Interview: Guo-Lian Yu, Ph.D â?? Executive Chairman, Crown Bioscience International, Taiwan

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Guo-Liang Yu, executive chairman of Crown Bioscience International, on the innovation-driven approach he has instilled since joining in 2013 and how this unique technology platform company now stands as the world leader in drug efficacy testing, enabling leading pharmaceutical companies to identify the right patients for the right treatment in their quest to develop game-changing oncology, inflammatory, and diabetes treatments.

You have achieved a lot in both science and business; co-inventing more than 420 patents and co-authoring 40 peer-reviewed scientific articles referenced by the scientific community more than 6000 times as well as founding and chairing Epitomics, a company that was acquired by Abcam for more than USD 170 million in 2012. What objective did you set yourself when becoming the executive chairman of Crown Bioscience in 2013?

When Sandy Chau, the co-founder and Chairman of Crown Bioscience, approached me to join the company, his idea was to leverage my industry experience honed at Epitomics to turn around the company. To be honest, at this time, I was not particularly excited by the idea of joining a company with a CRO business model, which I considered to be a very competitive and price-oriented market niche; most CRO companies displaying a broad market approach rather than an innovation-driven focus. As you can tell from my past experiences, the main driver throughout my career has been new drug development, and â?? in the grand scheme of things â?? trying to do things that no one has ever done before.

To convince me, Crown Bioscienceâ??s CEO, Alex Wu invited me to visit their offices and meet their scientists. The quality and the depth of the companyâ??s talent pool, which held at this time around 60 US-trained PhD holders, left a favorable impression on me. Beside this number being particularly substantial for a company that was still rather small at that time, talking with these scientists further convinced me that Crown Bioscience was not a traditional CRO and truly had the capacity of a science-based, innovation-oriented organization.

However, when a company holds such a depth of talents, the value it generates has to be in line with its cost structure to be profitable. When I became Crownâ??s Executive Chairman in 2013, I first decided to take a step back and ask our scientists in which specific part of the drug discovery process we held the potential to establish ourselves as an industry leader â?? to the extent that, within two or three years, our company could be recognized globally as the partner of choice of the most advanced pharmaceutical companies in critical therapeutic areas, such as oncology and diabetes. From my discussion with our scientists, it turned out that Crown Bioscience already held a second-to-none capacity in biology. As a consequence, I decided to concentrate all our resources in this specific area with the ambition to become a global leader in translational services and drug efficacy testing.

Narrowing our scope of action has marked a clear turning point in Crownâ??s history. Now, Crown proudly stands as the top company in the world for drug efficacy in oncology and diabetes, while we are also rapidly building a strong capacity in immunology. More importantly, the companyâ??s approach has changed too: more than three years after I initially joined the company, â??CROâ?• is no longer the appropriate term to describe Crown Bioscience, which has truly evolved into a very focused and innovative platform company. Crown now holds dozens of patents, while the company only had a few in 2013. This number has been continuously increasing, while our patents now target the most groundbreaking innovations. For example, our scientists recently identified specific types of microorganisms that enhance the efficacy of immunotherapies. This example perfectly illustrates how Crownâ??s unique innovation-driven approach enriches our customer-oriented services â?? and this is particularly exciting for me!

How do you explain why more than 95 percent of oncology drugs fail in clinical trials, and what are the solutions that Crown has been developing to increase its partnersâ?? chances of success in this challenging field?

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Oncology is a very personalized field. As a matter of fact, there are no two cancers that are the same. As you know, the development of malignant tumors is caused by gene mutations in the cells, and any aggregation of only seven to eight different mutations will lead to the formation of a cancer. However, up to 3,000 different genes are relevant for such mutations; hence, the total number of combinations potentially leading to cancer formation is absolutely huge. In the meantime, the number of relevant sets of gene mutations varies significantly from one cancer to another, ranging from a few hundred sets of mutation to up to 50,000 for some cancers! Finally, there is another level of complexity to consider: cancer mutates and is continuously evolving over the progression of the disease causing drug resistance, while it is constantly interacting with other cells in the body, whether they are tumorous or not.

Given the necessity of addressing the tremendous subtleties and variations that cancer actually encompasses, Crown has been building an unrivalled capacity in patient-derived xenograft (PDX) cancer models, allowing our partners to test the response to their experimental drugs on a very narrow patient population, whose cancer gene mutations better correspond to the specificities of their treatment. Until recently, the standard model in testing cancer drugs was the transplantation of

human cancer cell lines, which are highly homogenous, preserved in vitro. On the other hand, PDX tumor models are based on the transplantation of fresh human tumor specimens from a cancer patient directly into a mouse, preserving key features of a specific cancer such as invasiveness, desmoplastic reaction, tumor vasculature and cellular diversity.

Beside acquiring a large base of PDX cancer models, we are also developing our understanding of all the mutations by tracking disease progression in an increasing number of gene mutations. Little by little, we have been accumulating a unique database that has undoubtedly surpassed the usually limited information generated by clinical trials.

Concretely, what can a pharmaceutical company that holds a promising oncology compound expect from Crown?

When a pharmaceutical company has identified a new compound targeting a particular pathway for cancer, we can leverage our database to identify the specific sets of mutations for which this compound will work the best. Then, it is usually extremely difficult for pharmaceutical companies to identify and recruit human patients that meet such specific criteria â?? but Crown already holds the PDX models they will need to test this compound. We can then design a large number of different experiments using our PDX models and provide our partners with a level of visibility and clarity: we can try various settings, dosages, and also combinations with other drugs and even compare this compoundâ??s efficacy to that of products already on the market â?? all these options being impossible when tested on humans.

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Crown Bioscience and the pharmaceutical industry as a whole have something very important in common: we cannot be good at everything. As a result, we need to focus on our areas of expertise. This why our business has been growing so fast over the past years: we are a very focused company that has built an unrivalled expertise when it comes to testing drug efficacy, thanks to a breadth of knowledge and database generated from tested PDX models and immunoncology models that no competitors or pharmaceutical companies hold in the world. The benefits for pharmaceutical companies are obvious: instead of having to tell us how to test their products, we can tell them how to better leverage the therapeutic potential of their ground-breaking compounds.

You are already partnering with the most advanced biopharmaceutical companies in the world. What is your assessment of the R&D-driven Taiwanese industry?

Taiwanâ??s innovation capacity in oncology still lags behind some of the most advanced countries in the world, although the country has undeniably been catching up over the past few years. My perception is that, initially, Taiwanâ??s biotech industry followed the path of the very successful domestic electronics and IT sectors, which first gained international momentum by copying American products and manufacturing them at Asian costs â?? before eventually following a true innovation-driven strategy.

In the biotech sector too, the mentality has been changing recently. At the moment, our interactions with Taiwanâ??s innovative industry are still emerging, but they will undeniably gain in intensity as the local R&D-driven industry continues to climb up the innovation chain and look at developing more and more innovative treatments in oncology.

In this regard, Crown can contribute to bringing international expertise and make the local industry benefit from our pioneering technologies and PDX models â?? this is exactly why we decided to set up an affiliate in Taiwan! If any company in Taiwan is developing innovative oncology drugs based on novel mechanisms of action, then Crown undoubtedly stands as the best partner to help them

identify for which specific gene mutations and patients their compound will be the most efficient.

Since you joined the company, Crown has moved from being a CRO to a pioneering platform technology company. How do you see the company further evolving in the upcoming years?

First, we will continue to strengthen our technology platforms, enriching our overall capacity with an increasing number of PDX models and rapidly developing our immune-oncology models. Our first and foremost objective is to further expand our partnerships with leading pharmaceutical companies in oncology, immunotherapies, and diabetes.

On the other hand, we want to leverage our technology platforms and database to take over and reposition some of the 95 percent of oncology drugs that failed in late stage clinical trials, especially for efficacy reasons. Running our PDX models, we could then identify for which patients these drugs should be used. In this regard, we recently in-licensed a drug that failed in phase III clinical trials in ovarian cancer from a US company. We identified a set of biomarkers that would allow us to select the best patients for this drug, narrowing the target from hundreds to only a dozen gene mutations. If successful, this approach could reveal itself to be extremely rewarding for the company: these failed drugs are already phase III clinical trials assets, whose chances of success could be tremendously increased by leveraging our technology platform. If this first attempt happened to be successful, we will then probably repeat this approach and develop a brand new business model, potentially by partnering with pharmaceutical companies.

Third, we could apply our PDX models to clinical settings. In some countries, there are already more than 70 oncology drugs available to the patient and there are hundreds new drugs under clinical studies. Nevertheless, the traditional treatment pathway usually is to provide a patient with a given cancer drug, and then switch to another one as soon treatment resistance occurs. No patient in the world has ever had the chance to be treated with the cancer drug that offers the best match to his gene mutations.

Do you mean that you envision leveraging PDX models to directly service patients â?? and not only drug development companies?

Let me give you an example. We encountered a cancer patient in Beijing with a late stage colorectal cancer. We developed PDX models using his cancer tissue to test a dozen of drugs and combinations and eventually found out that only one combination of two drugs would work for this patientâ??s cancer. Although the patient initially had only a few months to live, this combination worked for 13 months before his cancer appeared again. This time, instead of simply running our models, we took off a 3D cell culture to build an organoid [*a miniaturized version of an organ produced in vitro in three dimensions, e.d.*], on which we tested different sets of drugs. Interestingly, we found out that â?? once again â?? only one specific drug would work for his cancer at this stage of development.

This example perfectly demonstrates how close PDX models are to clinical usage, and Crown is undoubtedly the best-positioned company in the world to explore this promising new field. We are actually about to set up a joint venture in China with a pharmaceutical company and a world-class university to start providing patients with this ground breaking service.

In the grand scheme of things, the more activities that Crown ventures into, the more data we generate and the more powerful the machine becomes â?? enabling us to start predicting a lot of things. I see artificial intelligence massively entering the biopharmaceutical industry in the mid-term, whether it relates to research, drug discovery or patient care. In this regard, the most important thing to me is fostering entrepreneurship and creative thinking in our company, while â?? in the meantime â?? Crown becomes a more mature organization and remains focused on building long-term value

for its shareholders. For a company like Crown Bioscience, the main growth driver is innovation, and we need to support and continuously nurture this critical asset.

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