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DETECTIVES

The university in a global battle against SARS

DISEASE DETECTIVES

The patient, Liu Jianlun, exhibited a raging fever, warned he was highly infectious, and died shortly after, giving no further clues. Puzzled doctors turned to experts at Hong Kong University.
Dr. Liu's symptoms were similar to avian flu, yet HKU scientists — some of the world's foremost researchers on the disease — were stumped. The deceased's tissue samples not only tested negative for bird influenza, they did not show traces of any well-known virus or bacteria, said Yuen Kwok-yung (M BBS '81, M D '98), head of the microbiology at HKU's Faculty of Medicine and chair of infectious diseases. Knowing that the deceased had come from Guangdong, an area experiencing a pneumonia outbreak, "I thought, oh no, here's trouble," said Professor Yuen.

So began the university's continuing battle with a disease that would draw on its intellectual and physical resources and involve everyone from a world-famous AID S researcher to animal experts and even the staff soccer team. It would put researchers — animal experts and even the staff social workers. The illness spreads to household contacts, infecting over 300 and killing five.

Mystery in China

February 2003

Outbreak of a respiratory illness strikes Guangdong, China, infecting over 300 and killing five. The illness spreads to household members and health care workers.

FEB.

March 3

Canada Bound

A 78-year-old woman dies of SARS in Toronto after having visited Hong Kong in February.

MARCH

March 27

Coronavirus Uncovered

Hong Kong University researchers led by Professor Malik Peiris report they believe SARS is caused by a coronavirus.

April 19

Results Published

University research (Coronavirus as a possible cause of severe acute respiratory syndrome) is published in the international medical journal, The Lancet.

APRIL

May 11

Collaboration

World-renowned AIDS researcher David Ho, with university scientists, announce promising experiments with peptides that may block the SARS coronavirus from propagating.

MAY

The university did not keep their potentially lucrative discovery to themselves

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The team's findings were later backed by the World Health Organization and the World Health Organization's China branch. The researchers knew that if the anti-virus antibodies were produced, it would indicate a single infection - but they weren't sure. After all, scientists knew the coronavirus to be a relative weak virus, the cause of common colds. It was only after Leo Poon, another member of the team, began isolating genetic fragments and running genetic sequencing tests that the team was certain that it was the coronavirus. Evidently, this variant of the coronavirus was a new member of the family. "It's not every day you find a new virus," Professor Peiris told the South China Morning Post.

The next step was to prove what the researchers had in their test tubes. They isolated genetic fragments and ran genetic sequencing tests that the team was certain it was the coronavirus. They developed the first significant weapon against SARS by creating an eight-hour diagnostic test for the virus. But it came amid mounting fears as the disease claimed more victims. On the same day HKU announced its diagnostic test, Hong Kong officials closed schools for nine days and quarantined more than 1,000 people who had close contacts with infected patients.

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Cacking the Genetic Code

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It was clear that the HKU doctors needed to develop better tests and start work on a vaccine. To do that, they had to crack the genetic code. Vice-Chancellor Tsui, a genome expert, called in the animal experts: Frederick Leung, Dean of the Faculty of Science and A sociate Professor in the Department of Zoology, and his

NOTE: Chan responded to the case according to a protocol that had been developed for such emergencies by the HKU Task Force on SARS, headed by Dr Kitty Chan, Director of the University Health Service.
A New Mission for Dr David Ho

David Ho (何大一), of the Aaron Diamond AIDS Research Center in New York, is widely credited with pioneering a “cocktail” therapy for the treatment of AIDS. He has set himself a new challenge: working with HKU to design a drug that would block the spread of the SARS virus. His own description of the work, from a May 11, 2003 press conference at Hong Kong University:

“Since three weeks ago, my colleagues, including Dr Zhang [Linqi], have been working hard on two specific areas. One is to make vaccines with the team here [HKU] ... but we also decided to focus on one treatment, to see if we could specifically design something that would block the SARS virus. This comes because of our experience with the HIV virus ... Due to the good work of Richard Kao and Leo Poon - they have been slaving away in the lab day and night to test inhibitors on the SARS virus (this not on animals, but the very first test on tissue culture) to see if peptides block the ability of the SARS virus to get inside the cell - we are pleased with the result. Several peptides actually protected the cells from the SARS virus; the concept is validated. There is obviously lots more work ahead, but it’s a nice first step. From here there will have to be many more experiments. Hopefully, we can push this forward to testing on animals some time.”

Dr L Leung’s team confronted a formidable task. They started with only a 182-unit sequence of base pairs, the building blocks of DNA and foundation of all living things. Most coronavirus sequences have 30,000 base pairs. Their challenge was like putting together a massive jigsaw puzzle - with the clock ticking away.

The first step was “landing” onto the genome. In general, scientists first find genes that match other known viral sequences from other species. However, the first 182 base pair showed that this virus was so new and only had about a 5% match with all known sequences. It was a “maddening process,” said Dr L Leung, “as you just didn’t know what piece fits with what.”

As Dr L Leung and his team laboured, the situation in Hong Kong and beyond grew increasingly grim. By April 2, SARS had infected 2,200 people in 17 countries, with 78 fatalities. Hong Kong officials closed schools for another two weeks as local cases topped 700. The WHO issued a travel warning advising people to avoid Hong Kong and southern China. Swiss authorities barred Hong Kong traders from attending a well-known jewelry exhibition.

Dr L Leung and the genetic-sequencing team realised that this coronavirus displayed only the barest similarities with other viruses in its class. It was something no one had ever seen before. The team went into overdrive, arriving early and staying late, seven days a week, sometimes tolling till sunrise.

It was a steep learning curve for Leung’s weary students, who said the research helped them develop new techniques in genetic sequencing. They discovered how to get more ribonucleic acid, or RNA, from virus samples so they could do more tests with less material. They also found new ways to “launch” extracts of RNA from the virus, which helped fit the first puzzle pieces together faster. Then, on April 13, the news came that a team from the British Columbia Cancer agency had completed genetic mapping of the virus. Two days later, the United States Centers for Disease Control and Prevention (CDC) also announced they had mapped the genome. It was a blow to the Leung team, who felt they were close to cracking the code. “I just wanted to go home,” said Carol Chau, one of the students. But Dr L Leung reminded his team that there could be differences between the viruses in Hong Kong and Canada, and more than one sequence might be needed to get the virus under control. “Finish what we started,” he told his team. On April 16, the HKU team finished mapping the virus and uploaded it into the Gene Bank at the National Center for Biotechnology Information in the United States. Later, both the Canadian and US groups edited their sequence to match the HKU sequences.

Te A moy G ardens Puzzle

With all this unfolded, members of the university’s Faculty of Engineering were trying to find out how the virus spread so rapidly at A moy G ardens - a Kowloon housing estate which saw over 300 SARS infections and resulted in more than 35 deaths. It fuelled widespread fears that the virus was not containable.

Were buildings in other densely populated areas of Hong Kong similarly vulnerable?
The HKU team included specialists in mechanical engineering, building services, fluid dynamics and air pollution. They sought to “provide numbers, not conjecture,” said Joseph Lee, Dean of the Faculty of Engineering. But initially there was much conjecture about the A moy G ardens outbreak. Two popular theories - viruses transported urine from neighbouring construction sites, or germ-carrying rats - did not explain why 70% of the infections were concentrated around Flats 7 and 8 in Block E. Had the virus been transmitted in the ways suggested, infections would have been more evenly distributed, Lee noted.

H is group created computer simulations of conditions in the residents’ homes. There were multiple variables to account for: wind flow temperature and humidity differences both inside and outside the block; with fans on or off, and windows open or closed. They examined the block floor by floor and surmised that the building’s construction design, combined with weather conditions, contributed to the virus’s spread.

One hypothesis was that the virus was ejected from a severely-contaminated bathroom through the exhaust fan into the re-entrant area of the building. W ith no proper ventilation to disperse it, the virus laden air slowly rose within the lightwell through a “chimney effect” and entered other apartments through open windows.

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Using technology originally developed for testing construction quality in the building industry, the team, which included C R Kumana, Chair of Clinical Pharmacology and Therapeutics in the Department of Medicine, and Dr Chan, investigated the Amoy Gardens outbreak by modeling the buildings’ toilets and pipes. They sought to provide numbers, not conjecture.

At first, recalled Dr Chan, things were “frustrating.” The team had high failure rates because camera snapshots of body-surface temperatures differed from internal core temperatures that were more traditional thermometers measured. To overcome the glitch they enlisted the help of the university staff soccer team. The researchers tracked the sweaty sportsmen’s temperature decline from side angles, discovering that they could get more accurate readings from around the temple and ear region than from the body. The team is now expanding its work, on a D apartment of H room-supported project with the Tsinghua University’s Research Institute at Shenzhen, verifying the application of infra-red thermography at Hong Kong’s border checkpoints.

Pursuit of a Cure

Back in the labs, Dr Leung’s gene-sequencing team was happy to have mapped the SARS genome in near-record time, with fewer people than the North American teams and less sophisticated equipment. But other challenges loomed, like improving the diagnostic method for SARS, and making faster and more accurate tests. A very big all, the researchers were acutely aware of the need to develop a vaccine. The coronavirus belongs to a class of RNA viruses, which, like HIV, are notorious for their rapid mutations. That will complicate the search for a vaccine.

H e d i came in the form of AIDS researcher Dr Hsu C. T. The university already enjoyed a close relationship with Dr Hsu. Last July H KU and the A nton Diamond AIDS Research Center - where Hsu is Chief Executive - jointly set up an AIDS institute at HKU’s medical complex. This May, Dr Hsu, prompted by what he saw as similar characteristics between the SARS virus and HIV, e-mailed the university asking what he could do to help.

Dr Hsu, who was named Time magazine’s 1996 “Man of the Year” for pioneering the use of drugs which inhibit the spread of the HIV virus, flew to Hong Kong with a team that included Beijing native and immunologist Zhang Lings. The team believed that they could use their experience with HIV to make inhibitors which would block SARS interaction.

Fighting Fear With The Truth

It was a schoolboy’s April’s fool joke that no one laughed at. The prank, a website rumor that Hong Kong would be sealed off to contain the epidemic, sparked panic throughout the territory. People shoved into supermarkets and emptied the shelves. The incident made it clear that the SARS outbreak was creating a ripe environment for rumor and hysteria.

Cecilia Chan, Director of HKU’s Centre on Behavioral Health, knew that Hong Kong needed a platform where people could get reliable information - and needed it fast.

Together with Albert Chau, Director of the General Education Unit, she set up a website and telephone hotline to distribute information about SARS. The team also established a phoneline tutorial service for home-bound students, amid the Hong Kong-wide shutdown of schools. Thus was born the “We Are With You” Movement. Wherever they turned in the university community, the Chan-Chau team found help. “No one turned us down,” said Chau. “Everyone wanted to help.”

Professor Chan and Dr Chau later sought to turn the SARS acronym on its head. It didn’t have to mean Severe Acute Respiratory Syndrome. Instead, it could mean:

Sacrifice

Appreciation

Reflection

Support

Sustainable Actions for Rejuvenation of Society

In the first week of April, an online program offering news and information about SARS and tutoring services to secondary students began operation. Some 200 student volunteers were taking the first calls from worried parents and students seeking help with assignments. The volunteers were trained by faculty members on ways to solve callers’ problems in the shortest time and to offer referral information for tougher cases.

The “We Are With You” Movement also produced videos with information on SARS, where experts of various backgrounds provided advice on coping.
In lab tests Dr Zhang experimented with creating synthetic peptides, or protein inhibitors, that could block the ability of the SARS virus to get inside cell cultures. To his delight, he discovered several peptides actually did so, gumming up the process so the virus was unable to fuse with cell cultures.

Since tests have yet to be conducted on animals, let alone humans, scientists are still cautious about the potential applications. Still, they hope the discovery will lead to the creation of “designer drugs,” said Professor Peiris, that can “target the vulnerable stage” of the SARS virus’s life cycle. At present, the most effective drug in the anti-SARS arsenal is the anti-viral drug Ribavarin, which was not designed to treat SARS, but hepatitis and other respiratory diseases. Taken in large doses, it has serious side effects, causing birth defects and the bursting of red blood cells.

The laundry list of challenges to be met remains dauntingly long. Uppermost on researchers’ minds: improving diagnostic tests so that speedier and more accurate results can be obtained. Making anti-viral drugs specifically designed to combat SARS. Creating a vaccine. “All this cannot be done without money, political conviction and support from the overall community,” says S K Lam (MBBS ’67; MD ’75), Dean of Medicine. “We are dealing with a disease without textbooks or journals,” he said, “we are writing the chapters as the disease unfolds itself.”

Reporting by journalism students: Tim Lee Master, Patricia Cheng and Wong Chun-fai

In hospitals, labs and offices around Hong Kong, many of our members laboured long and mightily in fighting against SARS. The examples are numerous, and include:

1. Dr Lo Wing-luk (勞永樂) (MBBS ‘79)
   President of HK Medical Association

2. Dr Kenneth Tsang (曾華啓)
   Associate Professor of Department of Medicine
   Physician-in-charge of SARS wards in Queen Mary Hospital.

3. Dr Leong Che-hung (梁智鴻) (MBBS ’82)
   Chairman of Hospital Authority

4. Dr Seto Wing-hong (司徒永康)
   Chairman of Infection Control, Queen Mary Hospital; Honorary Professor of HKU Department of Microbiology

5. Dr Ko Wing-man (高永文) (MBBS ’81)
   Director of Professional Services and Affairs, Hospital Authority; Acting Chief Executive of Hospital Authority when Dr Ho Siu-wei suffered from SARS.

6. Professor Leung Ping-chung (梁景輝) (MBBS ’83, MS ’88, HonDSocSc 2001)
   Chairman, Institute of Chinese Medicine Management Committees; Professor of Orthopaedics & Traumatology, CUHK

7. Professor Sung Jao-yiu, Joseph (沈祖堯) (MBBS ’83)
   Chairman of Medicine and Therapeutics and Associate Dean of Faculty of Medicine, CUHK; Recently appointed by HKU as Honorary Professor of the Faculty of Medicine

Both Dr Ho Shiu-wei and Dr Fung Hong were infected with SARS and later recovered.

Related Websites

- University SARS Web site
- Faculty of Medicine
- Yu Chun Keung Medical Library
- Clinical Trials Centre
- We Are With You Movement
- Mapping Atypical Pneumonia (SARS) Analysis of SARS data
- SPACE We Shall Overcome
- SARS Fund (Donation details)

Related Websites

- http://www.hku.hk/sars/
- http://www.hku.hk/facmed/
- http://www.hku.hk/ctc/
- http://www.hku.hk/gened/withu/
- http://facarts.hku.hk/georg/sars/
- http://www.hku.hk/sarsfund/

Photos: Ming Pao