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A groundbreaking research scientist noted for his work in non-invasive blood-based diagnoses, Professor Dennis Lo currently holds a number of positions at the Chinese University of Hong Kong (CUHK). Lo, whose work was first commercialised via the company Cirina - later acquired by GRAIL - outlines his current research focus on "fragmentomics," the progress of ongoing clinical trial programmes, and the pros and cons of Hong Kong as a translational research hub.

You have a career full of achievements. Could you introduce yourself to our international audience?

I was born and brought up in Hong Kong before attending Cambridge University in the UK for my undergraduate degree and then Oxford University for my Doctor of Philosophy (DPhil). After working as a faculty staff member at Oxford, I chose to move back to Hong Kong in 1997. I am considered a clinician scientist as I have a medical and science degree.

My studies were based on using genomics for clinical applications. In 1997, I was able to show that a pregnant woman's blood contains DNA from the Y-chromosome if she is having a boy. This technology then evolved, and we were able to use the testing to understand the genetic health of a baby and to check for chromosome disorders such as Down syndrome. This non-invasive prenatal testing is very different to the old system which required an injection and increased the chances of miscarriage.

25 years since this initial discovery, how were you able to take this innovation across the globe?

We licensed the product to LabCorp and Illumina in 2014 and they have been able to deliver it across the world to places like Europe and the USA. Locally, we founded the company, Xcelom, for Hong Kong and China. The market size globally is several billion USD, and looking back, if I had the knowledge then that I have today, I probably would have placed more of this technology within Xcelom, but that is very easy to say in hindsight.

After this discovery, I began thinking a baby growing in a mother is somewhat like a tumour growing in a human. Therefore, using this technology we were able to screen for any cancer and know where it is growing in the body. This was done using concepts from the field of epigenetics. Genetics studies DNA sequence changes, while epigenetics studies modifications of DNA, *without* changes in DNA sequences. If someone has cancer the epigenetic modifications of the DNA will be different, equally, each organ has a different modification. This means we can detect if someone has cancer and from which part of the body.

As a result of this discovery, I founded the company Cirina, and in 2017 we merged with GRAIL, a US company from Silicon Valley that was doing similar research to us.

In the universe of genetic testing, there is a lot going on and as technologies are emerging, they are just starting to show their capabilities. How has this research been internationally recognized?

I have been fortunate enough to have won some awards and I am grateful to be recognized by my peers and the industry. In 2021, I won the Breakthrough Prize in Life Sciences, which is given to researchers who have made discoveries that extend human life. In the same year, I won the Royal Medal, which is given by the Royal Society for contributions and advancements to the sciences. In

2022, I won the Lasker-DeBakey Clinical Medical Research Award, many winners of which have gone on to win the Nobel Prize.

How will such cancer testing technology be translated into standard of care?

Another important step is to make sure that there is an excellent level of clinical evidence. For example, for our cancer screening technology, GRAIL is conducting a large study with the UK NHS with around 140 thousand patients, and from initial data, it seems the technology can pick up multiple types of cancer. The level of accuracy depends on the stage of the cancer, with the latter stages being detected more accurately. Obviously, then you must look further down the treatment line of care, because if someone is screened positive you must pay for further testing, and then if it is a false positive, what happens next? This will be something to consider for payers in the future. But early clinical studies are showing promising results.

Building on the experience of these award-winning discoveries, what are your main research focus areas today?

I am working on a new field of research called fragmentomics. The DNA inside a cell are long molecules within the chromosome, but in the blood, they are very short, and this is due to the longer molecules being cut into these smaller ones. We can identify which disease a person has based on where the molecule is cut. For a simple comparison, if you get your haircut and the hairdresser uses different scissors, we would be able to tell which disease you have based on the cut marks of each scissor.

We are starting on this technology with babies and cancer for certain organs in the body, and thus far we have seen good success. The exciting part about this technology is it is relatively cheap to operate.

Another clinical analysis we have been studying is whether early detection of cancer makes a difference in terms of final outcome. In 2017, we published a paper for nasopharyngeal cancer using the screening test. Unfortunately, the majority of such cancers in Hong Kong (75 percent) are detected only in stages 3 or 4, but with our screening test, it is being detected at 70 percent in stages 1 and 2. This has dropped the mortality rate more than 10-fold from 40 to 3 percent. These are amazing results.

The trial was done in Hong Kong and cost around HKD 20 million, a relatively low amount. It entailed 20 thousand subjects and was published in the New England Journal of Medicine. In fact, it was quite interesting how we attracted subjects. We first made an announcement on television and then went to the different districts of Hong Kong every week and recruited around 200 people, so within three years we had enough cohorts for this trial.

How solid would you say that clinical data obtained in Hong Kong is when looking for regulatory approval in other international jurisdictions?

Very solid. Many companies are undertaking clinical studies here. Trial data generated in Hong Kong are acceptable as part of the data for approval by the US Food & Drug Administration (FDA), in addition to US-generated data.

Are there any other ongoing clinical trials that are particularly exciting you at the moment?

One exciting project that is funded by the Hong Kong SAR Government is the Hong Kong Genome Project. The objective is to look at the genomic sequencing of 50 thousand Hong Kong citizens and by analyzing this data we may be able to arrive at a diagnosis of patients with previously undiagnosed diseases. We have just completed the pilot phase of this project, so we are doing 10 percent of our target before we scale up. It is an exciting project using genomics on a large scale, with important implications for the future development of healthcare in Hong Kong and elsewhere.

Looking broadly, in your opinion does Hong Kong have the capabilities to have a leading life sciences ecosystem?

Yes, and this is why the Greater Bay Area is so important. Building biotechnology unicorns only in Hong Kong is challenging because of the small size of the local market, but it is possible, and we have shown that it can be done in other areas of technology. Chapter 18A – the Hong Kong Stock Exchange’s listing option for pre-revenue biotechs – is also a great addition to helping this development.

I believe the Greater Bay Area needs more serial entrepreneurs that build experience and can learn from their past mistakes. These people can then pass their knowledge on to their staff and teach

the younger generation how to build a company. Hong Kong has many good scientists, but it is not easy to find great scientists with great business minds. However, this is what is sometimes required, more than just an innovative idea.

Is the Hong Kong government doing enough to foster this ecosystem, in your view?

The government has invested a lot of money in the science park and launched many schemes. One such scheme is the InnoHK Initiative in which HKD 10 billion has been used to fund 28 laboratories, with half of them in the healthcare area. Overall, they are giving more money than ever before, but if you look at the percentage of GDP being dedicated towards research compared to other jurisdictions, there is still a lot of room to grow. I would say to any company, or researcher that Hong Kong is making a strong effort to build its technology ecosystem and it is an exciting place to do business and invest.

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