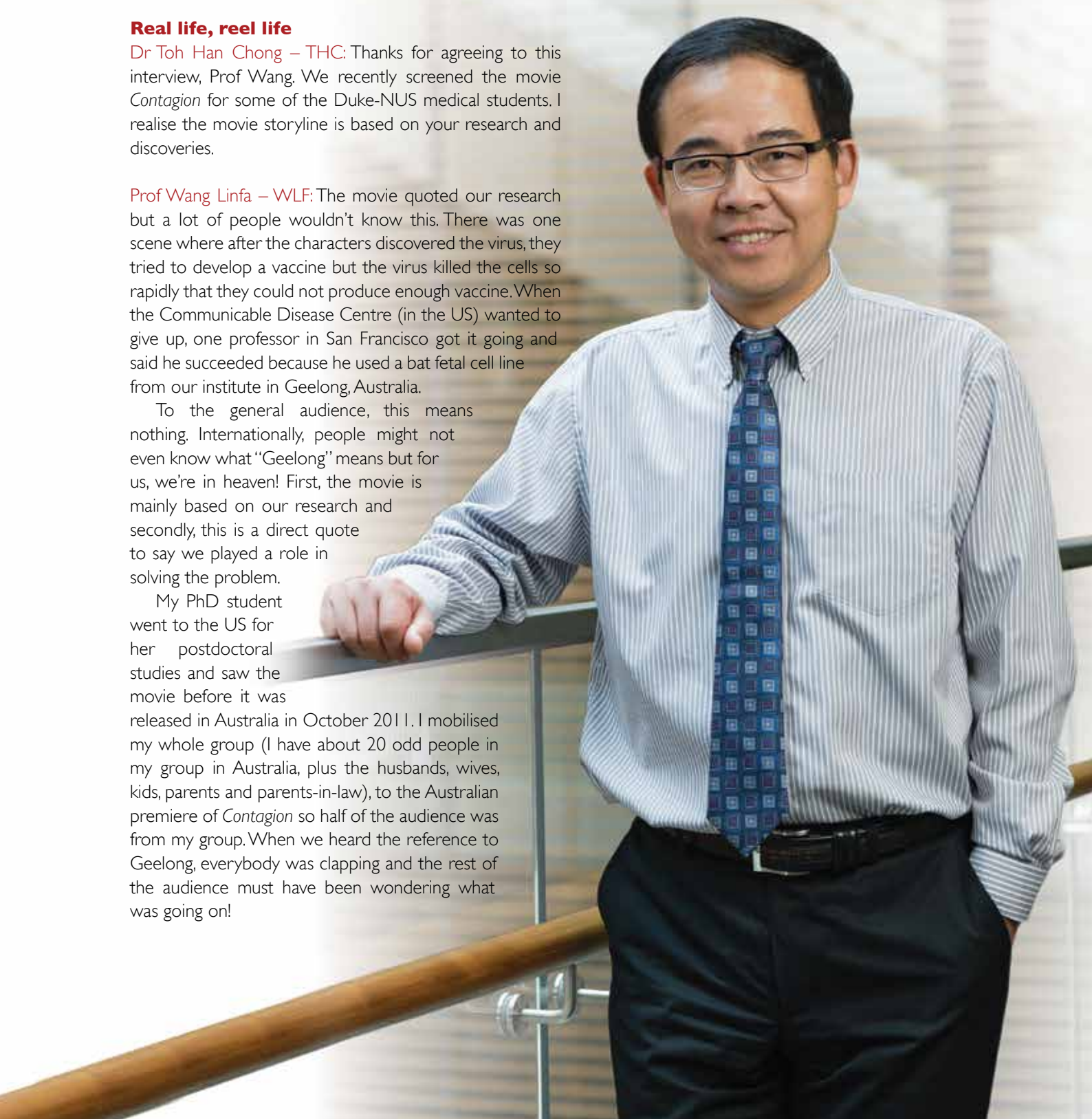
The Bat Man

By Dr Toh Han Chong, Editor

Prof Wang Linfa seeks to battle a different kind of attack on humanity. The Director of Duke-NUS Graduate Medical School's Program in Emerging Infectious Diseases (EID) led a research team that discovered bats were the host of the deadly SARS virus that devastated Singapore ten years ago, paving the way for further research efforts. Clearly passionate about his work locally and internationally, Prof Wang shares insights into the SARS epidemic in 2003 and the importance of cultivating a connected healthcare system.



Real life, reel life

Dr Toh Han Chong – THC: Thanks for agreeing to this interview, Prof Wang. We recently screened the movie *Contagion* for some of the Duke-NUS medical students. I realise the movie storyline is based on your research and discoveries.

Prof Wang Linfa – WLF: The movie quoted our research but a lot of people wouldn't know this. There was one scene where after the characters discovered the virus, they tried to develop a vaccine but the virus killed the cells so rapidly that they could not produce enough vaccine. When the Communicable Disease Centre (in the US) wanted to give up, one professor in San Francisco got it going and said he succeeded because he used a bat fetal cell line from our institute in Geelong, Australia.

To the general audience, this means nothing. Internationally, people might not even know what "Geelong" means but for us, we're in heaven! First, the movie is mainly based on our research and secondly, this is a direct quote to say we played a role in solving the problem.

My PhD student went to the US for her postdoctoral studies and saw the movie before it was released in Australia in October 2011. I mobilised my whole group (I have about 20 odd people in my group in Australia, plus the husbands, wives, kids, parents and parents-in-law), to the Australian premiere of *Contagion* so half of the audience was from my group. When we heard the reference to Geelong, everybody was clapping and the rest of the audience must have been wondering what was going on!

THC: When we screened the movie for Duke-NUS students, we had Prof Chua Kaw Bing, who discovered the Nipah virus, come in to speak to them. They were quite inspired by him. I understand that you were his academic mentor.

WLF: No, he isolated the Nipah virus even before we met. At that time, he had just started his Virology work after giving up practice as a paediatrician. I agreed to be his supervisor when he did his PhD research. His PhD degree was from the University of Malaya but the research was done in my lab in Geelong.

The origin of SARS and other insights into the virus

THC: Can you tell us where you were in 2003 when the SARS outbreak happened, and some of your feelings during that time of great anxiety and uncertainty?

WLF: I'm a bit more removed as I was working at an animal health laboratory then. As an infectious disease expert, I was monitoring this emerging atypical pneumonia in China with close interest. It's interesting because the class of virus I'm an expert in is the paramyxovirus, which is the class of virus responsible for measles, Hendra, Nipah, etc. When the SARS outbreak was happening in China and Hong Kong, there were debates about the original agent. Initially, the first group in Beijing thought that it was chlamydia, while another group in Hong Kong said it was a novel paramyxovirus. The possibility of it being a novel paramyxovirus made me really excited because I had seven unpublished novel paramyxoviruses that we had isolated from different species in my lab. I volunteered myself and wrote to the World Health Organization (WHO), saying that I had all these virus sequences. If they had a new paramyxovirus, I could help. Unfortunately, that theory lasted only three days. Over the weekend, I got excited, but by Monday, there was a new theory saying that it was not a paramyxovirus, but rather, it could be a novel coronavirus.

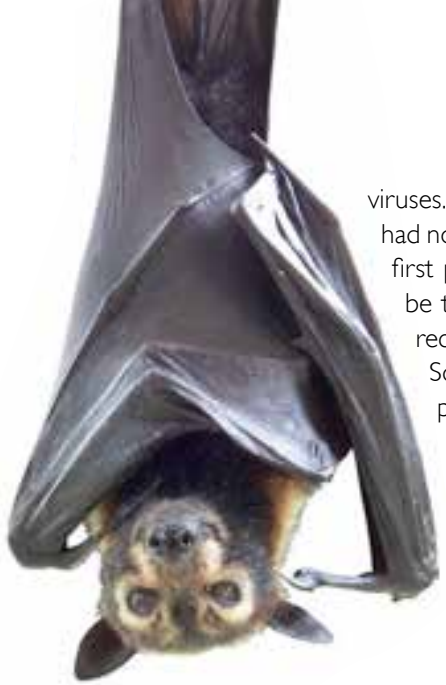
> ***"You have to train your soldiers during peacetime and make sure that everything is ready so that when there is a war, you're ready to fight.***

As we didn't have a single case in Australia and I was working in an animal health laboratory, it felt like I was watching SARS remotely. Then in July, WHO declared that the SARS pandemic was under control. But even then, we still didn't know why we had the SARS outbreak from China and where the virus came from.

WHO works by sending experts on special missions into outbreak countries. During SARS, they sent several missions. The first mission was to understand the disease, and the second one was to understand its human epidemiology. By July 2003, they needed a mission to work on the origin of the virus and study the initial transmission events. I was formally invited into this mission team. They wanted to assemble a team not only of medical doctors. At that time, it was pretty clear that SARS was not an existing human virus becoming more virulent. It was a new jump from animals to humans. They assembled eight experts. Two were resident WHO officials: one from Switzerland and one from Philippines. The other six were international experts from USA, France, Japan, Hong Kong and Australia. I was invited as one of the eight expert panel members, but was the only one who was lab-based. All the others were field epidemiologists. We were invited, went to the WHO office in Beijing, and received some basic training in diplomacy and politics. As a scientist, that was a huge learning experience. Your scientific knowledge is important, and for me, my language skills; and then there was the diplomatic and political briefings.

It was a learning experience because we worked from 8 am to 10 pm every day. We interviewed and worked with Chinese policymakers and scientists. We visited a few institutes in Beijing, and went to Guangzhou and Shenzhen. That was the beginning of my personal involvement with SARS and the main goal was to answer the questions about where it was from. If you don't know what the source is and what the early events of the transmission are, future outbreak prevention and control is very difficult. We worked there for two weeks. In a nutshell, we interviewed over 100 scientists and saw that civet cats were really on the news as a possible harbour for SARS. It was clear that civet cats were the animals that carried the virus into the restaurants and transmitted it to the early index cases, through the hospitals and then the rest of the world.

Out of the first six people who were infected, one of them came to Singapore and that's why Singapore was one of the earlier countries hit by SARS. My conclusion from that mission, and what I tried to convince other scientists of, was that yes, civet cats played an important role, but based on my own scientific judgement, there was not enough data to say that civets were the origin, the reservoir. We tried to convince the Chinese scientists to collaborate with the international team. Initially, there were some resistance but eventually, I was able to convince them that we should look beyond civets, and I had anecdotal scientific evidence to say that bats could be the source. In those days, bats were important for Hendra and Nipah



viruses. Even the Ebola virus, at that time, had not been linked to bats yet. I was the first person to suggest that bats could be the natural harbour for SARS, and received a lot of resistance for that. Some people said that it was a pretty wild guess.

Bats are much more difficult to work with because they are flying mammals. The first group I talked to was not too keen so I went to the second group. More importantly, I mobilised another Australian group, who are more experienced in the field of working with bats, and an American group who worked on bats there. From a humble hypothesis, perhaps we were lucky, but within 16 months, the team of five institutes from three nations had sufficient evidence to suggest that bats carried the SARS-like viruses. There were many important publications in the early days and our *Science* publication was a relatively later one published in 2005. If you think about the major milestones in SARS research, I think that was the last important one, which was to identify where SARS came from.

THC: How did bats transmit the virus to civet cats?

WLF: My hypothesis is that it all happened in the crowded live animal markets in Guangdong. What is interesting is that I had never heard of civets when I left China in 1982. Civet farming started in the late 80s, after I had left China, and grew exponentially in the 90s. Somehow, they think of civets as something that is very delicious and nutritious. They have civet farms in Guangdong and other provinces. We did a serological survey which indicated that the civets on the farms were clean or uninfected; but in the market, around 80% of the animals tested positive for SARS antibodies, so it's most likely a post-farm event.

The live animal market in Shenzhen had 135 animals crowded under one roof in one location, like snakes, cats, dogs, donkeys, civets, bats, etc. I don't know exactly how the transmission started but I think it might be related to trading activities: from transportation, wholesale and marketing. After our results were published in *Science,* people started to look for coronaviruses in bats. Without disappointment, all around the world, from Australia to Africa to South America, you can find coronaviruses in bats and lots of them.

Why do we do this kind of research? It will help to rapidly identify the source of new viruses. Look at the new coronavirus that emerged in the Middle East recently. In Singapore, this is one of the new viruses that the Ministry of Health (MOH) is really worried about at present. Last September, the first patient from Saudi Arabia died from a virus very closely related to a bat coronavirus in Hong Kong.

In 2005, when we published the *Science* paper, I had by then taken a lot of effort to convince everyone that bats could be the reservoir for SARS and SARS-like viruses. In 2012, when the new coronavirus virus jumped to humans in Middle East, everybody was looking for that virus in bats. I didn't need to convince sceptics anymore because most people think that it was very likely that the virus came from bats because its close cousins came from bats too. In this case, we have this new virus circulating among Middle Eastern patients in UK, France and Germany who have travelled to that area. This virus now has a higher mortality rate than the SARS virus in 2003. Currently, in the confirmed cases, its mortality rate is around 50% while that of SARS is only 10%, although its transmissibility is much lower than SARS. For viruses, all you need is a few more mutations and they can become more transmissible.

THC: Why is it that some people who were exposed to SARS in 2003 lived while others died so dramatically? There's this whole concept of the "super-spreader". What is the theory behind that?

WLF: These are two different questions.

"Super-spreader" just means that when you get infected, the virus replicates in different individuals to different levels. The super-spreader has a much higher level of virus in their body. When they cough, the droplets contain ten times or more virus than another SARS patient with exactly the same infection. The super-spreader transmits it to more people. The most classic super-spreader was a SARS patient in Hong Kong who got infected and caught a plane to Beijing, and coughed and did all the things we do on airplanes. He transmitted the virus to more than 30 patients in one flight. But the super-spreader may or may not die.

The second question is about the severity of the disease. This is a difficult topic to address. Usually, we believe that the severity of the disease is determined by multiple factors, such as genetic background and co-infection. Both are considered difficult areas of research for Infectious Diseases, and we are in the process of developing new platforms in our EID programme to expand research in these areas.

The other thing worth emphasising is that SARS does not kill people. The virus itself is actually not very destructive. What kills you is your body's immune response – such as the resulting inflammation and the over immune response or immunopathology.

THC: Are there challenges to creating a SARS vaccine?

WLF: We already have preliminary SARS vaccines in labs, so

it's definitely doable. But like I said, who would be interested in developing a commercial vaccine against SARS?

THC: Will we ever have a biosafety level 4 (BSL-4) lab in Singapore?

WLF: Well, that is a tricky question for me to answer because as a scientist, I've worked in a BSL-4 lab for 20 years. Realistically speaking, if you look at the countries surrounding us, much bigger countries like Japan do not have a functional BSL-4 lab. If you put it in that context, it's not realistic to build a BSL-4 lab. Instead, I think international collaboration will be a more productive approach.

SARS is a perfect example. It is tragic that so many people died, but if we did not have the SARS network and WHO's intervention with global travel warnings, we would be in a much worse position. Of course, we can do much better but to me, it's less important whether Singapore has a BSL-4 lab or not.

Most importantly, the role I can play is to be the mediator for Singapore's infectious disease community and the international community. I have appointments at Duke-NUS and Geelong because I wish to maintain the science which requires a BSL-4 lab, but the other more important consideration is as a director of the EID programme in a major institute in Singapore, I want to have the capability to help Singapore if we are hit by a SARS or Nipah virus pandemic again. Being almost in the same time zone, we can have the sample from Singapore General Hospital's Pathology department in my BSL-4 lab in Geelong within 12 hours. If I can do that, it's almost the same as having a BSL-4 lab in Singapore. Building a BSL-4 lab is difficult and expensive, but what is more difficult is maintaining the expertise to work there. I have a team in Australia that is one of the best. In my 25-person team, I have seven of them trained to access BSL-4 daily. Even by international standards, that is very good.

THC: Why did SARS disappear as quickly as it appeared?

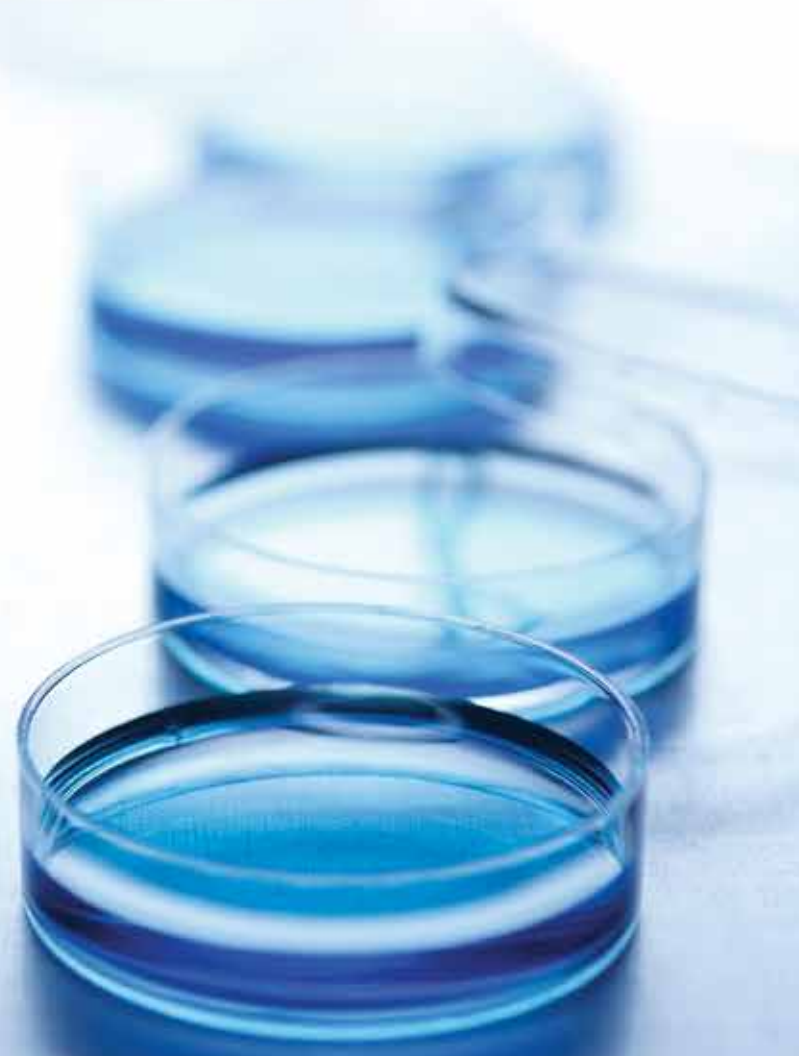
WLF: Because SARS is not maintained in civet cats or humans. Humans overcame SARS because we had good quarantine measures. As for civet cats, the infection was limited to animals in the market or restaurants, and they haven't established a coexisting relationship yet. For the virus to jump from bats to civet cats, it's a very rare event. By culling the civet cats and preventing the trading with bats, they cut the transmission link.

THC: Singapore was fantastic in handling public health and ring-fencing the pandemic, but in terms of academic output on SARS, Hong Kong seems to have done better than Singapore. What do you think are some of the reasons for that?

WLF: Not only Hong Kong, it was the same case as with the Nipah virus: Singapore had the chance because Singapore had Nipah virus cases as well. Chua Kaw Bing said that he was really worried that Singapore would beat Malaysia in isolating the virus, but that didn't happen.

First of all, I think it's a sensitive question. Secondly, maybe I'm not in a good position to comment because I was not here at that time, and now, I've only been here seven or nine months. To be frank, I think that Singapore can do better by having less organisations. For example, disease surveillance and control (such as those for dengue) by multiple agencies is very unique to Singapore. In most countries, it is mainly done through their Ministry of Health. To me, there may well be too many organisations at the highest level, and the culture of working together can also be significantly improved. I'm a strong believer in collaboration. For the very large project on bat genome studies, I led a collaboration of nine institutes from five countries. I'm a collaborator; I always want to bring teams together. And that's what I wish to do in Singapore.

To fight a pandemic like SARS, you have to be transparent with all involved parties and stakeholders. You also need daily brainstorming involving not only clinicians, but also basic research scientists. The reason why we responded so well to the Hendra virus outbreak in Australia is because the diagnostic and response teams always call upon the research team to join together as a task force when there are outbreaks of diseases involving unknown agents.



Photos: Duke-NUS Graduate Medical School, iStockphoto, Nipic.com and SMA

During my interview for the appointment of Director of the EID programme at Duke-NUS, I had the opportunity to meet with representatives from MOH. I made it clear that my interest in the position is beyond just research at Duke-NUS. I am keen to make a contribution to outbreak investigations as well. I am very pleased that MOH has already started to involve me in some of the task forces, such as the one dealing with the novel coronavirus.

THC: Could I ask if you are a Batman fan? (*laughs*)

WLF: (*laughs*) No, I've not watched any of the Batman movies. The bat, now, is the focus of a major area of research. In the whole history of evolution, there are only four times that animals acquired flight capabilities. There was a flying dinosaur (the pterodactyl) which is extinct. Then we have the avian species and insects which fly. For mammals, we have bats. It's a pretty rare evolutionary event to acquire flight. It carries an advantage of course. Humans dream to fly, but we couldn't, so we invented the airplane, as it allows you to travel long distances and do all sorts of things.

But there's a price you need to pay to be able to fly. As we know, at the cell biology level, when you have a fast metabolism during flight, the heartbeat goes up and the physiology changes; at the cellular level, you create a byproduct which damages your DNA. There is a direct link to cancer genesis and ageing. So during evolution, we all have evolved with something called the DNA damage response.

> ***"I learnt from my mother that if you are given an opportunity and you excel, the doors will open.***

I always think of cells as functional units just as one thinks of Singapore as a country – it's the same. There are two kinds of risk. One is invasion, people invade us; secondly, internal instability can overthrow a government or a country. A cell is the same. A cell can be damaged by an infection from outside or you generate a lot of these byproducts that damage DNA. When you accumulate so many mutations, you can even die from significant diseases such as cancer.

We sequenced the genome of two bat species: one from Australia which carried the Hendra virus, while the other one was from China. What we discovered is that the unique thing about bats, on top of being able to fly, is that they have very strong positive selection for genes involved in DNA damage repair. This makes sense because although they can fly, they live three to ten times longer than mammals of the same size. I talk to bat biologists from around the world and ask them for potential tumour tissue so that we can establish stable cell lines. But none of them has ever discovered any tumours in their careers.

THC: Do we need to worry about the avian flu outbreak in China right now?

WLF: Oh yes, we're watching the situation closely, especially in Singapore because we're situated close to China. Again, the early events are unclear – where the virus is from, how is it transmitted, etc. The good thing is that it is not very transmissible between humans.

SARS caused the economy to lose billions of dollars and almost 800 people died, so it's a huge loss. But if you look at it positively, SARS shook the whole world, from politicians to the general public to scientists. The whole world now really responds much better, thanks to the SARS crisis.

Career beginnings

THC: How did you discover your interest in Virology? Winding the clock back to your youth, how did it all happen?

WLF: My career is very interesting because to start with, I hated Biology because I never did it in high school. If I had a choice, I would have chosen Engineering or Informatics for university. China went through the Cultural Revolution and when they first started, I selected second-tier engineering schools but because my entry points were higher, they put me into a first-tier key university. As I didn't do well in Maths, they said, "You should study Biology."

I'm a person, where, if I'm given an opportunity, I want to do well. In university, I excelled and became top of the class and they gave me a PhD scholarship to study in the US. I tried to stay far away from living things so I chose Biochemistry, went to UC Davis and did a Biochemistry/Molecular Biology degree, which were very hot areas in the 1980s.

I have a friend from Shanghai who was in Australia, and in those days we did not have email, we used snail mail. His English was not good so he asked me to send him my CV as an example as he was preparing his. Without my knowledge, he gave my CV to the head of the Biochemistry department in Monash University and I basically got a job without applying for it!

To be really frank, I think I learnt how to use the tools of doing biological sciences but I had to decide which one of the three generic areas I was going to go for: human science, plant science or animal science. After being in Australia, I realised that they pay great attention to animal health. And the Commonwealth Scientific and Industrial Research Organisation (CSIRO) Australian Animal Health Laboratory, which I eventually got a job in, had fantastic

facilities. They have the world's largest biocontainment facility.

After one year in Australia, my wife and I liked it there, so we figured this could be a country that we could make a career from. When we saw two job openings at the CSIRO Australian Animal Health Laboratory, we both applied and got the jobs. We started there at the end of 1990 and that's when I first encountered a real virus!

THC: How did you decide to come to Singapore?

WLF: The Singapore Government is a huge driver in attracting top scientists.

During my presentation in January 2013 to the SingHealth core leadership group, I stated that one of the motivations for me to come to Singapore is to work closely with Singaporean clinicians and scientists in EID. I treat the EID team like an army, and we have peacetime and wartime. You have to train your soldiers during peacetime and make sure that everything is ready so that when there is a war, you're ready to fight. I said that I have been here in Singapore for six months and my feeling was that Singapore's scientific abilities, the infrastructure and the people on the ground, are the best in the region. Yet, in the last decade, Malaysia discovered so many new things, in terms of EID. They always ask me what is the difference, and the difference is that they have a champion and we don't. In Singapore, the infectious disease sector is rather segmented. I think we need to work more closely and collaboratively to make a greater impact in the region.

Concluding thoughts

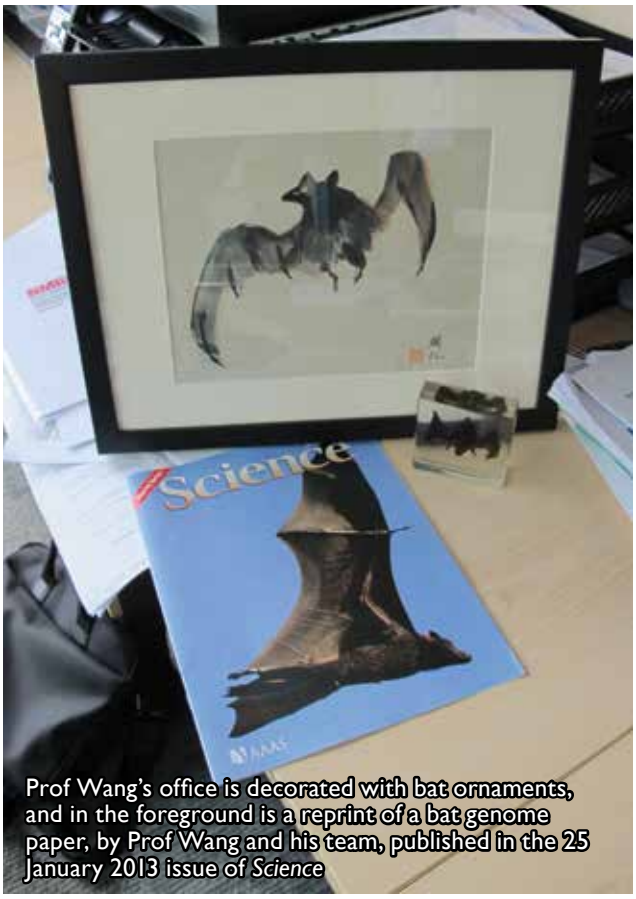
THC: What do you do to relax? Do you have any hobbies?

WLF: My dream was to be an electrical engineer. When I was in high school, I used to do a lot of electronic stuff. My hobby is fixing things around the house.

When my son was little, we tried to engineer and improvise toys, etc. So that was my first hobby. The other hobby is gardening. Maybe because I work in a secure environment where everything is unnatural, where temperatures and humidity are regulated, I try to use the weekends for outdoor activities so I do about half a day of gardening every week. I have redone my garden three times.

The third hobby I developed in my mid-30s was tennis. Unfortunately, all three hobbies are rather difficult to do in Singapore. I live in a rented house so there is nothing to fix, whereas in Australia, I have a bigger house so there was always something to fix, to engineer and invent.

THC: Last question, can you share with the readers of any person or persons who have inspired you in your journey so far?



Prof Wang's office is decorated with bat ornaments, and in the foreground is a reprint of a bat genome paper, by Prof Wang and his team, published in the 25 January 2013 issue of *Science*

WLF: It's interesting because I was talking to my daughter, who just finished her law degree in Melbourne, and she also asked that same question. I said that I grew up in a society and in a time where I had very limited exposure because of the Cultural Revolution. The only thing I read was Mao's *Red Book*. I had never been exposed to scientists when I was formulating my own path.

My biggest inspiration is my mother, who had zero education. She has this natural ability of motivating people and everything she does, she does really well. She worked in a restaurant and they promoted her to be the manager of the entire restaurant. She has interpersonal abilities, moral standards and communication skills. I think that her message to me has always been that the most important thing is to try your best to do well in whatever you're doing now, instead of dreaming to be someone else. I continue to carry that belief today. When I was younger, I didn't have any dreams because I was not allowed to in a communist society. For kids today, they would become very depressed and would want a change in majors. I learnt from my mother that if you are given an opportunity and you excel, the doors will open. My career is exactly like that. I hated Biology but I topped my class in a Shanghai university and was sent to the US. I did well in Biochemistry and Molecular Biology, and eventually, I used my knowledge and skills to do research in Virology and Infectious Diseases. SMA