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Dr. Grace Zhou, dean of SIIBR, discusses the Instituteâ??s priorities, the benefits of being located in Shenzhen and the cityâ??s potential as a global innovation hub. Zhou also outlines the major recent developments for her company, ImmVira.

To begin with, Grace, our readers would be extremely interested in hearing about your story. Firstly, to move from academic research to the commercial biotech space is a big step for many professors and researchers. Why were you interested in making this transition?

I have always been â?? and still am â?? incredibly passionate about fundamental science and basic research. It is exciting to never know where my research will take me. I started my career at the Shanghai Institute of Biochemistry, Chinese Academy of Sciences, spending almost 11 years there, receiving first my PhD and then a promotion to Associate Professor. At that time, I received the national award and a Special Government Allowance â?? I was the youngest person to receive this award! At that time, I felt like I knew everything. I was very proud to call myself a virologist. One day, my father came down with the flu, so he consulted me for advice. I told him, as there is no cure for the flu virus, there is nothing you can do except to rest in bed and drink a lot of fluids. After a few days, you will feel better naturally. His response? He looked at me and sighed, I cannot believe, after spending so much money on your education, your answer is to tell me you cannot even do anything for a simple flu!

He was joking, of course, but this little conversation has always stuck with me since. After working as a scientist for many years, at some point, I started to ask myself: what is the purpose of publishing so many research papers? I wanted to know if I could actually do something to help my family members. At that time, I did not have huge ambitions, I just wanted to be able to help the people around me. This is why I went to the University of Chicago to switch to studying human viruses.

Virology can sometimes seem rather hopeless, because it is incredibly difficult to develop a cure or vaccine. At the University of Chicago, we tried to develop a cure or vaccine for the herpes virus, but ultimately failed. The turning point came in 2005, when I started my work on oncolytic viruses, which hinted at potential breakthroughs in the treatment of solid tumors in the future. The biggest achievement for me here was the development of the first targeted virus that only targets tumor cells, not normal cells. We were granted three patents for this discovery.

This is when I started to ask myself seriously, can we do something more with this? Can we take these patents to the market to produce a commercial product that might help patients in the future?

Having built extremely successful careers in both Shanghai and Chicago, what motivated you to relocate once again to Shenzhen to help establish the Shenzhen International Institute for Biomedical Research (SIIBR)?

In 2009, the University of Chicago research team working on this oncolytic virus project â?? including some of the worldâ??s most renowned professors in this space â?? therefore established a company called Catherex, with the vision of developing this oncolytic virus and take it to pre-clinical studies. However, at that time, it was incredibly difficult to raise funds in the US because the oncolytic virus field was still unrecognized.

This was why I decided to return to China in 2013: to bring our IP here and see if it is possible to set up our company here instead. I toured many of Chinaâ??s largest cities, including Beijing, Shanghai and Suzhou, and ultimately chose Shenzhen as the ideal location for a very simple reason. The Shenzhen government not only supports the industry in words but also in policy and concrete action.

I am originally from Shanghai, so I did not have any connections in Shenzhen when I first arrived. As an academic, I initially also kept my distance from government officials. But Professor Albert Yu, Chairman of the Hong Kong Biotechnology Organization (HKBIO), connected me to the Shenzhen International Bio Valley initiative the Dapeng New District government in Shenzhen was organizing, and invited me to an official meeting HKBIO was having with them. I saw my opportunity in that meeting! I told them, if you really want to establish a biotech science and industrial park like this Bio Valley, you need to ensure that you have strong companies with commercializable products. I just happen to have the kind of product you are looking for!

I gave them our business plan but did not expect much. Later that afternoon, however, a senior government official called me to say, while he did not understand the science behind our project, he thought the team behind the project was extremely impressive. He invited us to return to Dapeng New District the following week to discuss potential opportunities for collaboration â?? which involved the establishment of this very institution!

The Dapeng government saw the caliber of our team and said it would be a waste to simply establish a company. After all, we have three members of the Chinese Academy of Sciences along with other extremely well-known scientists and professors globally. At that time, as well, Shenzhen was extremely eager to bring in high-level educational facilities and institutions. As three of our co-founders were affiliated with the University of Chicago, the idea was initially to establish a satellite campus here, but based on my knowledge of University of Chicago, I said this was not possible. However, what was possible was the establishment of an independent institution. Therefore, in April 2011, I suggested this to Professor Roizman, the team discussed it, and the decision was made!

The Institute has been operational for around two years now. What have been the advantages of being based in Shenzhen?

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The support from the Shenzhen government has been instrumental. There have been four official meetings with the team and senior government officials, including then-Mayor Xu and Vice-Mayor Tang. The first time Mayor Xu met us, he actually said, you have brought the projects that I have earnestly been waiting for!

This support has been critical to our operations. First and foremost, they actually provided a building for the Institute â?? where we are, now. They also funded the refurbishment of the building to our needs, through the Dapeng New District government. This was extremely important, because the Dapeng New District is a relatively new district in Shenzhen, established in 2012, without any existing biomedical or life sciences infrastructure. This was therefore a win-win for the District and for us â?? the Shenzhen government invested CNY 46 million in this.

We were also able to tap into the many sources of research and talent grants and funding across national, provincial, municipal and district levels! In 2015, for instance, my oncolytic virus project and team was awarded CNY 15 million under the Shenzhen governmentâ??s Peacock Plan. The rest of the five projects under the Institute applied for separate research funding and received CNY 3 million each. All these kick-started the Institute.

The arrangement was ideal. The management team â?? including myself â?? all hold foreign nationality, so we are aware that we need to demonstrate our commitment to our surrounding community. This is why the Dapeng government owns the building they have given the Institute to use, but we own all the IP that the Institute and its spin-off companies produce, which will generate our operational capital.

The Shenzhen government is also very smart, because it told us that it could fund our research but not our administrative operations, we had to also become self-sustainable. Therefore, in 2015, we decided to spin-off the two mature projects we had into companies and raise funds for them separately. This is where being based in Shenzhen also confers an advantage. The VC and investment scene here is extremely active. One of our first funders was Triwise Capital.

With significant capital being invested here and also top academics and researchers like yourself moving here, is Shenzhen ready to be a truly global innovation hub?

Shenzhen has many strengths and the government is very supportive. At the same time, they are also very aware of the cityâ??s current areas for improvement, which is extremely important as well. The current weakness is in education and healthcare facilities. When you consider the top universities in China â?? and indeed, the world â?? their reputation and quality have been built over centuries. Shenzhen cannot catch up organically within just a few decades, so the governmentâ??s strategy has been to bring talents from all over the world to Shenzhen. This is why we have a number of incentive policies like the Peacock Plan, which is now very famous, but also many others, like the Individual Talent program, and so on.

What is even more attractive is that Shenzhen uses a system of â??recognitionâ??, unlike many other cities that follows a review process by an expert panel. In Shenzhen, as long as an individual or team meets certain requirements or criteria, they will automatically receive the grant or award. For instance, two of my post-doctoral students met the criteria of a particular award and received a personal grant of CNY 1.6 million over five years â?? which can be matched 1-1 by the Dapeng district government! This is highly significant, and takes a lot of the financial pressure off research projects and institutions.

Similarly, the city still lacks experience in the establishment and operations of science and industrial parks and zones. It is not enough to construct some buildings, it is essential to have the necessary infrastructure, as well as the surrounding industrial ecosystem, for biotech companies to be able to

successfully commercialize their products. This is why the active VC environment here is very helpful. We are working with our investors and partners to bring in CROs into Shenzhen and Dapeng New District as well to build up the life sciences R&D ecosystem.

Companies will have to adapt and find the right niche. For instance, SIIBRâ??s location in Dapeng New District is extremely conducive to basic research because the environment is very peaceful. However, when it comes to development and commercialization, its distance from the city center is a bit disadvantageous, so we are also now looking to establish a virtual incubator closer to the city, for instance, in Futian, Nanshan or Guangming districts. We are also establishing an international network of local investors as well as international teams with incubator experience.

Shenzhen is definitely becoming a very â??hotâ?? city in this area. What advice do you have for professors or researchers looking to come here?

Interested individuals or teams looking to bring their projects here need to first ensure they are strong enough to compete. Shenzhen offers incredibly attractive incentives and therefore the competition for them is intense. It can be easy to look at some early successes like the Institute but now, it is very difficult to duplicate.

The city really considers the caliber of your team. It is not enough to have one â??bigshotâ?? â?? the entire team needs to be very strong and work well together. In addition, they need to be committed to working in Shenzhen. It is not possible to simply come in, win the grant, and leave. This also means that there must be a good fit between the team and the city as well. On the most basic level, they need to enjoy working in this city!

Teams also need to show that their ideas have market potential, and ideally, market support, with their own money invested in it, which shows their commitment to the project, and also VC backing, which shows validation of their project. The Shenzhen government wants to see that their money is just â??icing on the cakeâ?? and not the main source of funding, so to speak.

Can you share with us the projects that the Institute and its spin-off companies are involved in?

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The main research foci of our team members are infectious diseases and oncology, so naturally, that became the main area for the Institute. We also specifically wanted to bring in products with market potential, because this is an area that China is especially focusing on. We also wanted to focus on research areas most relevant to the Guangdong province.

The original team had two projects: mine, on the oncolytic virus, and one from Professor Ralph Weichselbaum, who is the Chair of the Radiation Department at the University of Chicago, the first one to combine the use of oncolytic virus with radiation in clinical studies. A number of other professors also decided to join us, bringing a project on antibiotic-resistant bacteria in hospitals (e.g. MRSA) by Professor Olaf Schneewind, who was awarded a Chinese Academy of Sciences this year; a project on anti-viral infection; and also small-molecule development from innate immunity to anti-virus. We now have six projects in total, all in the areas of oncology or infectious diseases. Out of the six, two have been spun-off: mine, ImmVira, in May 2015, and Professor Schneewindâ??s, in June 2015. We are now looking to spin off a third company very soon!

Over the past few years, the reputation of our Institute has grown internationally and we now receive many inquiries and visits from groups looking to establish similar institutes or start similar projects. Our success has been a good testimony for the Shenzhen government. Many of these companies or

teams have actually brought very mature products that are ready for commercialization, and we sometimes act as a consultant for some of them. We have also started to offer some start-up companies the use of our facilities as a sort of incubator.

As for your company, ImmVira, what have been the main developments over the past few years?

This is a company I co-founded with my mentor Professor Bernard Roizman, who is really the original inventor of the oncolytic virus. He was the first to discover that the herpes simplex virus 1 (HSV-1) could become an oncolytic agent, if you delete the viral Î³34.5 gene, then the virus will no longer replicate in normal cells, only tumor cells. As the virus replicates and starts to kill the tumor cell, the tumor cell degrades and releases oncogen, which stimulates local immunity. This is why he is known as the Father of the Herpes Virus! When he started his research on HSV in 1965, he was the very first in the world.

My discovery was the creation of the targeted virus. For oncolytic viruses, the challenge with using systemic delivery instead of intratumoral injection is that you will need to inject a huge amount to ensure that some reach the tumor. Typically, over 90 percent of patients will become infected. The best option is to create a targeted virus that can be used for systemic delivery. I managed to modify the virus so that it no longer goes to normal cells at all! We have changed the structure of the virus, its â??backboneâ??, completely, and possess our own IP.

In addition, the virus is also able to express anti-PD-1 (programmed cell death protein 1) monoclonal antibodies. PD-1 is a very hot topic these days, and everyone knows that the overall efficacy is around 26 percent. But increasingly, the research is demonstrating that there are significant side effects. What we have done is use the virus to bring the antibodies directly into the tumor, which reduces the impact of the side effects. In addition, since the virus replicates within the tumor, effectively it is using the tumor as a production factory for more PD-1 antibodies! We are also able to express the immune mediator Interleukin IL-12 â?? itself another anti-cancer virus that also has a strong negative side effects on the liver.

Finally, another benefit is that this virus is not associated with any checkpoints, so we can combine it with any other existing cancer immunotherapy.

This summer, we are beginning clinical trials for our virus + IO-12 combination therapy in Australia. We chose Australia because we do not need to receive IMD authorization prior to clinical trials, unlike in the US or China, which reduces the data required. Secondly, the Australian government is extremely supportive of promoting the country as a clinical research hub, so they are subsidizing 40 percent of the cost, which is a huge incentive. Finally, conducting these trials in Australia will also support us in the conduct of international multi-center clinical studies in both the US and China in the future!

What exciting developments do you have in store for ImmVira in the future?

We also hope to combine the oncolytic virus therapy with radiation. As I mentioned, another co-founder, Professor Ralph R. Weichselbaum, is a radiation. We are also doing research into oncolytic virus-resistant tumors. At the moment, combination therapy with oncolytic virus and PD-1 inhibitor has a great efficacy of 62 percent, but we want to see if we are able to reach the other 40 percent of tumors as well.

As a company, ImmVira is also preparing for an IPO on the NASDAQ Stock Market, so it is a very busy time for us. I am also now considering the question of my position following the IPO. While I have learnt a lot about business in the past two years, I am after all still a scientist by training, so I

may move to the position of Chief Scientific Officer post-IPO.

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But I will definitely continue to be very busy! Our team is already ambitiously considering the establishment of another company. I am also very interested in providing consultancy services to both biotech companies with interesting projects that are now approaching the Institute for help, as well as investment companies and VCs targeting the life sciences skills, who may lack the necessary technical knowledge or background.

As a final question, with so much on your plate as a scientist, professor, Dean and CEO, how do you manage your time and competing priorities?

I am fortunate that I am a rather quick learner, and also, very quick to take decisions and actions. This is very important â?? to be able to do things efficiently. I also actually enjoy multitasking, which is very helpful.

As the Institute has been established for a few years now with different departments running smoothly, it mostly runs on its own, and I simply participate in weekly meetings to ensure it stays on the right track. I spend most of my time at the moment on my company, because we are preparing for our IPO at the moment, so there is a lot of work to do.

As the President of the Institute, I actually still take a lot of pleasure from personally supervising students. Of course, I have not forgotten my original passion in research and basic science, and I am still very interested in that part. After all, you need to have a strong foundation in basic science to drive commercial efforts and obtain more insights. After the discovery and FDA approval of Talimogene laherparepvec (T-Vec) for advanced melanoma in 2015, many people started jumping on the oncolytic virus bandwagon, but it is essential that people working in this field really understands the virus on a fundamental level, instead of just trying to mimic other projects.

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