Interview: Dennis Lo – Co-Founder, Cirina; Professor of Chemical Pathology, CUHK

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Described as the first unicorn [a startup company valued at over USD 1 billion] of Hong Kong, Cirina has recently merged with Grail to further improve detection of cancer at its early stage. Pharmaboardroom sat down with Professor Denis Lo, the man behind Cirina's technology, to further discuss his groundbreaking scientific research and achievements in the field of non-invasive blood-based diagnoses.

To start with, what was the rationale behind the recent merger between Cirina and Grail?

Cirina and Grail have pretty much the same goals. We aim to detect cancer at a stage where it is still possible to do something. I believe that with our recent merger we have a very unique combination of resources – ranging from infrastructure and technology to talents to tackle this challenging problem. We really want to make an impact and do something about it.

What are the areas that are complementary in the two companies?

In the last 20 years, I worked in an area called circulating DNA – basically the DNA outside our cells circulating in our body. Because it is in our blood, half of the volume is occupied by this yellow fluid called 'plasma' and the other half is occupied by blood cells. Of course, everyone knows that DNA is normally located inside our cells, so when people do a DNA test they typically focus on blood cells. However, when I first started working on this area of examining DNA in the plasma, it was

regarded as a non-mainstream area and many people did not believe that this would lead anywhere. Essentially, in 1997 I wondered whether a fetus could release its DNA into the plasma of its pregnant mother, and be detected; it turned out to be the case.

I discovered that an average of 10 percent of the plasma DNA of a pregnant woman is derived from her fetus and after two hours the baby is born the fetal DNA is gone from the mother's plasma. We then developed this new technology called Noninvasive Prenatal Testing (NIPT) which we use to find out genetic information about the baby, e.g. whether the baby is a boy or a girl and this is useful because some genetic diseases are sex related – like hemophilia for instance. We also use this to determine the blood type of the baby, because sometimes if the mother and the baby's blood types do not match, the mother can produce antibodies which can cross the placenta and attack the baby's blood cells.

We also use this technology to detect Down syndrome. It took me ten years to develop a robust technology to do this. We came up with this technology around 2007-2008, then it took us another few years to do clinical trials. Eventually, in 2011, we launched it into what is now called NIPT. This non-invasive Down syndrome test is now available in 90 countries. This year, in China alone, it is estimated that some four million NIPTs would be carried out. We had licensed part of our NIPT patent portfolio to Illumina and Sequenom, which was then sublicensed to dozens of other companies. I had also co-founded a company, Xcelom, which provides NIPT service in Hong Kong.

It was Janet Wang, the previous Commissioner for Innovation and Technology in Hong Kong, who encouraged me and my colleagues to set up Xcelom which currently has approximately fifty percent of the NIPT market share in Hong Kong. Beyond NIPT, my research team hypothesized the phenomenon of a fetus releasing DNA into the blood of its pregnant mother is a mirror image of a cancer releasing tumoral DNA into the blood of a patient. Consequently, over the last twenty years, our research group worked on both phenomena in parallel and licensed the cancer detection inventions from CUHK into a new Hong Kong company named Cirina.

Cirina was founded with a team in California and one here in the Hong Kong Science Park. Cirina has a particular focus on cancers that are common in China, such as liver cancer. In contrast, Grail has an interest in cancers such as breast cancer and lung cancer. Also, many of the staff members at Grail come from technology companies in Silicon Valley, such as Alphabet. Working with them gives us access to powerful computer and data science expertise and infrastructure.

How is the company going to be structured? What will be the top priorities? Will you look at cancers simultaneously, will you be looking at the platform technology and to

which geographic areas are you going to expand first?

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I think this is a very competitive area. With just the resources of Cirina we have to prioritize much more carefully but with the assets and the combined resources of Cirina and Grail we can actually tackle more than one cancer in parallel. This is very important because, ultimately, we aim to save lives and we want to realize this goal as fast as possible.

We heard that academically speaking Hong Kong is very strong at academic research, but we also heard that professors tend to be a bit shy when it comes to commercializing their product. However, you seem to be an exception. To what would you attribute this commercial awareness?

I think there is a process of training and realization. I was quite lucky that from a very early stage in my career I started to learn to protect intellectual properties through the filing of patents. I did so ever since I was a medical student in Oxford and over the last 25 years I had many opportunities to hone these skills. When I returned to Hong Kong, I tried to pass on these skills to my students, even to first year PhD students. This is very important because you cannot build a commercial technology without a very strong IP foundation.

Also, for the last 20 years, because of the global interest in NIPT, we have experienced many different types of legal procedures involving patents. While it was very time consuming, it was very useful. The whole atmosphere in Hong Kong is changing as well. Twenty years ago, it was very difficult for an academic to found his or her own company. Also the students are more receptive to joining and even starting up new companies. The government is also increasingly supportive. Indeed one of my first large grants was from the Industry Support Fund from the Hong Kong Government in 1999.

How would you rate the attractiveness of Hong Kong as a biotech hub? Is it too late given the fact that Singapore, China and Thailand are big competitors? Where is Hong Kong’s niche?

I think that we need to be humble. We must acknowledge that in many aspects, Hong Kong is a relatively late-comer to the biotechnology space Many professors still approach research in a purely academic context, rather than from a translational angle. Hong Kong is also very expensive, especially with regard to space. However, one advantage is that we have a very good healthcare system. Here we can do clinical trials which are well recognized and accepted around the world. Of

course, there are also many areas where we need to improve. Some think that Hong Kong's legal system is good – that may be the case in general. However, in terms of IP litigation, the legal system in Hong Kong needs a lot of development, e.g. the training of lawyers and judges in the IP space, and the possibility of setting up specialised IP courts.

How close are you to developing this early detection of cancer in the blood?

When one has cancer, some tumour cells would release their DNA into circulation. I regard cancer as a genomic disease, because cancer is associated with mutations and other changes in the genome. We believe that by sequencing DNA in the blood we can see such changes and hence diagnose cancer early. Of course, we realize that there are many different types of cancer and that it is a very heterogenous disease. We have started our research and development activities in a number of well-defined cancer types first and from that experience we hope to expand to other types of cancer.

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Is there an advantage in being a biotech company working on this as opposed to the big traditional diagnostic companies?

I think that one advantage of my team is that we have been studying prenatal testing and cancer detection in parallel for the last 20 years. Developments and concepts generated in one area would frequently impact the other area.

Having moved from NIPT to this new field of cancer, how do you find it?

Now my team spends 50 percent of our efforts on prenatal and the other 50 percent on cancer. Almost every single characteristic that I can think of in the field of cancer detection using circulating DNA would have its parallel in the field of NIPT. For example, our genome can be seen as stretches of DNA that when linked together is like a string that is some two meters long. In reality, the DNA is broken down into tiny fragments, and strangely the DNA fragments from the fetus that are found in maternal plasma are shorter than those coming from the pregnant mother. To illustrate the power of working in both cancer detection and NIPT, we have also found that the cancer DNA fragments in plasma are also shorter than those from non-cancer cells.

There is also another phenomenon called DNA methylation. This is a type of natural biochemical modification of the human genome to control cell function. Indeed, cells from different tissues of the body have their genomes modified in different ways. Recently, we have developed a new technology called "Plasma DNA Tissue Mapping", in which we use DNA methylation patterns to

locate aberrations that we see in the blood plasma. Hence, if we find telltale signs of cancer in someone's blood. Plasma DNA Tissue Mapping can tell us in which organ that cancer is likely to be located.

Is it a surprise that no other companies or researchers have seen the links between the two types?

Most groups working in the field typically work on either NIPT or cancer. That said, in recent years, a small subset of companies and researchers are now looking at both.

You have a strong commercial sense. How involved are you in the commercial process of Cirina and Grail?

My first love was science so I am on the technology development side to generate patents. I am serving on the global scientific advisory board of Grail.

We heard that it is quite hard to go to the US as a Hong Kong based company to showcase indigenous technology. There seems to be a lack of branding and reputation. Where do you hope to see Hong Kong Science going in terms of international recognition?

Well you basically need more success stories. Our strength is our people. We need more people who are academics, scientists, engineers and entrepreneurs to start our own companies and make a name for ourselves.

What would you say is Cirina's contribution to Hong Kong's innovative ecosystem?

I hope that people will look at us as a success story and with time that we are able to create a technology that has a global impact.

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