Li Chen – Founder, Executive Director, CEO and CSO, Hua Medicine, China

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While others have failed during the last 30 years, Hua Medicine has finally succeeded in developing a breakthrough diabetes treatment controlling blood glucose levels by taking a novel approach and modulating the glucokinase enzyme. The company is now applying the same principles to develop treatments for

CNS disorders. Hua Medicine's CEO, Dr Li Chen, explains his innovative approach to drug development based on his background in laboratory automation and drug discovery, the synergies between the new drug and existing treatments, and lays out his ambition to get his first-in-class treatment to all the diabetes patients around the world who desperately need it.

Dr Chen, before Hua Medicine you had spent 18 years at Roche. What made you decide to start your own company?

I joined Roche's R&D centre in New Jersey in 1992 and spent 12 years working on drug discovery and development. Notably, I was involved in the development of the high-throughput technology that allowed the company to do science on a larger scale. In 2004, I became the founding CSO of Roche's R&D centre in Shanghai, the first such centre established by an MNC in China. The centre's aim was to look at the link between genetics and disease differentiation. Huge unmet needs in China then, as now, include diabetes, cancer and infectious diseases. During my four years, we

established a strong portfolio of drug candidates, including a first-in-class Type 2 diabetes drug, dorzagliatin, which was discovered jointly by Roche researchers in China and the U.S. – the drug for which Hua Medicine is now conducting clinical research and development.

I moved from Roche to establish Hua Medicine following a very interesting discussion I had with Bob Nelson, the founder & Managing Director of ARCH Venture Partners, one of the leading VC firms in the hi-tech and biotechnology sectors. He told me, China needed true innovation like the first-in-class drugs I helped develop at Roche China. “What do I really want to do?” he asked me. I told him that what I really wanted was to create innovative drugs to address the types of diseases linked to genetic, lifestyle and environmental factors, which affect a large number of people in China today. He replied “in that case, we should probably start a biotech company! How much money do you need?” I suggested that USD 50 million would be enough to bring an innovative drug from scientific concept to Phase II clinical proof of concept. He said, “let’s do it!”

For me, it was the best time to set up a company like Hua Medicine. The environment was ripe to leverage global innovation, China’s expertise, the fast-growing technology platforms in order to develop a truly innovative drug in China. Roche and other multinationals had established R&D centres here. Innovative biotech companies, supported by government incentive programs and infrastructure, were sprouting at Zhangjiang Hi-Tech Park and other places. Medical and research institutions across China were starting to seriously engage in innovative research. Competent local CRO companies like WuXi AppTech and Tigermed had been established, and further supported the innovative ecosystem. Finally, international and local venture capital firms had started to pour funds in this ecosystem, which is important, because bringing disruptive discoveries to life requires the fusion of science and capital.

Dorzagliatin is a diabetes treatment with a novel mechanism of action based on the regulation of glucokinase. Many companies, including Merck and even Roche, have tried and failed to bring a similar drug to market. How will Hua Medicine succeed where Big Pharma has failed?

In terms of innovative drug development, Big Pharma and biotech companies do things differently. Big Pharma innovation happens according to a very well-timed clock. After initial drug discovery, if you can advance through clinical trials at a reasonable pace, you continue. If you cannot, you have to stop. Where the disease pathology and the mechanism of action are well-established, this modus operandi works very well. In more complex areas, where the connection and interplay

between the drug target and the disease are not as well-established, it takes more detailed scientific intervention, in-depth clinical research and translational work to determine the link between the target and the disease.

When Roche started GKA research back in the early 1990s, I was actually involved in the lead generation process. Roche was actually the first company to discover that GKA has the effect of increasing insulin secretion in the pancreas, thus reducing blood glucose levels. If the glucokinase enzyme has a defect, it causes early-onset diabetes. Many companies have worked on GKAs but many failed to even enter clinical studies. The few that did encountered safety and efficacy issues. We have taken a very different approach to develop dorzagliatin, which is both efficacious and safe.

I like to use the simple analogy of an automated system. Inside the body, blood sugar control is actually fully automated. Any automated system comprises a sensor and an operation system. The sensor receives the signal and sends a command to the operator, which interprets it and then delivers its operational function. In our bodies, we have a glucose sensor and a glucose processing system. There are glucose sensor proteins, Glucokinase (GK), located in the pancreas' beta-cells and alpha-cells as well as in the tissues in the intestines, which sense glucose change and release hormones to augment the glucose processing to maintain the glucose balance in the body. GK is also located in the liver and plays one of the important post-meal glucose processing role to store glucose as liver glycogen in the body and thereby reduce blood glucose levels. What others missed is that the glucokinase enzyme is not only meant to trigger insulin secretion for blood glucose reduction, its actual job is to maintain blood glucose levels within a very narrow optimal range, between 4 and 6.5 mmol/L i.e. glucose homeostasis, which is critical for maintenance of brain and peripheral nerve function.

At the time, this knowledge was not fully understood. Even though the theory about glucose homeostasis existed, the scientific community did not understand exactly how it is controlled and how the defect of the GK enzyme in the pancreas, the liver or the intestine contributes to the disruption of homeostasis. What is also important is to enhance the capabilities of the GK enzyme without damaging its core function as a sensor. Many other earlier GKAs actually trigger insulin release even when the blood glucose levels are at 2.5 mmol/L, far below the normal levels of 4 mmol/L. Accordingly, while the drugs were effective in lowering blood glucose, it went too far to the other extreme resulting in hypoglycemia. Dorzagliatin is engineered to activate the GK enzyme in a glucose-dependent manner, which means it functions only as needed during periods of high blood glucose levels, reducing the risk of hypoglycemia. This finding was established in our Phase II

clinical trial, and the results were published in the May 2018 edition of *Lancet Diabetes and Endocrinology*.

Your drug is clearly a truly innovative first-in-class treatment for diabetes. What do you expect the impact on patients to be?

Hua Medicine's mission is to discover and develop disruptive medicines for patients' benefits. Diabetes is a major and growing issue in China. China now possesses a quarter of the world's diabetes population with over 120 million patients – 8.6 percent of China's whole population! – while an additional 150 million to 400 million could be pre-diabetic. As of 2017, the diagnosis rate was 47.3 percent, compared to 72.4 percent in the United States. Moreover, the number of diabetes patients is growing at 2.7 percent each year. For many diabetics, the control rate of their blood glucose is less than 30 percent.

As there is no cure for the disease, just disease management, most of the time diabetics develop a host of complications like renal failure, loss of eyesight, cardiovascular diseases and neuropathy. Of course, from the country's perspective, all of these complications also cost the healthcare system billions in taxpayer money.

Our dream is to rescue the patients from the diseased state – to provide a cure for diabetes, if possible! We have two ongoing Phase III trials in China and two ongoing Phase I in the US and have finished eight other clinical trials already. The drug is definitely doing its job. First of all, the drug is improving the function of the glucose sensor, as demonstrated in a study on healthy volunteers. We gave them the drug under fasting condition and waited four hours. Their blood glucose levels dropped because of the reduction in hepatic glucose output by working on the alpha-cell, without causing hypoglycemia. There was no insulin secretion. When subjects finally ate, we immediately observed insulin secretion. Thus, the molecule's ability to modulate the function of alpha-cells and beta-cells is very well demonstrated.

We conducted another study in Type 2 diabetes patients under the same conditions and observed similar results! Blood glucose decreased, no hypoglycemia, and insulin secretion after eating. We also showed that the drug reduced insulin resistance and improved beta-cell function. Beta-cells' most important sensor function is to be able to quickly trigger early-phase insulin secretion. Except for dorzagliatin, no drug thus far has been able to correct this effect.

The diabetes market is currently dominated by big players such as Novo Nordisk, Eli Lilly, Sanofi and Merck. How do you plan to compete with these behemoths?

Hua Medicine does not plan to compete with them! Our drug dorzagliatin is actually best used in combination with available treatment options such as insulin and GLP-1 because these drugs act on the operator while our drug acts on the sensor. By fixing the sensor, the workload on the operating system is reduced, making other treatments more effective and reducing their side effects. In combination, they work synergistically to rebuild the whole system – perhaps more so than any other drug combination in other therapeutic areas! As a result, I think Hua Medicine is actually a natural – and thus far, only – partner to these big pharmaceutical firms.

Hua Medicine is already conducting a series of clinical trials for such combination therapies to determine which available drug works best with our molecule, including metformin, insulin, GLP-1 agonists as well as DPP-4 and SGLT-2 inhibitors. For instance, dorzagliatin actually increases the release of GLP-1 in the body. In combination with DPP-4, we believe that dorzagliatin will improve the pharmacological effect of endogenous GLP-1, removing the need to inject it and suffer the common GI side effects associated with GLP-1 therapies. In the case of SGLT-2, dorzagliatin is a natural partner since one reduces blood pressure while the other decreases blood glucose. Also, dorzagliatin can actually counteract the main issue of SGLT-2 inhibitors, ketoacidosis, which can be fatal. Therefore, I am very optimistic that such combination therapies will improve the life of patients immensely.

This is very positive because I believe a more fine-tuned, personalized care approach to diabetes is necessary. Increasingly, there is more research showing that Type 2 diabetes may not be just one single disease but can be broken into multiple sub-categories. Hua Medicine is already engaged in developing a more personalized diabetes care approach. For instance, we have developed an algorithm to accurately diagnose the disease sub-category of individual patients to help us predict who will benefit most from our drug. For instance, for Type 2-a patients, dorzagliatin can achieve a response rate of over 80 percent. This study and its results were published in the April 2018 edition of *Diabetes, Obesity & Metabolism.*

You mentioned the drug is now undergoing Phase III clinical trials in China. What is your commercial strategy both for China and globally?

It is certainly not easy to deliver our novel treatment to 120 million diabetes patients in China, let alone hundreds of millions more globally. We have a strong commercial strategy already in place,

especially for China.

First, we have assembled an expert sales and marketing team with prior experience in diabetes drugs launches in China for MNCs. Second, we have already conducted two Phase III trials involving 110 clinical sites and hundreds of physicians, which means they are all already familiar with the treatment works. We estimate that there are about 2,000 such clinical sites in China. Third, China has recently implemented its tiered healthcare reform aimed at providing more localized healthcare through community hospitals and clinics, which means patients with diabetes will not have to go to the top Tier-3 hospitals for treatment. Tier-3 hospitals and community hospitals will work together as a healthcare network and this will help us access both current and newly diagnosed type 2 diabetes patients in both urban and rural parts of China. Finally, we plan to leverage the burgeoning e-pharmacy and e-hospital environment by working with companies like Ping An Healthcare, which is actually one of Hua Medicine's investors.

Globally, we would also like to partner with MNCs to launch the drug. We are already collaborating extensively with partners in the U.S. and Europe to perform clinical trials. But while we currently plan to commercialize ourselves in China and Asia-Pacific, we believe that in markets like the U.S., Europe and Japan, we will need to work with major players to deliver our treatment to patients much faster and in compliance with local regulatory environments. This will be a critical step towards Hua Medicine's global success.

Apart from diabetes, Hua Medicine is also working in Central Nervous System (CNS) disorders. Why did you decide to enter this completely different therapeutic area?

It is a common belief that diabetes and CNS disorders have nothing in common but the approach we are using to develop novel treatments for CNS disorders is actually very similar and based on the analogy of the body's processes working as an automated system. As I explained earlier, the GK enzyme modulates glucose sensors in the liver and pancreas. In the brain, the metabotropic glutamate receptor subtype 5 (mGluR5) is the sensor for glutamate variation. Glutamate is an essential neurotransmitter for cognition and movement but cognition is not only the result of glutamate and other neurotransmitters: any defects would cause Parkinson Disease and Dyskinesia. Also, our central nerve function depends on proper glucose metabolism in the brain! As a result, abnormal glucose metabolism can lead to all sorts of cognitive disorders such as Alzheimer's disease. Moreover, there is a strong connection between blood glucose management and proper functioning of the peripheral and central nervous systems.

Therefore, our strategy for mGluR5 is to also try and modulate its activity allosterically, meaning not on the glutamate interaction site, as the agonist/antagonist of the receptor, then adjust its activity depending on the glutamate concentration as we did in dorzagliatin development. Our portfolio of novel mGluR5 allosteric modulators have demonstrated excellent potency, selectivity and preclinical efficacy profiles. They may offer a transformative new mechanism of action with the potential to become best-in-class drugs in a variety of CNS disorders.

Hua Medicine's future looks very bright. What would you like the company to achieve in the next few years?

In the next two years, I am confident we will receive approval for our diabetes drug in China and will have executed a successful launch here. In the next five years, our ambition is to make this treatment available to Type 2 diabetes patients all around the world by forging partnerships with global players. During that time, we would also like to launch a holistic diabetes personalized care system covering prevention, diagnosis and treatment for patients both through physical healthcare centres and online channels.

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