Interview: Du-Shieng Chien Ph.D – President & CEO, TaiRx, Taiwan

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Du-Shieng Chien, President & CEO of TaiRx, a Taiwan-based biopharmaceutical company focused on unmet medical needs, provides insights into the recent development of CVM 1118, a revolutionary cancer treatment targeting breakthrough mechanisms to tackle tumor development and the first drug of its kind to have already started clinical trials in the US, as well as an update on Rexis

®' advancement, TaiRx's groundbreaking treatment for sepsis that could soon enter the global market.

Could you provide our international readers with a brief introduction to TaiRx and explain why you decided to take the leap of faith to start your own biotech company?

So far, the development of innovation-driven, biopharmaceutical companies in Taiwan has mainly occurred through two main patterns. The first one mostly concerns historical Taiwanese companies, essentially focused on generics, which are transitioning to an R&D- focused model by investing a large share of their revenues to develop their research capacity. The second one relates to the creation of *ex nihilo* biotech companies, usually financially backed by local investors, whether it is another pharmaceutical company and/or a venture capital funds. TaiRx's development model however does not really fall within one of these two traditional patterns.
In late 2009, I, and my co-founder Dr. Yi-Wen Chu, started to gather a team of very experienced pharmaceutical professionals and scientists, which displays two fundamental assets: a remarkable experience in drug development and strong business connections to international markets,

accumulated through decades of experience in the US and Europe for companies like Pfizer, BMS, and Bayer. We then decided to found Efficient Pharma Management Corp. (EffPha), a consultancy focused on providing Taiwan's thriving biotech companies with our team's expertise in drug development.

As part of our consulting activities, EffPha was assessing the attractiveness of promising drug leads coming out of Taiwan's most prominent universities and research centers. This is how we came across CVM 1118, which was still at the discovery stage at that time, in the laboratories of Taiwan-based China Medical University. We identified this compound held the potential to become a breakthrough small molecule and decided to take care of its development. We then licensed-in this compound and founded TaiRx in 2011. Starting from scratch, we sent this promising compound to independent laboratories all over the world before upgrading its IP-linkage and raising funds from other pharmaceutical companies and venture capitalists funds to ensure we would hold the financial means that drug development requires.

What makes CVM 1118 so special that it motivated you to embark on this new adventure?

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CVM 1118 is a completely New Chemical Entity (NCE) in the oncology area, which is targeting breakthrough mechanisms to tackle tumor development. Without entering into too precise scientific details, CVM 1118 looks at halting vasculogenic mimicry, a tumor development process that used to be a moot point among oncology researchers before being now widely accepted by the scientific community. Vasculogenic mimicry relates to the now-proven capacity of highly invasive and genetically deregulated tumor cells to create their own blood-delivering tubes, independently from classical angiogenesis. The tubes that these smart tumor cells build are dangerous not just because they allow them to receive needed blood: they also foster the migration of tumor cells to new parts of the patient body (metastasis), which is responsible for most cancer deaths.

As a result, blocking vasculogenic mimicry appears as a completely new approach to tackle cancer progression. At the preclinical stage, CMV 1118 has already displayed very promising results by altering the activity of Nodal, a gene that drives vasculogenic mimicry. In 2015, CMV 1118 then became the first drug in the world targeting vasculogenic mimicry to enter phase-I trials in the US and in Taiwan, while we now expect to receive these data before the end of 2016. Looking forward, we plan to start phase-II trials in the US in 2017, probably through two or three different sites.

When it comes to phase-III, multi-center trials, most Taiwan-based biopharmaceutical companies look for partners to jointly handle this critical stage. Considering your recent

progress with this pioneering molecule, what is your strategy to further advance its development?

We indeed also envision to license out our drug to larger-scale pharmaceutical companies that could perfectly assume a multiple-center, global phase-III trial. As a matter of fact, we had integrated this next step in our strategic plan since the very beginning of the clinical development of CVM 1118. For example, we see that many Taiwan-based biopharmaceuticals companies are now leveraging TFDA's recognition to exclusively conduct phase-I clinical trials in Taiwan before moving to the US and Europe for the phase II, mainly in order to save cost or because of language issues.

Nevertheless, considering the pioneering therapeutic approach of CVM 1118, we did not want to take any risk to delay the development of our compound or compromise US FDA approval. As from the beginning, we then adopted a global development approach and filed an IND application to the US FDA. After this first step, we went replicated the same process toward Taiwan TFDA.

We now expect that it will be easier and faster to license out this compound to international partners, thanks to the extra layer of data transparency we can display after having conducted all our clinical trials in the US. Furthermore, our partner will also be able to progress to late-stage clinical trials more rapidly, as they will not have to repeat trials on Caucasian patients – as it could have happened with trials conducted only in Taiwan.

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Regarding the opportunity to license out this groundbreaking molecule, would you be interested in keeping the rights of CMV1118 for some specific geographies ?

Once we will license out the US and other global rights, our strategy will be to keep the rights for Taiwan, before using these data to receive market approval for the Chinese market. Considering the current political context and the remaining frailties in the Chinese IP framework, entering this market is an opportunity we are currently assessing, but no decision has been taken yet. China undoubtedly is a target market for us, but don't want to take the risks to compromise any of our past achievements by entering too suddenly this promising market. Overall, our approach would be able to bring out treatment to international markets without losing four years between our entry into the US and its launch in other strategic geographies, such as Mainland China.

Although nothing has been signed yet, we are already discussing with one pharmaceutical company the opportunity to license out the global rights – excluding China and Taiwan – of CVM 1118. In addition to China and Taiwan, we are also negotiating to keep the rights for Korea and Japan, where we think we might hold more experience than our partner to develop this compound in these countries.

In April 2016, TaiRx's Rexis®, an add-on injection therapy for patients with sepsis,

received Taiwan FDA-approval to start a phase-III multi-center clinical trial. Why did you choose to focus your effort on a treatment targeting sepsis?

That’s probably one of the most distinctive features of TaiRx: we are exclusively focused on challenging health issues! Considering the sheer scientific expertise that we gather within our walls, we believe we have a responsibility toward patients to concentrate our efforts on targeting unmet medical needs, whereas many Taiwan-based pharmaceutical companies however content themselves with developing me-too drugs, which are based on established chemical structures. Although me-too drug development tremendously reduces the risk exposure of the company, we definitely have chosen a different development path for our company.

Rexis ® doesn’t escape this trend and indeed targets sepsis, a very complex but also life-threatening, multiple-stage disease. First, patients get infected by the bacteria or virus, which is extremely common in hospitals – especially in intensive care units. Then, sepsis worsens; blood flow to vital organs, such as brain, heart, lung, liver and kidneys becomes impaired. Sepsis can also cause blood clots to form in, which can lead to varying degrees of organ failure and gangrene. Although patients usually recover from mild sepsis rather easily, the mortality rate for septic shock (the last stage of the disease) is nearly 50 percent. Furthermore, any episode of severe sepsis tremendously increases the risk of future infections to happen again. Rexis® aims at maintaining a sound balance between the auto-immune and the inflammatory systems of patients infected by sepsis, in order to prevent them from entering the stage of multiple organ failures.

As pharmaceutical scientists, we foresee that still-unknown viruses and infectious diseases will continue to emerge and threaten the global population, as we unfortunately saw it happening with the outbreak of SARS that hit Southern China in 2003. In the situation of such large-scale epidemics, hundreds of thousands of people may get infected, which will inevitably nurture a skyrocketing prevalence of sepsis. As a consequence, there is an urgent need to develop a game-changing treatment in this field.

Why did you choose to develop this product in Taiwan?

Despite Taiwan cannot yet objectively be considered one of the most advanced countries in the world in terms of clinical research, we however still belong to the high-end of the global medical spectrum. Furthermore, we noticed that each region of the country displays different responses to the development of sepsis, allowing us to produce a deep quantity of data while only conducting a single six-center phase-III trial in Taiwan. This trial also proudly stands out as the very first phase-III trial for sepsis ever conducted in Taiwan.

We now expect to finish patient enrollment by the beginning of Q2 2018, and we will need another quarter to examine and release our data. We then plan to start manufacturing this treatment in Taiwan, where we already closed an agreement with a local manufacturing company. We will also

license out distribution and manufacturing rights for international markets as well as for Taiwan.

As President and CEO of TaiRx, what are your strategic priorities?

First and foremost, we need to finish phase-II trials for CVM1118 in the US and Taiwan. Depending on the evolution of the macro-economic environment in Mainland China, we may be tempted to initiate clinical trials in the country, while starting trials in Japan will also be one of our mid-term priorities.

On the other hand, we need to ensure that Rexis®'s phase-III trials come to their end without any disruption.

In the meantime, we will increasingly work on new formulations of current cancer and chronic diseases treatments, mainly with the objective to reduce the increasing pill burden that is hindering patient adherence, especially for elderly population.

As a result, the next two and three years will be extremely busy for us, both from R&D and commercial points of view, while we plan to IPO on Taipei Exchange at the beginning of 2018.

How do you want TaiRx to be seen among the international biopharmaceutical landscape over the next five years?

When founding TaiRx, our initial objective was to become the first biopharmaceutical company from Taiwan to bring an NCE to the global market. This achievement would definitely prove Taiwan has managed to transition from an industry historically focused on generics to truly join the small number of advanced countries that can bring new, innovative treatments to patients in the whole world.

Drug development has indisputably become a global competition in which companies from various scales and with different levels of resources are involved. I however deeply believe that if you hold the right team, a small company like TaiRx can make a real difference and deliver to the world a molecule that holds the potential to save lives, although we will have to look for worldwide partners to fully unlock its therapeutic potential and bring it to the global market.

In the grand scheme of things, TaiRx's overall objective is to turn cancer into a chronic disease that could be controlled as long as patients follow the right treatment. This objective could be reachable within a decade, maybe only five or six years, but in this endeavor, our priority will remain to preserve the quality of live of our patients, which should always come before our ambition to bring ground breaking treatments to the market.

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