Working at the epicenter of the SARS epidemic, a small group at the University of Hong Kong is at the forefront of the investigation into this mysterious disease

Up Close and Personal With SARS

HONG KONG—For a virus hunter, Hong Kong in the spring of 2003 was the right place and the right time. And virologist Malik Peiris, colleagues around the world are saying, proved to be the right person. Peiris and his team at the University of Hong Kong (HKU) were the first to isolate the agent causing severe acute respiratory syndrome, or SARS, early in the week of 17 March—although at first they didn't know exactly what they had. And the Hong Kong lab was one of three groups that several days later—and within hours of each other—identified the culprit as a new coronavirus. Peiris and his team were amused and a little irritated when one of the groups issued a press release on 24 March touting its detective prowess without crediting the other two groups. But having to share some credit doesn't detract from the pride Peiris feels "in the group and the job we did."

Regardless of bragging rights, fellow disease detectives say the contributions of the HKU group highlight the importance of having a first-rate research team on the ground near the source of an outbreak. "Without Malik, we would know much less about SARS," says Christian Drosten, a virologist at the Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany, whose lab is part of a global network seeking the cause of SARS under the sponsorship of the World Health Organization (WHO). Virologist Klaus Stöhr, the network coordinator, simply says that Peiris "is one who produces and delivers."

Peiris landed in that place and time through a circuitous route. Born and raised in Sri Lanka, he earned his Ph.D. at Oxford University's Sir William Dunn School of Pathology in the U.K., where he impressed the faculty both scientifically and personally. Siamon Gordon, a cell biologist who was a mentor and collaborator during Peiris's student days at Dunn in the 1970s, says, "He had a broad interest in a biological understanding of infectious diseases, not just a narrow interest in viruses." And Gordon adds, "He was always a gentleman, in the original sense of the word," remaining unruffled and gracious even under pressure. Colleagues say he is also a man of few words. "He doesn't talk a lot, but whenever he speaks, people listen, and whatever he says is waterproof," says Stöhr. Both traits are serving him well in the friendly but competitive race to understand SARS.

After academic stints in Sri Lanka and the U.K., Peiris landed in the microbiology department at HKU in 1995, just in time to see firsthand the frightening potential of the 1997 avian flu outbreak. The virus killed six of the 18 people it infected—more than three times the mortality rate of typical flu epidemics. Peiris set aside his research and pitched in, helping develop a diagnostic test for the causative H5N1 virus. It was later determined that infection spread from chickens to humans but not between humans. The outbreak was contained by slaughtering every chicken in Hong Kong.

The incident hooked Peiris, who wanted to understand how the disease jumped from an animal reservoir and why it proved so lethal. He refocused his research on influenza, the disease interface between animals and humans, and the interaction of viruses and the human immune system.

The high mortality rate and fears that the H5N1 virus—or the next one—might develop the ability to spread from human to human also alarmed health authorities around the world. Flu expert Robert Webster, who had been tracking emerging flu viruses from his lab at St. Jude Children's Research Hospital in Memphis, Tennessee, won a grant from the U.S. National Institutes of Health to regularly screen healthy animals in Asia for viruses posing a pandemic threat. The surveillance work in Hong Kong was subcontracted to the Influenza Research Group within the microbiology department at HKU. The group was originally headed by virologist Kennedy Shortridge, who retired last year, leaving Peiris in charge.

The hunt for viruses and Peiris's interest in the animal-human interface fit in with a decision made at about this time by the department to concentrate "our limited resources" on emerging diseases to maximize the group's scientific impact, says department chair Yuen Kwok-Yung.

In January, Peiris's group was ready. The researchers heard rumors of an unusual outbreak of pneumonia in Guangdong Province, which borders Hong Kong. "The first thing going through our minds was that the H5N1 virus had possibly acquired the ability to transmit from human to human," Peiris says. The preceding December, several geese in Hong Kong parks had died from the H5N1 virus. The influenza team was already working overtime screening samples from flu patients for evidence of H5N1 infection (*Science*, 7 March, p. 1504).

By early February, the Hong Kong Department of Health and the Hospital Authority had started an intensive surveillance effort to spot unusual cases of severe pneumonia. Peiris's lab was charged with identifying the cause. The H5N1 hypothesis got a boost in mid-February when that virus was confirmed as having killed one member of a

Location, location. Malik Peiris says his group, which discovered the causative agent of SARS, was in the right place at the right time.

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family that had visited Fujian Province and having sickened another. It was the suspected cause of death of yet a third family member who died in China.

But H5N1 proved a "red herring," Peiris says. By early March, epidemiologically linked clusters of cases of what was later called SARS began appearing. WHO announced its global SARS alert on 12 March, and by 17 March, Stöhr's network labs were sharing data in daily conference calls. One of the first things the groups heard from Peiris was that "none of the other SARS patients had any evidence of H5N1, nor did they have any evidence of influenza, nor did they have any evidence of any other respiratory pathogens." At that point, Peiris says, "We knew we were dealing with something completely out of the blue."

To track it down, the team took three parallel approaches. Virologist Guan Yi tried to isolate and identify a causative agent by exposing cell lines normally not used for viruses to blood and tissue samples from patients. Molecular virologist Leo Poon started random genetic screening of infected tissues to identify some scrap of DNA that might provide clues to the nature of the bug. And pathologist John Nicholls started studying tissue samples with an electron microscope.

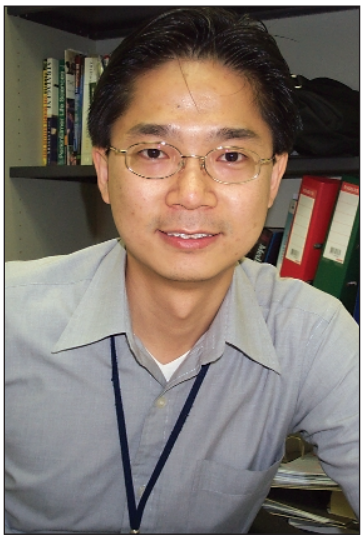
Similar efforts were under way in labs around the world. But the heat was particularly intense in Hong Kong. The government was under fire for its handling of the crisis and was facing decisions on whether to close schools and quarantine individuals who had been in contact with patients. In addition to his research, Peiris was a key governmental adviser who regularly appeared at press briefings. Poon says that during this period he was working 17-hour days. "I just had time to go home to take a shower, get a brief nap, and then come back to work," he says. "But Peiris had it worse."

Early in the week of 17 March, the researchers got a break. Tissue cultures isolated from two patients were killing cells in a line typically used to grow hepatitis A. To link the agent to the disease, the team tested blood serum taken from patients during the acute phase of the disease and during recovery. When placed on the tissue cultures, the acute phase samples showed no antibody activity, whereas the convalescent phase samples did, strongly suggesting that whatever was in the cultures was related to the disease. At that point, Nicholls had what he calls "a 'Eureka!' moment." Electron microscope images of the tissue samples showed virus particles surrounded by little spikes—the halo suggestive of a coronavirus.

By the time the researchers had the images, it was late Friday afternoon, 21 March. Accounts of what happened next vary. Peiris says he had to attend an evening meeting of governmental advisers and missed the daily WHO SARS network phone conference. But he later e-mailed his colleagues telling them he strongly suspected a coronavirus. Larry Anderson, chief of the CDC's Respiratory and Enteric Viruses Branch, says the Atlanta group mentioned during the conference call that it had identified coronavirus-like particles by electron microscopy, not knowing that the HKU group had also done so.

Over the weekend, the HKU group sent samples to a Hong Kong government lab equipped to stain tissue for electron microscope imaging. These images showed even more clearly that it was a coronavirus. The CDC researchers, meanwhile, sequenced fragments of genetic material from their sample and could find no matches in searches of known viruses. A collaboration of European groups was making similar progress. By the time of the 24 March conference call, the three groups confirmed they were closing in on what seemed to be a novel coronavirus. Later that day, when it was nighttime in Hong Kong, CDC issued a press release headlined "CDC Lab Analysis Suggests New Coronavirus May Cause SARS."

"The Centers for Disease Control and Prevention (CDC) announced today that a previously unrecognized virus from the coronavirus family is the leading hypothesis for the cause of severe acute respiratory syndrome (SARS)," it read. The WHO network was mentioned further down, but its role in fingering the virus was not explained. The HKU and European groups were not mentioned at all.



A civilized pace? Leo Poon says the group is scaling back its grueling hours—a little.

"I don't want to take credit away from the CDC, but our group here deserves some credit as well," Peiris says, betraying an uncharacteristic trace of annoyance.

CDC's Anderson claims they were unaware the HKU group had isolated and identified a coronavirus until later. "We certainly did not intentionally downplay the work [Peiris] or [his] group did," he adds.

The Europeans were also slightly miffed by the CDC press release. But Drosten of the Bernhard Nocht Institute says, "We don't care about press releases, we care about publications." And on this point, the record is clear. The HKU group's paper in *The Lancet* appeared online on 8 April with reports from the other groups appearing online in *The New England Journal of Medicine* on 10 April. "That's simultaneously," Drosten says. The identification of the coronavirus was later clinched by animal experiments carried out at Erasmus Medical Center in Rotterdam, the Netherlands.

Being in the thick of the race boosted the morale of the HKU group. "This is an historic moment for the University of Hong Kong," says Poon. "With limited people and limited financial support, we're very happy to make this contribution," he adds.

But Peiris is not celebrating yet. "It's hard to smile when SARS remains such a serious disease," he says. Scientists need better diagnostics to be able to quickly separate real from suspected cases of SARS and to identify asymptomatic carriers. And Peiris says there are "hundreds of other questions," starting with whether the coronavirus acts on its own or opens the door to other diseases and where the virus came from in the first place. But having helped identify the virus, HKU researchers are allowing themselves some luxury; Poon reports that he is now working only 12 hours a day. **–DENNIS NORMILE**

With reporting by Gretchen Vogel in Berlin and Martin Enserink in Washington, D.C.

Image not available for online use.

Telltale evidence. Blood samples from SARS patients showed antibody activity when exposed to cells infected with the suspected SARS virus.

CREDITS: (TOP TO BOTTOM) D. NORMILE; M. PEIRIS, Y. GUAN, L. POON, AND K. H. CHAN/UNIVERSITY OF HONG KONG