THE HEPATITIS B PROGRAMME

Interview with

Dr Gabriel Oon Chong Jin, Pioneer Scientist

Dr Gabriel Oon is a pioneer in primary liver cancer research, and has played a key role in Singapore's hepatitis B vaccination programme. *SMA News* speaks with him on his involvement in the vaccine project and the challenges his team faced, his sporting glory in his youth and running the Apex Harmony Lodge for dementia patients with his aunt Dr Oon Chiew Seng, who recently received the National University of Singapore (NUS) Honorary Doctor of Letters at 104 years old.

Tell us a bit about yourself and how you became involved with primary liver cancer research and the hepatitis B vaccine.

I returned to Singapore in June 1975, soon after obtaining my Cambridge University MD in cancer immunology. Profs Seah Cheng Siang (head of Medical Unit I, Singapore General Hospital [SGH]), Khoo Oon Teik (my boss) and K Shanmugaratnam (head of the Singapore Cancer Registry) asked me to conduct research on liver cancer, then the number one killer in Singapore and the Asia Pacific region, and to start oncology and immunology research.

I was given a small attic room for a laboratory, which was called the Ransome Research Laboratory, named after Prof Gordon Ransome. With a $10,000 donation from the Lee Foundation, the laboratory soon brought in a laboratory technician and a research scientist. We were intricately linked to the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO), which provided regular advice.

One of the research projects then was to look into aflatoxin, a potent liver carcinogen. We were curious about how much aflatoxin there was and where it was commonly found in Singapore. Through food histories, it was found that 4% of volunteers had ingested it through fried food, satay and exposed rice. They had the highest numbers of aflatoxin exposure then, followed by some medical staff and laboratory staff.

Singapore then was a free port and very porous with importing medicines and goods. Legislation banning importation of food containing aflatoxin was brought in, marking the start of stricter enforcement of food and medicines entry into Singapore.

The hepatitis B virus (HBV) was an ancient killer, killing millions since the time of the Bronze Age where 4,500 years old human remains were found to have HBV. The virus was not identified until Baruch Blumberg discovered it in 1963 and named it Australia antigen (Au). In 1976, WHO named this DNA virus the hepatitis B virus – a parenteral transmitted virus in contrast to the orally transmitted hepatitis A. There were many sick children in the paediatric wards suffering from fever, diarrhoea and jaundice; among adults, many were dying from bleeding varices and terminal liver failure. It was sad to see so many weeping families.

HBV is ubiquitous, not only among humans but also in the animal kingdom. The key antigen was the "a" epitope present in them and humans. From different parts of the world, we identified various human subtypes: "ady", "adr", "adw", "ayr" and "ayw", but all had the same epitope "a" for which the vaccine was made to target.

Hepatitis B research was conducted in three prongs: vaccine manufacture, finding a treatment for HBV carriers, and early detection of liver cancer. Wellferon, a natural lymphoblastoid alpha interferon, was the first drug used. It was able to prevent recurrence of liver cancer in high-risk HBV resected cases via three monthly interferon treatments, and it inhibited or reduced liver fibrosis. Later we developed the HBV DNA assay. The first ultrasound machine was brought in to screen for early liver disease and cancer, and I worked with the late Prof Lenny Tan on diagnosis and transarterial chemoembolisation, and with Dr Felix Sundram on radioisotopes.

There were no well-established biomedical manufacturing industries in Singapore then, but our team dared to proceed with manufacturing. With a grant of S$1.3 million from the Ministry of Trade and Industry, we worked with both NUS and Ministry of Health (MOH) teams and made a vaccine to the level of animal testing. The team felt that if we succeeded, it would be the inspiration for a local medical industry.

A lifelong adventure with vaccines

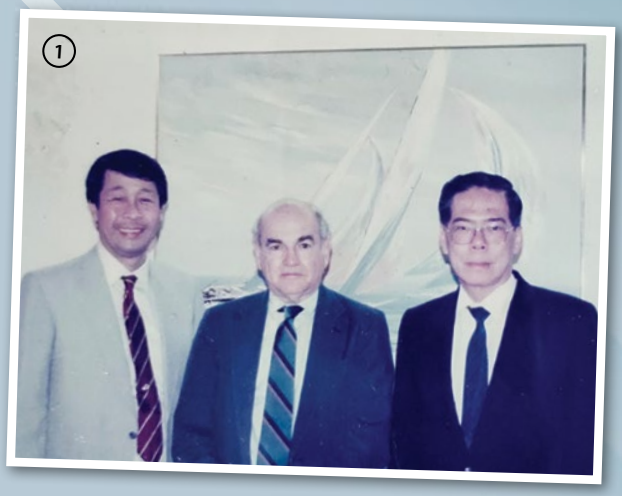
You were appointed the Principal Investigator by the WHO and IARC for Singapore's hepatitis B vaccination project. What were the events leading up to this appointment?

In 1978, as the Secretary General of the Asia Pacific Association for the Study of the Liver, I gathered scientists from the region and requested for help from WHO regional advisor Dr Shoichi Endo. Alan Linsell, IARC/WHO regional representative, saw our work in progress and put us in contact with WHO Geneva. I persuaded Dr Lorenzo Tomatis, director of IARC/WHO, and the IARC Council in 1982, that one country was needed to prove that the HBV vaccine works in preventing liver cancer. It would be the first vaccine to prevent a major cancer. We looked at every country for feasibility. Singapore had a small population of 2.5 million at the time, a national cancer registry linked with IARC, good academic and Government support, and a method to trace every vaccination delivered and received. Singapore was thus chosen and I was appointed the Principal Investigator in 1983, with US$25,000 to start the project.

The commitment to this project and then-Prime Minister Lee Kuan Yew's expectation of "300% safety" would require me to monitor it for almost a lifetime. On 4 July 2019, with the help of MOH, the Singapore Cancer Registry, and through publications in the *Singapore Epidemiological Bulletin*, it was officially announced at a Duke-NUS Medical School public lecture that HBV and liver cancer had been eliminated in all those vaccinated and under the age of 40 years, with no major disasters.

What were some of the challenges you and your team encountered during the project?

There was a constant need for funding and getting the best clinicians and scientists to join us. Our group was called the Hepatoma Research Group, in the University Department of Medicine in SGH. I am grateful to Dr Shaw Vee Meng, Chairman of the Shaw Foundation for his long-term financial funding.



In treating hepatitis B, we explored adoptive immunotherapy, using immune leucocytes from family members who were negative for hepatitis B surface antigen (HBsAg) but had hepatitis B surface antibodies (anti-HBs), hoping that immunity could be transferred to the carrier. It reduced the titre of the virus but did not eradicate it. Later, we discovered that this was due to integrated HBV in the nucleus of the hepatocyte, and only removal of the infected liver by liver transplant would remove the HBV. Experimentally, we found that HBV grew and fed voraciously on cultured human liver tissue but died when these were removed.

Treatment with Wellferon in 1985 had good success in preventing recurrences in the resected cases within the first five years, and thereafter for some 20 years.

In manufacturing the HBV vaccine from the blood of carriers, there was the danger of being infected as we had no immunity. We had to get huge volumes of high titre HBsAg, and these would come mostly from the HBsAg- and hepatitis B e-antigen-positive carriers.

In closely monitoring all vaccinations in the clinical trials serologically, we noticed an unusual persistence of anti-HBc IgG in some individuals which were expected to have disappeared within three months. The sera of these persons were isolated, the nucleic acid sequenced, and we discovered that these were molecular new viruses. We brought some samples to Prof Arie Zuckerman in London who oversaw the WHO Collaborating Laboratories for HBV, and he confirmed them as vaccine escape mutants. These were dangerous, as they were not picked up by conventional immunoassays, and not killed by natural nor vaccine-induced anti-HBs. Subsequently, it was found to be due to zealous use of urea, pepsin and formaldehyde in sterilising, which damaged the epitope of the plasma vaccine. With the onset of the yeast recombinant vaccine, there were no more problems.

Ransome Laboratory was designated the WHO Collaborating Centre for HBV vaccines. Lacking industry experience, we sought WHO's help to choose the best manufacturers to train our staff in vaccine manufacture technology, and to select the technology which would help us to leapfrog to future vaccine technologies. With their advice, we chose Merck Sharp & Dohme.

Additionally, due to some difficulties within my department, MOH appointed me as Principal Investigator in their new Department of Clinical Research in 1986 to monitor the vaccine project safely and to continue my research on liver cancer and hepatitis.

How did you come to vaccinate yourself and your family with the then-untested hepatitis B vaccine?

When our hepatoma research team decided to make the vaccine, I pondered, "Are we too gung-ho?" We had no backups of industrial experience nor any local biopharma industries, but we decided to try and get WHO to help.

Our French colleagues were kind and offered us a few vials of plasma-derived vaccines which they had been using. Then-Permanent Secretary of Health Dr Andrew Chew, who oversaw the project and who was one of my mentors said: "Chong Jin, you and your team should have it first as you are continuously handling dangerous infected materials daily. "

Dr Aw Swee Eng, laboratory technicians and myself were the first to be vaccinated, followed by the rest of the laboratory staff. When we were well after a month, and more plasma vaccines were available, volunteer nursing, medical and laboratory attendants at SGH received the vaccine, and all remained well.

Three months later, we looked at vaccinating all high-risk babies born to HBV-positive mothers. Before vaccinating them, I felt I should vaccinate my two sons first, aged six and eight years. When I mentioned this to my wife Susie, she said: "Then you must vaccinate me too. If we die, we all die together." And so, our entire family were among the first in the region to be vaccinated.

Life journey

You studied medicine at Cambridge University, attained your MD there and stayed on in the UK to further your career. What made you decide to return to Singapore?

I was in the UK from 1954 to 1975. I did my "O" and "A" Levels in the Perse School Cambridge, and then proceeded to study medicine.

I used to travel to give lectures in Singapore, Hong Kong and China. Three eminent persons, Prof Seah CS, Prof David Todd (Head, Department of Medicine, Queen Mary Hospital, Hong Kong) and Mr Song Zhiguang (Chinese Ambassador to UK) said to me separately in 1973, soon after I had passed my Cambridge MD, to go back East and help our people. I pondered about where to go and what to do, though I had a yearning to go back to the East with Susie. My aunt Dr Oon Chiew Seng advised me on the benefits of coming back to Singapore and offered to put us up at her place.

The decision was further affirmed because I felt the need to return and serve my homeland. Here, I implore readers to consider this question: " When your country calls upon you, will you answer the call to serve?"

You and your brothers were talented badminton players, each winning many international titles. Tell us about how you started playing badminton.

Our uncle, the legendary badminton world champion Wong Peng Soon, used to stay with us when he prepared for the Thomas Cup. He said to us, "Be the best. Be humble" and this has been my motto in life – to always try to be the best in whatever I do.

I won the All England Junior Singles at the age of 16 years, and as many as 30 trophies in championships in the British Isles and Europe between 1956 and 1965. My last championship was the All England Men's Doubles in 1965. Badminton was not yet in the Olympics nor world championships, and the All England was the equivalent of a world championship then. I was recalled to help defend the Thomas Cup in 1964 – a very distinguished honour – but I had to turn it down as it was three months before my Cambridge MB examinations, and qualifying as a doctor was my priority. The next year, I reached the All England Doubles Men's Finals and it was the pinnacle of my badminton career. I retired after that to concentrate on medicine.

You are currently the Board Chairman and Chairman of the Medical Committee at the Apex Harmony Lodge for dementia residents, established in 1995 by your aunt Dr Oon Chiew Seng. How and why did you decide to join in the running of the lodge in 2007?

I am a Catholic and in 2003 was invested into the Order of Malta. It is a chivalrous and noble Order which defends the faith and carries out many missions of mercy to help devastated areas of the world. I have helped in several rescue medical missions since.

So, in 2007, when I was asked by a psychiatric colleague to help oversee the care of some 200 residents of Apex Harmony Lodge, I agreed. It was a sad scene as many of them had multiple medical conditions, and were on at least ten different medications. Residents were often discarded because their loved ones had died, and no one else could care for them.

Being on the medical committee which oversees medical and nursing care, my duties include ward rounds, chatting with residents, and watching their activities which include drawing, gardening, mahjong and drumming. Those doing better can have outings. It is a training ground for nurses and is very professionally run by experienced administrative staff. My aunt, who founded it in 1995 and was its first chairperson till 2012, set up the Oon Chiew Seng Visiting Fellowship at the NUS Yong Loo Lin School of Medicine and now we are forming a Department of Dementia, which would use the Apex Harmony Lodge as a hands-on training ground for future medical and nursing students.

Personal thoughts

We understand that you have just retired from active medical practice. Given your extensive experience in medicine, do you have any words of advice for medical students and doctors?

I give this same advice to all doctors, scientists, writers and missionaries.

Integrity, honesty, kindness and compassion are key values to embrace. Be humble and do whatever you can even for those who cannot repay you. Treat them as you would treat yourself.

If you are a prayerful person, a prayer is soothing when facing enormous obstacles and difficulties in accomplishing your mission.

"Lord… It is your Will… let your Will be done."

This prayer gives you the comfort that God is with you in overcoming the obstacles. ◆

Legend

1. Visit of Prof Baruch S Blumberg, the Lee Kuan Yew Distinguished Visitor, to the Department of Clinical Research, Singapore General Hospital on 24 August 1992

2. Dr Oon at age 17 with the badminton challenge trophies won between 1957 and 1958