Zhou Mingdong – Founder & CEO, Zensun, China

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One of the earliest innovative biotech companies in China, Zensun has developed what its founder Dr Zhou Mingdong calls a rare made-in-China first-in-class therapeutic candidate, the cardiology treatment, Neucardin®. With regulatory approval in the bag, Zensun is now expanding its new drug development to therapeutics for ageing-related diseases associated with deteriorating organs, including Alzheimer's Disease and functional constipation.

With its nearly 20-year history, Zensun is one of the pioneers of biotech innovation in China and is still standing. What has made Zensun so resilient?

The reason is we are at the cutting edge of science. Our cardiology treatment, Neucardin® (Recombinant Human Neuregulin-1), is a very rare first-in-class drug developed in China. The specificity of Neucardin® is that it directly improves the myocardial structure and strengthens the systolic/diastolic function of the cardiac muscle in patients suffering from chronic systolic heart failure (HFrEF). Neucardin® stands out from existing drugs that mainly rely on vasodilation of the artery, reduction of the heart rate and natriuresis. Further, Neucardin® could potentially bring breakthrough benefits to patients suffering from diastolic heart failure (HFpEF). Currently available drugs have not been shown to improve the prognosis of HFpEF or reduce associated mortality, for example, vasodilation treatments are largely ineffective at reducing morbidity and mortality in HFpEF patients given their un-dilated phenotype and relative normal ejection fraction. Therapeutic effect on cardiac muscle by administration of Neucardin® may be a promising hope for patients

afflicted by HFpEF. Based on encouraging preclinical results, Zensun is also developing other cardiovascular indications of Neucardin®, such as acute myocardial infarction (AMI).

Years ago, we faced challenges in bringing this treatment to market. Back in 2012, we filed an NDA based on promising results from a Phase II clinical trial. This trial was conducted on NYHA class III to IV chronic heart failure (CHF) patients. We found that class III patients benefited significantly from the treatment with a staggering 60 percent decrease in mortality rate, while no change was observed in class IV patients. We had hoped that the CFDA would approve the drug for subgroups patients. Ultimately, the agency considered the patient group size (less than 200 for each group) too small for the results to be statistically significant and did not approve the drug.

We got back to work and started Phase III clinical trials on a larger patient group. Although China's heart failure patient population is huge, conducting clinical trials in China is not easy due to a lack of infrastructure and capabilities. We were able to recruit 679 patients, which is still considered a small population pool for heart failure survival trials. Again, we found that patients suffering from mild forms of heart failure (NYHA class II and III) benefited the most. We observed an about 20 percent reduction in mortality rate, which, while remarkable, was less than the effect seen in the previous Phase II trial. We faced the task of increasing the sample size to 10,000 patients for rendering this result statistically significant.

Fortunately, we identified a way to subgroup mild to moderate CHF patients with a certain baseline level of NT-proBNP, which is a well-known biomarker associated with the severity of CHF and commonly used for the diagnosis and classification of heart failure. The pooled data from three independent studies of patients with a baseline NT-proBNP level of less than 1600 fmol/mL are shown to have a high degree of statistical certainty with the relative reduction in mortality to be about 70 percent!

Meanwhile, we have been pleased to witness a revolutionary regulatory reform in China in the last several years for accelerating the approval of innovative drugs, including the introduction of "conditional approval." Recently our Neucardin® NDA for treating these target patients was accepted by China's NMPA.

Although six years have passed since our first NDA filing, Neucardin® remains a rare first-in-class drug developed in China in late-stage clinical development. I firmly believe in the potential of Neucardin® to become the first made-in-China global blockbuster.

Why do you think biotech innovation has not yet blossomed in China?

The outside world is under the impression that China is becoming an innovative superpower. But I think this is still an overestimation. While China is good at making incremental improvements to existing technologies, we have yet to see a made-in-China technology breakthrough.

Nevertheless, things are moving in the right direction in China. The Chinese government has implemented dramatic changes to foster the local innovative pharmaceutical industry. New drug approval timelines have been shortened considerably by NMPA. China's capital markets are also opening up to innovative companies with the pending establishment of the Shanghai Stock Exchange sci-tech trading board.

Apart from cardiology, Zensun has also expanded its pipeline into very different disorders such as functional constipation and Alzheimer's disease. Why did Zensun decide to move into these treatment areas?

Although these two diseases have attracted a significant amount of research and investments, these efforts have not yielded a cure. They present a great challenge to scientists. Zensun decided to tackle this challenge head-on with novel therapeutic strategies.

Functional constipation and Alzheimer's disease (AD) seem like totally different conditions, but in our drug discovery program, both are ageing related organ deterioration diseases linked to energy metabolism dysfunction. For instance, the levels of energy metabolism differ significantly between normal brains and the brains of AD patients. All living cells use ATP produced by the mitochondria as fuel. We therefore asked, might these aging-related chronic conditions be related to ATP production?

We explored ways to increase ATP production in animal models. Through trials and error, we combined different approaches and started seeing a small increase. We then increased ATP production significantly by adjusting dosing. Do our therapeutics help with these aging-related diseases? The answer is a resounding yes. If all goes well, we expect to start clinical trials soon for the two mentioned indications.

Now that Zensun has a solid pipeline of drug candidates, are you looking for partners to help you with clinical trials and/or commercialization?

Yes, we are looking at opportunities to work with Big Pharma. We expect to do a deal with our emerging Neucardin® clinical results. So far Big Pharma companies have focused on the oncology field in China, investing in biotech companies developing anti-cancer drugs such as PD-1/PD-L1 and CAR-T cell therapies, and have overlooked the cardiovascular field. However, innovative cardiovascular treatments are garnering increased attention as the industry expects to see leaps and bounds in this therapeutic area in the near future. One example is Amgen, which is developing a drug candidate for heart failure in collaboration with Cytokinetics. Zensun is open to collaboration with international companies who are leaders in cardiovascular research.

Regarding human resources, other innovative companies have told us about the challenge of finding talent suited to innovative pharmaceutical development and commercial success in China. Has Zensun faced this issue as well?

Finding the right talent is definitely an issue in China. The talent pool is limited, and obviously the best and brightest are looking to join the most promising companies. At Zensun, we had recruiting challenges in the past when we went through hard times. We compensated by cultivating in-house talents and built a team of excellent young scientists. Now that our cardiology project is in advanced development, it has become easier for us to attract talent with abundant Big Pharma management experience.

If our readers should remember one thing about Zensun, what would it be?

Zensun is the crown jewel of the Chinese biotech ecosystem, a China-based creator of first-in-class drugs tackling hard-to-treat diseases.

As I said, Neucardin® has been shown to reduce mortality in systolic heart failure and may well be the first efficient treatment for diastolic heart failure. We have also developed novel treatment strategies for aging-related diseases, which may lead to a breakthrough in meeting huge challenges such as Alzheimer’s disease.

Discerning investors have realized Zensun’s incredible potential. In 2018, we secured funding of RMB 504 million (USD 76 million). We have overcome many challenges in our twenty-year journey and are now in the position to reap the rewards of all our hard work.

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