Yiming Yao – CEO, Ronnsi, China

Currently, I believe that we might be the only company in the world working in the area of ovine heparin

18.07.2019

Tags: China, Biotech, Ronnsi, Halal Medicine

Serial entrepreneur and Ronnsi CEO Yiming Yao discusses the inspiration behind the company's formation, its unique specialization in ovine heparin, and his strategy to take the firm to the next level globally.

Mr Yao, you are a veteran entrepreneur, having co-founded a number of biotech companies in China. What was the inspiration behind Ronnsi?

Ronnsi was established because I was interested in working with heparin-related products. Heparin, a glycosaminoglycan, is a natural product discovered over a century ago in 1916. It has been used within the clinical setting for over 70 years now. It is listed on the World Health Organization's (WHO) List of Essential Medicines, used mainly as an anticoagulant in surgery and dialysis. However, the potential of this compound has not been fully explored yet and there are many properties still to be discovered as we know that heparin interacts with over 70 proteins in our body.

The specific opportunity came after some discussion with my friend, Choon Teo and my Indonesia partner Steve Yang, who also owns his own company in Indonesia. At that point, Indonesia had introduced legislation mandating that all pharmaceutical products had to be Halal-certified. Heparin is currently isolated chiefly from the intestinal mucosa of pigs. Therefore, to develop non-porcine-based heparin is highly desirable for the Muslim population.

Additionally, 80 percent of porcine heparin is produced in China. This creates an immediate supply chain risk as a single incident of widespread Africa swine fever in the country will jeopardize the continuous supply of this life-saving medicine. The issue is further complicated by the lack of rigorous quality control in the raising and monitoring of pigs' health in China. The issue is pressing enough that the US FDA has an initiative for the reintroduction of bovine heparin into the market.

A major speedbump hampering the re-introduction of bovine heparin into the US is the fact that bovine heparin has different characteristics when compared to porcine. Therefore, different specifications must be developed for this reintroduction. This is especially true for its anticoagulant activities, which are significantly lower than those of porcine.

We at Suzhou Ronnsi Pharma have developed a new product: heparin from sheep (ovine) intestines. From our extensive characterization studies and also studies conducted in third-party laboratories in the US and Italy, we have demonstrated that our ovine heparin is extremely similar to that of porcine-sourced material. The scientific tests conducted have even gone beyond USP requirements as we want to ascertain the sameness of our product.

Currently, I believe that we might be the only company in the world working in the area of ovine heparin. In collaboration with world-renowned experts and leading institutes like Professor Jawed Fareed, Professor Robert Linhardt and Ronzoni Institute, we have developed the world's first non-porcine-based enoxaparin (low molecular weight heparin), ovine enoxaparin.

We are already in the process of regulatory filling in Indonesia. The Indonesian authority has required a bioequivalence (BE) study to proceed with the regulatory submission. We are required to demonstrate that our product is biologically equivalent to the reference standard to obtain approval. This is a very critical year for us and we target to receive approval for our ovine enoxaparin product in Indonesia this year!

We are also currently working with the US FDA to prepare for a US submission. Authorities in Pakistan and Iran are also amongst the people whom we have discussed this with and have shown high interest in introducing this product into their markets.

Ronnsi has built a world-class scientific advisory team as well as a very experienced and talented executive management team, with our VPs of manufacturing and quality having worked for top US and Europe pharma companies for many years.

Could you share the advantages of your ovine heparin over existing alternatives to porcine heparin?

Currently, the major source of non-porcine heparin, especially in the Islamic world, is bovine heparin. However, bovine heparin is significantly different from porcine heparin. Firstly, the chemical structures of bovine and porcine heparin are quite different, whereas ovine heparin is structurally comparable to porcine heparin. No qualified bovine enoxaparin can be made from bovine heparin due to the structural difference.

Secondly, functionally, bovine heparin is less efficacious when compared to both porcine and ovine heparins. By weight, you need around 1.5 times bovine heparin to achieve the same *in vivo* activity This is even more important because one of the major side effects of heparin is heparin-induced thrombocytopenia (HIT). By dosing more bovine heparin, the occurrence of HIT will likely increase.

Additionally, we have identified a robust supply chain for ovine heparin. China has the largest sheep population in the world, with approximately 170 million sheep out of a global total of approximately 1.9 billion sheep. We are also looking to secure alternative suppliers in countries like New Zealand, Australia, Pakistan and Iran. The supply of bovine heparin is rather limited as a result of a number of historical issues, in particular, the bovine spongiform encephalopathy (BSE) crisis in the 1990s as well as the heparin adulteration crisis in 2008, which caused bovine heparin to be withdrawn from global markets.

In 2014, the US FDA started a high profile initiative (champion by Margret Hamburg, the then-US FDA commissioner) to reintroduce bovine heparin into the US market. However, due to its difference and potential safety issues, it has been five years since the US FDA begin this initiative, and bovine-sourced heparin sodium is yet to be approved as the regulators are challenged with new specifications definition and clinical requirements to accommodate such stark differences.

What other projects is Ronnsi working on?

We focus on truly innovative and novel projects. For example, we have another product in preclinical development that is derived from sea cucumber. As you know sea cucumber is used a lot in Chinese cuisine as well as Traditional Chinese Medicine (TCM), and it is known to boost your immune response. We have isolated a very interesting compound and we are looking to file an IND next year.

The compound showed remarkable anti-cancer efficacy in suppressing primary tumour growth, tumour angiogenesis and metastasis. The anti-metastasis properties were demonstrated in multiple mouse cancer models, especially in surgical removal SUIT-2 pancreatic tumour induced metastasis. It inhibits multiple targets including angiogenesis, P-selectin and heparanase. It also induces TFPI release, especially TFPI-2 release. TFPI-2 has been recognized as a potent tumour suppressor. It inhibits the migration and invasion of human cancer cells. Our studies demonstrated that the compound is a promising therapeutic agent for metastatic cancer and cancer-associated thrombosis management. We are very excited because it has the potential to be a truly first-in-class drug.

A similar molecule was withdrawn from clinical development due to insufficient clinical efficacy. We believe that we have identified the reasons for the lack of clinical efficacy. We are now confident that we will be able to increase our dose escalation regime while maintaining the toxicity of our molecule to demonstrate clinical efficacy.

With such exciting and novel projects, how is Ronnsi designing its commercial strategy?

For our ovine heparin products, we currently have partners in Indonesia. We have also received a significant amount of interests from a number of Muslim-majority countries, such as Malaysia, Iran, Turkey and Egypt. The Muslim-majority countries are severely undermedicated, at 5 percent in terms of heparin, when compared to the US and Europe. With a total of 1.7 billion Muslims globally, the market potential is huge.

We target to have our product approved by the Indonesian BPOM this year. Once approved by Indonesia, we will expand into Malaysia, Bangladesh as well as the Middle East. These are all emerging markets with significant demand for non-porcine heparin. Indonesia is seeing annual GDP growth of five percent, much like China two to three decades ago.

Besides the religious reasons, the regulated markets have been actively searching for a viable alternative to the porcine derived heparin. With the current African Swine Fever epidemic in China and most part of Asia, the shortage of porcine derived heparin is slowly materializing. The price for porcine-derived heparin sodium API has steadily climbed from $35/mega at the beginning of 2018 to the current price of $60/mega. This trend is expected to rage on as there is no end to containing this epidemic. This epidemic has also hastened the pace for regulators in US and EU to find an alternate source.

We are extremely excited about the commercial potential of our sea cucumber-derived product. Although cancer treatment has achieved great success in recent years, especially with immunotherapy and targeted inhibitors, the prognosis for pancreatic cancer remains poor. Pancreatic cancer patients have a 20 percent chance of survival for one year and around a 4 percent chance of survival for five years. Our product addresses this huge unmet medical need, with a potential USD 5 billion market globally!

How has Ronnsi been financing these projects so far?

We have raised a small amount of money but we have also produced some contract research work to generate revenues. In addition, we also work with partners to reduce the costs of drug R&D. For instance, we are working with a company in Suzhou on a profit-sharing basis. They helped us build our GMP facility. This also avoids the need for us to raise a huge amount of capital from the very beginning.

Looking at the industry today, particularly in China, the biotech space is very active but investors are mainly crowded around the immunotherapy such as PD-1/PD-L1 and bispecific antibodies products. We have spoken to a number of investors but I believe their valuations of Ronnsi are too low as we are working in such niche areas. This is why we are focusing on getting our first heparin products approved first. This will prove that we are on the right track and our ideas work. That would give investors more confidence in our company and we would be able to raise more capital.

We have many projects in the pipeline that we are very keen to work on but currently we have to focus first on our two flagship projects because of the limited resources we are working with. In addition, our products are all complex drugs, not single molecules, so the discovery and development processes are very complicated. Therefore, we want to build Ronnsi step-by-step.

On a more personal note, as an experienced entrepreneur, do you have any advice for other entrepreneurs?

My first advice is to find a really good partner who shares similar value and integrity. That is very important to the future success of the company.

Secondly, as an entrepreneur, you have to stick to your goal. Once you set a target, do not waver or change it, even if it seems very difficult. Even if you fail many times, you have to continue to

work on it until you achieve it.

As a biotech entrepreneur, I think it is also very important to do something new and creative. There are so many interesting research topics out there so why should we follow the crowd and jump on the bandwagon? If I sold Ronnsi now, I can start another business with a totally different idea. The important thing is to look at your background and your own experience to identify your own interests and strengths.

Looking forward, what are your priorities for Ronnsi over the next few years?

The major target now is to have our first heparin product approved, after which we can raise more money and/or IPO, so that we can launch additional research programs. We want to carve out our own path. We do not want to follow the trend. My aspiration is to create novel pharmaceuticals to fill unmet medical needs.

See more interviews