of cases doubling every week, also the number of deaths. The lockdown is an opportunity for us to rapidly scale up the capacity to have enough resources to manage, isolate and provide intensive care for those who needed it. Both measures going hand-in-hand could have a reasonable effect on flattening the epidemic curve.

The revisions in testing strategy involving accredited private laboratories too could not solve the issue since only a particular number of suspected can be tested in a day. With its high population, testing everybody in India is out of the question. Therefore, we need to follow mitigation measures. I recommend the syndromic approach now, wherein we need to manage every case of fever, cough and respiratory distress as COVID-19 unless otherwise proved. Once testing is scaled up, this can get better.

## Should India find all suspected cases in the community and test them, as per WHO's

## recommendation?

This virus effectively hides and quickly doubles. By testing only suspect cases, we might miss many of those who are asymptomatic during screening. The best strategy is to test among the SARI (severely affected respiratory infections) admitted in the hospitals and the OPDs of these areas. Many States have not even begun testing such cases. This is part of March 23 national recommendations. Therefore, strong national and local surveillance review is needed. There is a potential to cause illness suddenly in large numbers of people. Without having an idea of the total number of cases, it would become guesswork to plan for the future management of COVID-19.

## Can contact tracing, quarantining and testing of contacts of people who participated in the religious congregation in Nizamuddin alone be sufficient?

Tracing such contacts, quarantining them and testing such cases are definitely most necessary but not sufficient by themselves. Wherever hot spots are present, stricter enforcement of lockdown, even beyond what is already announced is needed. There should be enforcement of active surveillance in these areas for any flu-like illness, and people should be encouraged to self-report. Other measures such as providing accurate information and building awareness in the hot spots, especially on personal hygiene, hand hygiene and cough etiquettes are necessary.