Dong Wei â?? CEO, EdiGene, China

For patients suffering from genetic diseases in China, the frequent and chronic healthcare models that we see in the US and EU may not work

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Dr Dong Wei, CEO of EdiGene, shares the fascinating story behind the establishment of EdiGene, including his close relationship with EdiGene founder Professor Wensheng Wei; the insights he bring from his extensive and varied industry career from biotechs to Big Pharma; and the mission of EdiGene to translate the potential of current gene-editing technologies into novel platforms and therapeutics that truly serve the needs of patients globally.

Dr Wei, your career background is very interesting and varied so could you start by giving us a brief overview?

EdiGene was founded in 2015 by Professor Wensheng Wei at Peking University, whose gene-editing lab is arguably one of the best in China â?? and the world. Professor Wei and I were actually classmates at Peking University, both class of 1987. Four years later, we both headed to the US to pursue our PhD at Michigan State University. Thereafter, we both went to San Francisco Bay Area â?? but there our paths began to diverge. Professor Wei went to Stanford University to pursue a postdoc research with Professor Stanley N. Cohen, while I went to join the US biotech, Chiron, which was subsequently acquired by Novartis.

In Chiron, I worked in the research group led by CSO Lewis â??Rustyâ?• Williams, focusing on drug discovery. After that, I moved on to Applied Biosystems, specifically single-nucleotide polymorphisms. That really piqued my interest in R&D management, so I pursued an MBA at the Wharton School of University of Pennsylvania and thereafter, joined Deloitte for three years of

strategy consulting.

However, my true interest was still translating science into medicines that could help patients, so I returned to industry. I joined BioMarin to focus on taking R&D projects all the way to NDA or BLA approval. By this point, I had moved away from pure science â?? I had to consider other factors like clinical practice, manufacturing standards and so on. This was followed by a number of years at Elan Pharmaceutical (acquired by Perrigo Company) and Johnson and Johnson, both with a focus on Alzheimerâ??s disease.

That has basically been my â??Big Pharmaâ?? career. My friends have an ongoing joke about me: they say that most people start working for bigger companies and then go smaller and smaller. I am a fish that goes backwards: from smaller companies to larger ones. This has allowed me to experience truly exciting science, which, while risky, could still be translated to help patients. That is what fundamentally motivates me.

Why did you decide to join EdiGene?

Unlike me, Professor Wei returned to China after his postdoc in Stanford and became a Principal Investigator at Peking University. In 2010, he developed an interest in genome editing technologies â?? even before CRISPR was discovered. He focused on asking the biggest questions in biology: how to use cutting-edge technologies to solve major questions.

He founded EdiGene in 2015 to focus on building a strong foundation for the application and development of genome editing technologies as both therapeutic and tools. There are many directions you can pursue with such a revolutionary technology. About two and a half years ago, the company really started to take off, with some of their early-stage research projects starting to show significant promise, and consequently, they felt the need to focus.

This is when I came into the picture. Professor Wei and I have very complementary strengths and backgrounds. With my translational experience, I can help to take some of these exciting new ideas into the clinic to develop therapeutics for patients. I was really excited because it would be the first time I have ever worked on a project in China. I know it is a high-risk, high-reward enterprise â?? that is what excites.

What are some of the key challenges that you have faced when setting down a business model focused on genomic editing in China?

There are three main challenges. The first challenge is how to bring my US management style and drug development principles into China. Believe or not, I suffered from â??reverse culture shockâ?? when I first arrived. I had never worked in China before and I did not know how to speak in Chinese for management or science. When I first left China, I dreamt of the day where I would stop thinking in Chinese or having to translate from Chinese to English before saying anything. Now, it is the opposite.

The second challenge is the technology itself: how to translate cutting-edge science into something that could actually help patients. This can be impacted by external factors that are outside our control. For instance, in November 2018, Chinese researcher He Jiankui announced that he had edited the CCR5 gene of two babies, which became extremely controversial globally due to the unresolved ethical issues surrounding gene-editing in humans. This triggered a massive backlash in

part against the technology and in part against Chinese researchers. In that context, Professor Wei and I consider it our responsibility to realize the great positive potential of the technology.

The third challenge is dealing with HR against the backdrop of explosive biotech development in China. For the past few years, Chinaâ??s biopharma industry has grown exponentially, resulting in an overflow of capital and a lot of competition for talent. The challenge is how to recruit the right team to develop our technology. The success of a company ultimately depends on recruiting the right team â?? and this is more difficult for gene-editing companies like EdiGene, which I will explain later.

Cell and gene therapies are still relatively new, and gene-editing therapeutics is even fresher. What is the potential in this area that EdiGene is focusing on developing?

For patients suffering from genetic diseases in China, the frequent and chronic healthcare models that we see in the US and EU may not work. Here, access to healthcare facilities is a big issue. For these patients, it would be phenomenal if we could find a one-time cure to their disease. This is why our first program is an autologous hematopoietic stem cell transplant (HSCT) therapy being developed for patients with beta thalassemia, an inherited blood disorder.

The standard of cure in the US and EU consists of the infusion of red blood cells every couple of weeks. After the infusion, the patientâ??s major organs (heart and liver) may absorb the iron, leading to an iron overload. This treatment requires access to a blood bank, very close monitoring via regular MRI assessments, and iron chelation therapy to avoid organ failure. Patients that do not have access to this technology will ultimately suffer from organ failure, especially beta thalassemia major patients. In EU, about 65% of beta thalassemia major patients can expect to live past the age of 50. In China, they will barely live past the age of 20. This is why it is key to develop a one-time cure.

Another treatment is allogeneic HSCT. But people have different types of white blood cells. To avoid immune rejection, we need to find people with the same human leucocyteâ?•associated (HLA) antigens. Without an HLA match, the patientâ??s organs will start failing and they will be placed in the priority list for organ transplant. However, finding a donor takes time.

EdiGeneâ??s goal is to be able to take the patientâ??s hematopoietic stem cells from the bone marrow, modify one little gene and re-introduce it into the body. These patients will carry their own cure in them â?? and this cure could be a one-time cure.

EdiGene offers a portfolio of *in-vivo* and *ex-vivo* genome-editing therapies for a range of diseases. Can you tell us more about them?

There were two main things to take into consideration when we build our portfolio. First, the need to focus on genome editing. Second, the need to develop other platforms in our portfolio, since genome editing is not easy and there *will* be a bump in the road.

We have two *ex-vivo* platforms: our hematopoietic stem cell transplant platform on which our beta thalassemia therapy is being developed; and our powerful T Cell platform, on which our allogenic CAR-T therapy is being developed. In China, patients cannot spend USD 400,000 like in the US, so affordability with regards to CAR-T is always an issue. Our technology will address this issue â?? we aim to produce a CAR-T therapy from a single healthy donor that can be supplied to hundreds of patients. This will drive the cost down and the quality up.

We are also developing *in-vivo* therapeutics, applying an RNA base-editing technology called *leveraging endogenous ADAR for programmable editing of RNA* (LEAPER), to treat selected genetic diseases. A lot of genetic diseases are caused by point mutations; as a matter of fact, almost half of the mutations we see are guanine to adenine (GÃ A). Our LEAPER technology happens to be able to change A back into G. Other *in-vivo* genome editing technologies usually need to introduce an exogenous protein into cells. For instance, to apply CRISPR system, people usually have to use a virus to deliver a CRISPR-associated protein and a gRNA. Our LEAPER application is easier to use. All we need to deliver is only an arRNA, which recruits native ADAR enzymes in cells for editing. In this case, lipid nanoparticles could do this delivery efficiently. We are very excited about our unique technology! This is our starting point for developing our *in-vivo* genome editing platform.

What is your commercialisation strategy for your therapeutic products?

We hope to advance the therapy for beta thalassemia into clinical trials soon, and we are preparing to talk to the Chinese regulators sometime next year. Recently, two US-based companies, Sangamo Therapeutics and CRISPR Therapeutics, reported positive data for a stem cell treatment for beta thalassemia. This makes everything very exciting! We look forward to attending the American Society of Hematology (ASH) Annual Meeting in December in Orlando to hear more about it, as well as share our own pre-clinical data.

We are mainly planning on launching our product in China. The patient population is mainly concentrated in the southern part of China â?? there are many patients here that urgently need our help.

You mentioned that in addition to therapeutic uses, EdiGene was also working on developing gene-editing technological tools. What is your strategy here?

The other direction that genome-editing can take is in technology innovation â?? and Professor Wei is particularly good at developing novel derivative advancements based on existing technology platforms to solve technological problems. As a result, we have many proprietary technology platforms through which we can help MNCs solve their complex programs. Professor Weiâ??s lab is also known for its expertise in high-throughput genome editing screening. Today, most MNCs are focusing on targeted therapies and a big question is how gene mutations cause tumors to become more or less drug-resistant. A better method is to knock out all the 20,000 genes in the human cell and see which cells survive. Doing this one gene at a time would take up to 5 years. Instead, we use hundreds of millions of cells and perform a whole genome knock-out using CRISPR, shortening the time dramatically. The use of gRNA in CRISPR can be tricky because you are not always able to determine which gRNA you designed is ultimately responsible for that specific cell behavior. Professor Weiâ??s lab developed an elegant solution called iBar^{TM}: mark each gRNA with four barcodes, which allows you to not only compare and analyze the data of hundreds of millions of cells, but also screen fewer cells because the barcodes themselves can also trigger the self-replication needed in the process. Overall, this technology means less labour, better results and fewer artifacts.

Another example is a new platform calledCRISTMAS^{TM}, which allows us to evaluate functional amino acids for a potential lead compound/drug target. The main challenge for targeted therapies against cancer today is the development of drug resistance through mutations, which is why companies are developing second- and third-generations of the same drug. There is a traditional Chinese proverb that means â??there is a constant fight between the shield and the spearâ??: once

you develop a better shield, the spear will evolve, and so on in an unending cycle.

Our story is the same. We need to develop better spears for every new drug mutation shield we encounter. In oncology, the tumour might return after having used a drug against it, perhaps due to a point mutation. We have developed a method that allows us to identify the potency of a specific drug when it comes to killing tumour cells. Professor Weiâ??s technology can change or delete every single amino acid of a protein in its native biological state, which ultimately allows us to identify and link the patientâ??s point mutation to the failure of that drug in the patient. This technology also allows us to evaluate the success of a clinical trial: if there are too many patients with that point mutation, then the trial might fail.

Our technology platforms are helping us optimize target therapies, and this is why so many MNCs have chosen to collaborate with us. We are also looking to collaborate with domestic companies, especially if they have unique cell or animal models. The combination of unique systems is what gives us unique insights.

Biotech investment is a hot topic in China. How are investors responding to EdiGene?

Since I joined in August 2018, we have raised a total of about USD 36 million. This is very important because drug R&D is extremely expensive. When I first came back to China to work in EdiGene, I told my investors and management team that this was the smallest budget I had ever managed: drug development is extremely expensive, especially as you move into clinical trials. We also have to ensure the safety of the product for patients, which sometimes means importing GMP-grade raw materials for our activities. This is why fundraising is so important.

EdiGene is among the top companies for genome editing in China. We have a robust portfolio, great support from investors and also the government â?? and of course, a very strong team.

Many of the Chinese biotechs we have met have told us about the difficulties of finding the right talent fitted for the current level of technological innovation. How are you attracting and keeping talent in EdiGene?

Our goal is simply to recruit people who are excited about the program and the platform. Head-hunters find it difficult to get perfect matches for us in terms of strict domain expertise or experience because the area is so new that experienced people barely exist! Antibody and small molecule companies have easier access to people with the right background. In the case of EdiGene, we do not have a readily available talent pool. Instead, we have to go one step further â?? for every role, we need to study closely whether they have the right technical background and aptitude, and of course, whether they are excited about the project.

When we interview potential employees, we want to see excitement from them. We do not want to hire people that wish this technology had already been done. We have the scientific expertise and the patient need; now, we need a team that will make it justice. Sometimes our newly recruited employees do not last more than three months.

Overall, we have managed to build a very strong manufacturing and clinical team, while extending our research team. At the end of the day, you are only as good as your team.

Looking forward, what do you plan to achieve in EdiGene within the next 5 years?

In the short term, we hope that our technology can become a viable product to save patients and transform lives. In the longer-term, we aspire to become one of the top companies for genome editing with the capabilities to save the lives of patients globally.

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