Interview with Alex Wu, CEO, Crown Bioscience

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Hu Jintao recently announced his ambitions for China to be â??an innovative countryâ?• by 2020? Could you speak to the likelihood of achieving this in terms of biotechnology as you see it?

In the biotech area, China has come a long way. I got my college undergraduate degree in China and went to the US for post-graduate studies, where I got my MBA and Ph.D. The first trip I made back as a professional investor was in 2001. I was looking for biotechnology opportunities, and I found almost nothing. All the major Chinese companies were focused in generics, and some in branded generics, but no innovation in the way of a Western biotech model. When I started to co-found Crown Bioscience in 2006, five years later, things had changed pretty fast. At that time, the most exciting opportunity was service CRO, and for good reasons. To start a US type innovative biotech, you need many things, but two are essential. The first is finance. Itâ??s important to have sophisticated investors who know the area well, and the risk-reward profile, and also know that the horizon is very long, and that drug development operates on a long cycle. Therefore you need patient and sophisticated capital, which China really lacked. Secondly, and maybe more importantly, you need people, a team that knows how to work together and complement each other to discover new drugs. In 2006 and before, we simply couldnâ??t find such a team. Outsourcing services were a nice way to get there, because there were much lower requirements for capital and an experienced team of drug discovery talents compared to biotech.

Crown started as a biology service venture, and we tried to develop and validate very conventional animal models to test the efficacy of compounds designed and made by our clients. The timing was right, because lots of companies at that time were looking for more efficient and cheaper ways to innovate. Big Pharmas realized their old models of doing everything in-house was not as productive. They looked for outsourcing, first to the US, then Europe and Japan, but gradually because of Chinaâ??s cost advantage, they came here. Many investors became excited about this, and Crownâ??s initial investors were based in Silicon Valley, with prior investments in telecom, software, and IT. They had dealt with Chinese outsourcing in these industries, so they thought they could understand outsourcing services, even if biotech was not their specialty. They understood an outsourcing model â?? the revenue, customers, and profit â?? as a typical business.

In an article about outsourcing in the US, one consultant was quoted as saying, â??The emergence of firms like Crown is a worrisome trend for the U.S. economy.â?• He sounds jealous â?? but is he right?

First of all, the interesting thing is that Crown is a US company! Weâ??re registered in California, our headquarters is still in Santa Clara. We contribute many of our top executives which still live in the

US, and we still pay U.S. tax. Any profit we make still gets consolidated into the US In the way Crown has helped China grow, I wouldnâ??t be worried. Also, itâ??s a market economy. Interestingly, last year we acquired a US company based in North Carolina, and expanded their operations. Itâ??s a flat world. Capital goes wherever it expects the biggest return. And the bottom line is that the US still has an advantage in innovation, especially in biotech in hubs like Boston, and U.S. will maintain its advantage in innovation for a long time, because it remains a centre of attraction for global talents. And it will continue to do so. The US will persist in being the worldâ??s main source of innovation but China will gradually gain regional strength, and in doing so must make some contribution. Crown got a break, in a sense, with the turmoil in the US pharmaceutical industry, restructuring and layoffs. People who had a difficult time finding jobs in the US looked to China. Even those who remained in Big Pharma may feel depressed and unhappy in the constantly restructuring organizations, wherein bureaucracy and inertia of the decision-making process really kills morale. Itâ??s an interesting dynamic, and China as an emerging market offers good opportunities for CROs compared to other markets. Crown attracts top talents because we do similar activities as in Big Pharma, i.e. drug discovery and innovation, with the main difference that we get paid to do it. We try to maintain a US culture, a US biotech-like atmosphere to nourish innovation and also try to avoid the kind of bureaucracy and slow decision-making and risk-averse culture. Great scientists are happy doing what they do here with a less burdensome system and culture.

You are a member of ABO, whose members have tripled their turnover since 2009, and now count 50% overall contribution from international partnerships. You have partnerships with big bluechip firms like Pfizer, and domestic players like Yangzijiang Pharma or Jiangsu Hengrui. Whatâ??s the importance of the international market to Crown?

Crown was set up to be a service company with international aspirations. Although revenue from China grows very fast, they still remain very low in absolute terms. Crownâ??s major market will remain companies based outside China for some time. Weâ??re focused on Big Pharma and leading biotechs. The advantage of this approach is firstly that itâ??s a major validation. Their hurdles are very high, and once they recognize you and work with you, itâ??s a stamp of approval. Weâ??re trying to position ourselves as a premium partner in China for global pharmaceutical and biotechnology companies. Weâ??re very specialized, focused on oncology and diabetes; those are the areas we want to be the best and be globally competitive. We have dug deep into science and collaborations with laboratories and leading hospitals and cancer centres in the US and Europe, with the aim of getting even more globally recognized experts to join us. For instance, our entry into diabetes occurred because of an acquisition of a company led by a leading diabetes expert, a globally-renowned scientist. Her expertise immediately brought us to a global level. We try to be leaders in whatever niche we choose, and thatâ??s the only way we can get strategic collaborations with global pharma.
Multinationals are slowly getting into territory traditionally occupied by domestic firms, and MSD, BMS, and Pfizer among others have acquired companies and entered joint ventures. The Chinese government is doing a lot to encourage innovation. Domestic pharmaceutical companies are big taxpayers, and they have got tax breaks, rebates, and sometimes outright grants from the government to encourage innovation. The fact is that it takes time to build up in-house capability, and thereâ??s a big need for innovation, particularly in early discovery, to contribute NMEs and NCEs. There are opportunities for collaboration whereby Crown provides initial innovation, while Chinese companies fill in the gaps in late-stage development, regulatory filing, and marketing and sales. The need is there; Crown can fill the void.

What projects or case studies would you highlight as exemplars or the best stories for our readers?

Crown is most proud of two parts. The first is building very specialized animal models. The traditional cell-line based cancer models are very lousy in predicting clinical outcomes. The cell lines are two-

dimensional and far removed from real clinical settings. The predictability of these models to clinical outcomes is very poor. Sometimes less than 30%; often less than 10%. Thatâ??s why you see so many clinical failures of cancer drugs, mostly due to lack of efficacy. Crown has commercialized a clinically relevant model. We have taken tissue samples directly from dissected patient tumors and have them grown in immune compromised mice. Itâ??s a much more relevant model. The beauty is that you can do a lot of experimentation. Crown has the largest collection of such models in China, and possibly globally. We can do pre-clinical phase 2 trials, because we have a critical mass, for lung and other cancers, as well as the experience in animal model testing for efficacy. With this approach you can see responders and non-responders, and go very deep to find out why they are working â?? or not. This achieves two things: de-risk, to kill projects earlier, before they go on to very expensive clinical trials; and also to go on to define critical clinical populations. Because once youâ??ve found out the biomarkers or biosignatures associated with those responders, you can validate them in clinicals and try to recruit and screen patients for those positive biomarkers that will respond to your drug. This also helps to accelerate the clinical trial, by targeting a smaller patient population with a shorter duration. All targeted cancer therapies in the future will get approved with a companion diagnostic, and this is also called personalized medicine. Especially when dealing with cancer patients, you realize that not everybody is created equal; there are different genetic backgrounds, and tumors are different, so people are really looking for biosignatures to try to target the treatment to the right patient population.

This is important because first of all the cancer drugs are very expensive. And secondly, and more importantly, you donâ??t want to miss the therapeutic window. You want to treat the tumor as early as possible with the most effective drug. After you miss the window, it could be metastasized and advance to a life-threatening stage. Personal medicine and preselection of patients is the future for cancer medicine, and maybe even other indications and disease areas, and Crown is leading the way by providing this cutting-edge animal model approach.
The second point of pride at Crown is that we have established a very powerful in-house proprietary drug-discovery program. We are not working simply in the old way of large chemical libraries and high through put screening. Instead, we do very targeted discoveries, with our own proprietary fragment-based library and very powerful in-house structure biology. Crown can basically crystallize the target protein and resolve a 3-dimensional structure with a fragment from the library, and itâ??s like a lock and key relationship â?? when you really resolve the 3-dimensional structure of the lock, you can find your key that fits the lock much faster. In one project with Yangtze River Pharma, Crown synthesized only about 400 compounds, yet we found an extremely powerful drug. That program is already ready for clinical development after only 18 months. Crownâ??s approach is very fast, very efficient, and we find very good molecules. The molecule we developed for Pfizer has also been selected for clinical development. Crown began this approach only a couple years ago, and now we have several compounds available for clinical candidates. Combine that with our proprietary animal modelling and we really have a powerful proposition. Itâ??s a very exciting position to be in for us and for our investors!

One element you have alluded to, and that is featured in the literature about Crown, is your industry-leading low turnover. Whatâ??s the secret to that success?

Number one is the basic economics. Top talents especially have nice packages at their original employers â?? usually Big Pharma. Fortunately, Crown has been very well-funded through three rounds of financing, so we have the financial muscle to afford those packages. On top of that, you need a good culture. Good scientists get excited for the opportunity to discover new drugs. They want to contribute to the benefit of the patient through their innovation which will also enhance their reputation. Itâ??s a huge reward if they can discover something that can impact peopleâ??s lives. What Crown does is foster an extremely innovative culture, and my job is to provide a platform where everybody can excel and innovate. They can contribute to innovation and come up with novel

molecules, and thatâ??s the attraction for the top scientists. We actively encourage collaborations with academics, universities, hospitals, and research institutes, and we encourage publication and filing patents. Crown wants to be a leader in our area, and the key to keep at the cutting edge is collaboration with experts, both in China and globally.
Itâ??s no exaggeration to say that my number one worry is my team. I always ask myself: Are they happy and doing the best they can? Team-building is a top priority, and I like to develop programs to nurture their growth. Crown isnâ??t just a scientific research institute, weâ??re a business, so the scientists on the management track do a fair bit of managerial work as well, and of course need some training to grow into a good manager and not just a pure scientist. We like to have a very deep deck of good scientists and a large pool of good managers. For the company to rapidly expand, the biggest limit is our people. Without a large number of top talents in science and management, the company canâ??t grow very fast.

When you first sought out investment opportunities in 2001 in China, not much was available. Fast forward five years, and you had founded Crown. Five years later weâ??re at the present day. What will Crown look like five years from now?

Crown has three powerful platforms. The company started as a service provider, generating revenues, profits, and thatâ??s the base of the company: a service platform. The second is using our predictive models to develop a PDX platform â?? a predictive biomarker developer. Crown can work with partners who develop biosimilars, â??me-tooâ?• and â??me-betterâ?• programs, and we can help them find a niche, and test their compounds for new indications. We have models that can quickly develop resistance for reference compounds on the market, and we can find compounds to overcome this resistance. Once you have that data, you are not merely a biosimilar or â??me-tooâ?• producer, your molecule now becomes a second generation compound. This is a very powerful proposition for our partners. The third is that we can develop innovative medicines, more in line with a biotech company, with IP protected molecules and the supporting biomarkers. Crown can develop next-generation molecules that are not only best-in-class in efficacy and safety but a compound with reduced risks and with a well-defined clinical path.

Expanding these three platforms will be the basis for Crownâ??s further growth in the next five years. Crown will probably become more like a holding company with those three separate businesses, and while we deepen our expertise in existing niches of oncology and diabetes, we will also expand into other disease areas such as immunology, or CNS. However, no matter which space Crown enters, we will be a specialized player, and dominant one within the niche. We wonâ??t become a Walmart with a broad market appeal â?? we want to be a specialist in everything we do, a premium provider and a leader in whatever we provide.

China is a very exciting place. For US executives in pharmaceuticals and biotech, they need to think very seriously about their strategy, and broaden their scope beyond the US, Europe, and Japan. In terms of market opportunities, emerging markets are growing much faster. And in pure size, China is already number 3. They should not want to miss it, as a huge and growing source of consumers and also as a potential contributor of innovation.

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