Coronavirus: Front-line Fighters

S'pore labs join global race to learn about virus

Having made a diagnostic test kit, scientists here now hope to develop a possible cure

Audrey Tan
Science Correspondent

How does the fight against the spread of a disease begin, if the virus causing it is something that no one has seen or heard of before?

As with most mysteries, it starts with first seeking answers to the most basic of questions: What is it? How does it spread? How severe is the infection it causes?

Enter the scientists, the detectives of the microbe world.

Working in laboratories, away from the glare of the public spotlight, scientists are in a race against time to answer these questions – answers that others could build upon to save lives, improve patient care and boost public health through developing diagnostic test kits, drugs and even a vaccine.

As the Health Ministry's chief health scientist, Professor Tan Chorh Chuan, told the media last week: "To fight a war, you must know your enemy."

The mystery virus first surfaced in Wuhan, China, late last December, with those infected exhibiting pneumonia-like symptoms. Since then, the virus – now identified as Sars-CoV-2 (the disease itself is Covid-19) – has spread around the globe, including in Singapore.

Many unknowns remain about it, although scientists around the world were handed an important clue when Chinese scientists first uploaded the genome of the coronavirus on a public database last month.

It allowed scientists to determine that it was related to the one that caused the severe acute respiratory syndrome (Sars) in 2003.

The availability of the genome was also a good starting point for scientists in Singapore, paving the way for the development of a diagnostic test kit, enabling clinicians to quickly screen for patients infected with the coronavirus, with high accuracy.

Developed by experts from the Agency for Science, Technology and Research (A*Star) and Tan Tock Seng Hospital, the kit has been rolled out at a number of public hospitals here and also delivered to China.

A diagnostic test "flags" parts of the viral genome unique to Sars-CoV-2 in a patient sample.

Care is taken to ensure the genetic sequence flagged is the more stable part that is less prone to mutation. But this does not rule out mutation occurring, which viruses are prone to doing.

If it does, the test has to be modified quickly.

Says Dr Masafumi Inoue, co-developer of the diagnostic test kit, who is also head of the diagnostics group in the translational sciences division at A*Star's Experimental Drug Development Centre: "This is why we have to work closely with the A*Star researchers at the Bioinformatics Institute who study the genome of the virus.

"The latest analyses show that the virus has not mutated in our targeted region of its genome."

With Singapore already having the capability to quickly screen patients for the virus, the next step is to find out how they can be treated.

This is what Professor Lisa Ng, senior principal investigator at A*Star's Singapore Immunology Network, aims to find out.

She studies how the virus works, and how the human body reacts to it, by analysing samples from patients in Singapore, and by working closely with clinicians and healthcare workers who interact directly with patients.

"In the presence of a virus, the immune system will mount a protective response. By studying these mechanisms, it could pave the way for the development of therapies and even a possible vaccine," says Prof Ng.

Since the Sars outbreak, the research community has become more organised over the past 17 years, notes Prof Tan, and advancements in technology have also yielded new capabilities, such as rapid whole genome sequencing.

He adds: "R&D is integral to preparedness and effective response."

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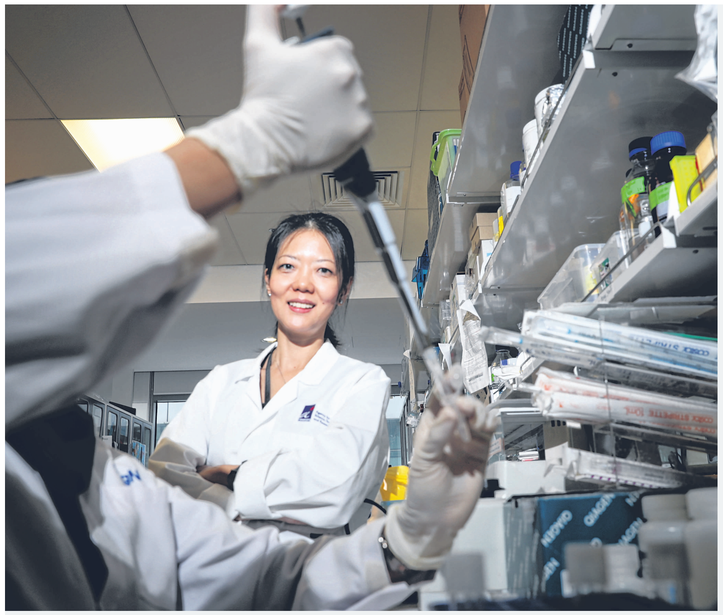
NO MUTATION SO FAR

The latest analyses show that the virus has not mutated in our targeted region of its genome.

DR MASAFUMI INOUE, head of the diagnostics group in the translational sciences division at A*Star's Experimental Drug Development Centre, on how the diagnostic test would have to be modified quickly if mutation occurs.



Professor Lisa Ng was part of a team at A*Star that developed a kit which could test for the Sars virus in patient blood samples in 2003. ST PHOTO: KELVIN CHNG

Search for cure like finding needle in a haystack: Investigator

Professor Lisa Ng, 46, is part of a team searching for a cure for Covid-19 – the "mystery" disease with pneumonia-like symptoms originating from Wuhan, China, that only recently got a name.

It is a noble task, but one that can feel like searching for a needle in a haystack, says Prof Ng, senior principal investigator with the Agency for Science, Technology and Research's (A*Star) Singapore Immunology Network.

Before a cure or vaccine can be developed for Covid-19, which has infected more than 67,000 people worldwide, scientists must first understand how the human body responds to the virus infection.

This is necessary in order to develop immune-based therapies that can stimulate the body's natural protective response against the virus, which provides a longer-term protection for the patient than drugs.

But studying how the body responds to the virus is a long process. The first step entails the search for immune system indicators – such as protein levels and the presence of antibodies – in samples taken from patients who have recovered.

As there can be thousands of such indicators present in a human body at any given time, it can be challenging to identify the specific elements of the immune system mounting the defence against the virus causing Covid-19, says Prof Ng.

The immune system comprises many different elements which all work together to rid the body of bacteria, parasites and viruses.

An important component of this system is antibodies, which are found in the blood. They detect the presence of a virus and latch on to the infected cell, flagging it so other elements of the immune system can kick in to destroy it.

When faced with a new or previously unidentified threat, the body will typically manufacture new antibodies to get rid of it.

"So, when it comes to searching for clues to how a person's immune system mounts a defence against this specific virus, which is so new, it sometimes feels like we are going in blind," Prof Ng tells Insight.

"But we are guided by certain basic understanding of biology, immunology and patient physiology," says the viral immunologist, who studies how humans respond to other vector-borne diseases such as chikungunya and Zika.

Though she had always been interested in the study of diseases in humans, Prof Ng says it was her experience during the severe acute respiratory syndrome (Sars) outbreak that changed her perception of the role of scientists in such outbreaks.

She was part of a team at A*Star that developed a kit which could test for the Sars virus in patient blood samples back in 2003.

At that time, the most common way to test for the presence of viruses that cause respiratory diseases in patients was to first collect nasal samples from them.

But Prof Ng had learnt that this method could expose healthcare workers to infection risk. In the early days of Sars, clinical sample collection equipment for infectious pathogens was not as sophisticated as it currently is.

The development of a diagnostic test that could detect the presence of the virus in blood samples – which have lower levels of the virus than nasal samples – was a breakthrough that also gave healthcare workers some peace of mind.

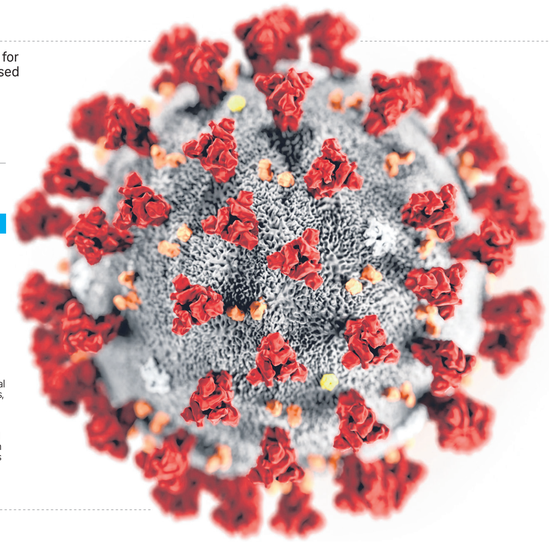
Prof Ng says: "That experience taught me that being a scientist is not just about hiding in the lab, looking at cells and then just about publishing papers about it.

"It's also about how we can help to improve and save lives."

Audrey Tan

Racing towards a cure

Scientists around the world are looking to develop a cure for Covid-19, the disease with pneumonia-like symptoms caused by a novel coronavirus originating from Wuhan, China. **Audrey Tan** speaks to Singapore scientists to learn more about therapeutics – the branch of medicine that looks at treatment methods used to alleviate or prevent a particular disease.



To tackle the current outbreak, scientists are looking to develop three broad categories of therapeutics.

TREATMENT

1 Antiviral drugs

How they work:

- These drugs work by preventing the development of the virus inside the human body.
- Just like a guided missile, these drugs target viruses at different stages of their life cycles in order to disable and block their development.
- By doing so, these drugs ultimately reduce the number of virus particles in the body, and prevent them from spreading.
- This could help shorten the length of symptoms and give the body's immune system time to fight off existing virus particles in the body.

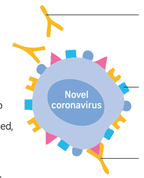
Current status:

- Most antiviral drugs are specific to one or, at most, a handful of similar viruses. A few are "broad-spectrum" and are able to target a wide range of viruses.
- As the novel coronavirus at the centre of the current outbreak comprises a single strand of genetic material known as RNA, antiviral drugs that work against similar RNA viruses are currently being tested.
- Singapore, for example, will likely be participating in a multi-country clinical trial testing a variety of antiviral drugs, including the combination pill lopinavir/ritonavir, which is used to treat the human immunodeficiency virus, which is also an RNA virus, said Associate Professor Hsu Li Yang from the National University of Singapore's Saw Swee Hock School of Public Health and programme leader for infectious diseases.

2 Monoclonal antibody therapy

How they work:

- Monoclonal antibody therapy essentially works by flagging the presence of the virus in the body, so that the immune system can work to get rid of it.
- The immune system comprises many different elements which all work together to rid the body of bacteria or viruses. An important component of this system is antibodies, which are found in the blood.
- When antibodies detect the presence of a virus, they latch on to the infected cell. By doing so, the presence of the problem cell is flagged, and other elements of the immune system can kick in to destroy it.
- In such therapy, laboratory-produced antibodies, known as monoclonal antibodies, are injected into the patient's bloodstream.
- They serve as substitute antibodies that mimic the immune system's attack on infected cells.



Current status:

- Monoclonal antibody therapy is a more specific type of treatment compared with antiviral medication.
- This is because scientists need to find out how exactly antibodies in an infected patient latch on to the virus cells. This latching on is usually done via a lock-and-key approach – the antibodies usually have to take on a certain "shape" before they can bind with the virus.
- As the virus is so new, research is still under way to understand this mechanism, before monoclonal antibodies can be generated in a laboratory, said Professor Lisa Ng, senior principal investigator from the Agency for Science, Technology and Research's Singapore Immunology Network.

PREVENTIVE

3 Vaccines

How they work:

- Vaccines are a preventive strategy that could inoculate the vast majority of the population before they get infected.
- There are two main types of vaccines – live vaccines and inactivated vaccines.
- Both types essentially involve injecting a tiny amount of a less- or non-infectious strain of the virus into the patient, to kick-start the body's protective response to it.
- That way, if the patient later gets infected by the virus, he would already have sufficient levels of antibodies in his blood to get rid of the virus before symptoms develop.

Current status:

- Scientists are now trying to understand more about the virus and how the human immune system responds to it. Such information will help in the development of a vaccine.

Sources: LISA NG, HSU LI YANG, CANCER RESEARCH UK
PHOTO: EPA-EFE SUNDAY TIMES GRAPHICS

The 'sixth sense' and long nights behind virus test kit

As merrymakers ushered in the dawn of 2020 with high spirits, infectious diseases experts in Singapore were on high alert. Their radars, honed by experience, had picked up on a series of pneumonia-like cases in Wuhan, China.

By the time the Chinese authorities alerted the World Health Organisation on Jan 31 that they had an outbreak of an unknown virus on their hands, scientists here were waiting to spring into action.

On Jan 2, Dr Masafumi Inoue, a scientist at the Agency for Science, Technology and Research (A*Star), sent a text to Dr Timothy Barkham, who works at Tan Tock Seng Hospital (TTSH), saying: "How are you, Tim, how's your holiday?"

It was not a run-of-the-mill greeting from a friend.

The two infectious diseases experts first met during the severe acute respiratory syndrome (Sars) outbreak in 2003, and over the past 17 years, have collaborated on the development of diagnostic kits for other disease outbreaks, such as the swine and avian influenzas.

In his message, Dr Inoue attached a link to a news report about the pneumonia outbreak in China.

Dr Barkham replied: "Lots of noise, but no diagnostic details. Happy New Year."

The conversation ended with the pair agreeing to meet soon.

Dr Barkham, 55, a senior consultant medical microbiologist at TTSH's department of laboratory medicine, tells Insight: "We are constantly on the lookout for possible new infectious diseases. And we get reports of possible outbreaks all the time. Often, they turn out to be isolated cases, but we are always waiting to see what's next."

No one knew what this virus was, how it related to other known viruses, or where it had come from.

With no reported cases in Singapore, there were no patient samples to work with.

But Dr Inoue had a "sixth sense" it would be significant. "Based on what I observed of past events, such as the 2009 swine flu and the 2016 Zika outbreak, I had a hunch," says the head of the diagnostics group in the translational sciences division of A*Star's Experimental Drug Development Centre.

On Jan 12, the full genome of the Sars-CoV-2 virus, which causes the disease now known as Covid-19, was uploaded onto a public database.

A virus' unique genome serves as a "fingerprint" to distinguish it from other viruses.

Once the genome was made available, scientists could determine that the coronavirus was related to the virus that caused the 2003 Sars outbreak which killed almost 800 people.

Scientists from A*Star and TTSH, including Dr Inoue and Dr Barkham, were now able to develop a diagnostic test kit to help clinicians at public hospitals diagnose infections with high accuracy.

Tests for 10,000 patients have also been delivered to China, as part of Singapore's efforts to help tackle the international outbreak.

To develop the diagnostic test, Dr Inoue's team first compared the genome of the new virus with that of related viruses, such as Sars, and identified parts of the genetic code that were unique to Sars-CoV-2.

The test flags these unique areas in a process known as polymerase chain reaction (PCR).

The diagnostic test kits were developed and rolled out in less than a month – a record, considering that a similar one for Sars took months – but its speed belied the effort that went into it.

Both men and their teams had many sleepless nights and countless discussions over text messages, e-mail and the occasional beer, to troubleshoot problems, fine-tune the product and overcome challenges such as disruptions in the supply of chemicals needed.

A day after Singapore diagnosed its first coronavirus patient on Jan 23 – a 66 year-old man from Wuhan who had stayed at a hotel on Sentosa – Dr Inoue and Dr Barkham met to discuss the development of the diagnostic kit at – of all places – Sentosa, where a food festival was taking place.

Asked if they had been afraid of getting infected, Dr Inoue says: "No. That's one important thing to note – that the risk of infection is very low in an open space."

Dr Barkham says the close synergy between the hospitals and research scientists was crucial in the development of the diagnostic test, and is the result of a close partnership that began in 2003.

He said: "At the hospitals, our aim is to deliver a service to patients. What may work well in a lab setting may not be that practical in the hospital. So we have to constantly give each other feedback on how to improve the diagnostic test so it will benefit patients."

This includes, among other things, being able to try out the diagnostic tests on real human samples, which could have other molecules or compounds that could disrupt the test, giving it false positive or negative readings, he says.

Also, for the readings from the PCR machine to be accurately used by clinicians in diagnosis, both teams worked to optimise them, carrying out the test at different temperatures to see which temperature registered the clearest reading.

Though there can be differences in expectations between scientists who develop the tests and those who implement them, both want the same thing: for the science to benefit the public.

Talks are now ongoing to scale up production of the diagnostic kits for distribution to other hospitals here, says A*Star.

Dr Inoue says it is important for Singapore to develop and manufacture its own diagnostic test kit in a disease outbreak. "We have the technology. And if we develop one ourselves, we won't be put in a situation where we have to rely on others to help control the outbreak."

Audrey Tan

Dr Timothy Barkham from Tan Tock Seng Hospital and Dr Masafumi Inoue from the Agency for Science, Technology and Research worked with other scientists to develop a test kit to diagnose infections with high accuracy. ST PHOTO: JASON QUAH

The measures taken here are based on experience and data from previous viral outbreaks which have been effective, says Professor Tan Chorh Chuan, chief health scientist at the Ministry of Health. ST PHOTO: KELVIN CHNG

More prepared, less fearful now than during Sars

Joyce Teo
Senior Health Correspondent

The chief health scientist at the Ministry of Health (MOH), Professor Tan Chorh Chuan, sheds light on the measures Singapore has in place to fight the coronavirus outbreak.

***Q** There are fears that the coronavirus is airborne. Is this the case?*

A We really need to look for more data. Infections that spread mainly by airborne transmission tend to be more infectious than what we see now – it would be conditions like chicken pox.

We reference how coronaviruses tend to be spread, and it's usually through droplets and hand contact.

In Wuhan, there are many reasons it spread so quickly. The whole city was isolated and conditions are very different, so it may not be representative of where we are at in Singapore.

***Q** What are the changes you have made to your lifestyle now that there is local transmission?*

A I continue to do what I normally would do, except I am much more careful about keeping my hands clean. It'll actually be hard to live normally if we went way beyond that, because we will always be in situations where we come into contact with people.

There's uncertainty with a new virus when it first appears. There is what we already know from other types of similar viruses and there's a period when concerns are raised, fears go up. We need to try to understand these issues and how best to address them.

It's part of confronting a new virus that we have not encountered before and learning as quickly as you can about it.

In the meantime, the practices that we are putting in place are based on experience and on data from previous types of viral outbreaks which are similar and which have been effective in those circumstances.

***Q** As MOH's director of medical service from 2000 to 2004, you were responsible for leading the public health response to the 2003 Sars epidemic. What's the key difference now?*

A People are more confident and less fearful. During Sars, many people and healthcare professionals were very fearful. I was very fearful because we had never experienced an outbreak like it before and our systems were not as prepared.

Today, for instance, there is proper use of PPE (personal protection equipment), measures to separate potentially infected patients from those who are not, working in split teams.

When Sars first started, we didn't have enough protective equipment so I had to ration the supplies. Now, we are well prepared in that regard.

Research has also improved globally and in Singapore – we can sequence much faster and develop diagnostic kits much faster. All this speeds up our understanding of this virus at a much faster rate.

During Sars, we had to manage the first five weeks without a diagnostic kit. Can you imagine trying to control an outbreak without a diagnostic kit?

***Q** What did we learn from the Sars epidemic when it comes to handling infected patients?*

A I remember, early on in the Sars epidemic, there were groups that recommended that wearing one set of masks was not good enough, you have to wear two sets.

But when we managed all the patients within Tan Tock Seng Hospital and all the health professionals were properly trained and used protective equipment, we saw that no other healthcare workers were infected.

So, you definitely didn't need to wear two or three masks. In fact, what we are using now for PPE is sufficient to protect health professionals.

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