Dajun Yang – Chairman, Executive Director & CEO, Ascentage Pharma, China

Today, we are the world's second-largest pharma market. I hope that in a decade or two, China will also become the world's second-most innovative pharma market

04.12.2019

Tags: China, Biotech, Ascentage, Strategy, Oncology

Speaking in May 2019, Dr Dajun Yang, chairman, executive director and CEO of Ascentage Pharma, shares the company's top highlights over the past decade; their strong product pipeline and portfolio of innovative therapeutics focusing on protein-protein interactions (PPIs); and their global strategy to become an international, world-class biotech company.

Dajun, as founder and CEO of Ascentage, could you first share a couple of highlights for the company in its ten years of development?

To provide some context, one of Ascentage's three co-founders – Dr Shaomeng Wang, chairman of our scientific advisory board, and I – have been working on innovative drug discovery and development for over 20 years in the US. Before we founded Ascentage, we had actually established a company in the US. When we returned to Shanghai in 2005, we first established a China R&D centre to continue our work in the US.

Ascentage itself was officially established in 2009 in Shanghai's Zhangjiang High-Tech Park. From the very beginning, we had our sights set on global innovation. We wanted to be 'in China for global'. This is why we also registered the company in Hong Kong at the same time in 2009 because we thought Hong Kong was a good gateway to international markets.

I am very proud because we have persevered in our core areas of focus over the past decade. Ascentage focuses on the very challenging area of protein-protein interactions (PPIs), specifically dealing with apoptosis pathways. Despite the difficulties and complexities of these areas, we have been progressing persistently over the past ten years as a company – and for some of our team members, over the past 20 years. Currently, there is only one approved oncology drug on the market with this mechanism of action, which shows the challenges of working in this area.

We are proud that our efforts have paid off. Today, we have eight molecules in the clinic in China, the US and Australia, all of which are new targets and new molecular entities (NMEs). In terms of the productivity and novelty of our pipeline, I daresay we are comparable to much larger-sized biotech companies and probably even the oncology divisions of some Big Pharma MNCs.

When you established Ascentage in 2009, the regulatory and market environment of China's pharmaceutical industry was still not as conducive to innovation as it is today, following the reforms, the most significant of which started in 2015. How challenging was it to focus on innovative R&D in those times?

To be honest, our early years were very difficult. We had founded Ascentage in the middle of the global financial crisis. Funding for innovative biotech companies in China was virtually non-existent. My cofounders and I did not take a salary for the first year of the company. I remember that for three extremely difficult months, we were not even able to pay the full salaries of our employees as we were still in the middle of fundraising. We were very honest with our employees and told them about the situation. We said we had to cut their salaries by half, and we would understand completely if they left the company, but once we had the funds, we would pay them back. These are the early days of a start-up biotech company.

However, our aspiration was always to work on global innovations. For us, this meant two things. The first was global patent protection and IP rights. Without global IP, you cannot be a global biotech company. Today, we have over 80 issued patents with expiration years ranging from 2025 to 2037, and over 200 pending patent applications globally.

The second was international standards. We had to align with international standards from the very first day. In order to develop innovative products for the global market to benefit patients globally, you need both elements. It has been a long journey but I believe our approach was correct.

Another major challenge was the ecosystem in China. When we returned to Shanghai in 2005, the Chinese pharma industry was virtually completely generics-based. Between 2005 to 2009, we worked a lot with local companies and service providers to build up their capabilities and educate them about international standards. For instance, instead of auditing CROs and rejecting them if they failed, we would go through the audit results with them, point out areas for improvement, establish SOPs in line with global standards, and help them improve. This not only benefited our company in terms of establishing close relationships with trusted service providers, but also supported the development of the overall ecosystem.

As a biotech company, Ascentage's core focus is on apoptosis, an area that is still relatively underexplored in terms of cancer therapeutics within the industry. What drives your conviction that this is the right direction for Ascentage?

Certainly, over the past ten years, many new technologies like cell therapies and checkpoint inhibitors like PD-1/PD-L1s have emerged. But we continue to believe that apoptosis is a very key area for two reasons. Firstly, biologically, apoptosis is a very important regulatory pathway for cancer. This has been known for over 30 years but the main challenge is that it is very difficult to develop molecules targeting this pathway. Secondly, we see that many companies have tried and failed in this area in the past. This means that the playing field is not as crowded, which means it is easier to differentiate and position ourselves.

I also believe we have a strong edge through our expertise in PPIs. Dr Wang has strong expertise in chemical biology and medicinal chemistry and has advanced many molecules from lab into the clinic over his career, assembling a strong compound library. He is currently a Warner-Lambert/Parke Davis Professor in Medicine at the University of Michigan, Ann Arbor, where he directs their molecular therapeutics and other drug discovery programs, as well as the editor-in-chief of the *Journal of Medicinal Chemistry* since 2011. Through him, we have a very strong discovery unit.

In addition, while drug discovery in this area is very challenging, once we established the molecule, it is highly potent and highly active, so all that hard work is rewarded.

We have worked in this area for a very long time and we want to move our products from the clinic to the market to benefit patients worldwide. We are at the forefront of developing novel apoptosis targeting therapies in China as well as globally, and we have a fully integrated R&D organization that is able to move a molecule from design to optimization all the way through to pre-clinical and

clinical development.

Already, we have six molecules in clinical trials in the US and the majority of them were accepted by the US FDA within 30 days upon one-time review, which speaks to the quality of both our scientific and regulatory teams.

According to a Chinese report published in April 2019, in terms of the total number of INDs accepted in the US, Ascentage ranks third amongst the entire Chinese biotech and pharma industry, following Jiangsu Hengrui with seven, and Fosun Pharma with six. We just got our sixth IND in June so now we have the same number of INDs as Fosun Pharma.

At the same time, Ascentage also has a few candidates that are next-generation kinase inhibitors. How do these complement your apoptosis assets?

Around six years ago, we decided that while we were very committed to the area of apoptosis, we wanted to mitigate the inherent risks of innovation so we started to explore other areas to diversify into. Currently, we have three molecules in the next-generation kinase inhibitor space, all of which are validated targets with products already on the market.

The first is our HQP1351 candidate, a novel, third-generation BCR-ABL inhibitor, for patients with Tyrosine Kinase Inhibitor (TKI)-refractory chronic myelogenous leukaemia (CML), particularly for patients with the T315I mutation.

This is also a significant area of unmet medical needs in China as there is currently no third-generation Gleevec available in China. We were the first to bring this molecule into the clinic three years ago and have already benefited many patients through our clinical trials. This molecule has also been selected to be showcased at an oral presentation at the American Society of Hematology (ASH) meeting last year because it was the first novel structure in a first-in-human trial coming from China in this area. We are starting a Pivotal Phase II trial in China for this molecule at the moment.

We also in-licensed HQP8361, a c-Met molecule from MSD (Merck & Co. in the US and Canada) for solid tumours, the first Chinese innovative pharma company to do so from MSD. We also have APG-2449, a third-generation potent FAK/ROS/ALK inhibitor.

We are working on differentiating these compounds so that they can occupy a unique leading position within the China market.

The biotech and relatedly, the biotech investment scene, in China are now heating up, and we are seeing cash pouring into new biotech companies, many of which are entering very crowded spaces like PD-1/PD-L1, for instance. As a more unique and differentiated biotech company working with novel compounds, how do you communicate the risks of innovative drug discovery and development to your investors?

Innovation entails risk. Innovation is not a buzzword for raising capital, it is a long-term, fundamentally risky business. But today, it has become a very fashionable word.

For companies working in more crowded or popular areas, perhaps there is less risk on the R&D side because their targets have been validated and proven but they will face risks when it comes to the commercial side. Once their products are approved, will there be demand for them on the market if they have to compete with many other similar products? This kind of commercial risk might end up becoming more costly for investors and biotech companies.

Biotech innovation requires long-term planning, focus and persistence over decades, not just years. In China, over the past few years in particular, it seems that there are some people that expect quick returns and quick money from this sector. There are simply no shortcuts. You cannot invest in something that is low-risk and high-returns.

Ascentage and our team have invested a lot of time, effort and resources into our work and we are seeing the fruits of our labour today. We will stay focused on our mission.

Could you briefly outline Ascentage's commercial strategy for the China and global markets?

Within China, our strategy is to become a fully-integrated pharma company from R&D to manufacturing to commercialization. We are currently building an R&D centre and a manufacturing site in Suzhou's bioBAY. Once our products are approved, we will start to build our commercial teams. What is helpful is that within oncology, and especially in our areas, which have significant unmet medical needs, you do not need a huge salesforce.

Globally, for our apoptosis-targeting candidates, we usually only have one or a few competitors. Our molecules have also been carefully differentiated to either be first-in-class or to improve significantly on current molecules. For instance, for our APG-1252 candidate, a Bcl-2/Bcl-xL dual

inhibitor, we spent five years simply working on extensively reducing the problem of platelet toxicity.

Outside of China, we are actively looking for potential partners to support us in advancing high-quality clinical development quickly. As a company at the forefront of novel apoptosis targeting therapies for global patients, we have actually received a lot of interest in our molecules. We would like to partner with both Big Pharma MNCs as well as companies whose portfolios have great synergies with ours.

Ascentage has established a number of partnerships and collaborations with a diverse range of industry players, from MSD (Merck & Co in the US and Canada), Unity Biotechnology, and MD Anderson Cancer Center. How did these come about?

Our partnership with Unity Biotechnology is very interesting. Unity Biotechnology is a NASDAQ-listed company in San Francisco Bay Area focused on anti-ageing therapies through the elimination of accumulated senescent cell (aged, non-functional cells that remain in the organs and secrete cytokines that damage surrounding cells). Their goal is to find ways to eliminate these cells from the human body to restore organ function and increase the ‘healthspan’ of individuals. When they were screening different small molecule drugs, they identified some of our Bcl-2 compounds and we signed a compound library agreement three years ago.

In general, we like to say that Ascentage is mining for gold in our approach to finding new cancer therapies. In our search for gold, we also managed to uncover a diamond through this partnership with Unity Biotechnology.

I also want to highlight our alliance with MD Anderson Cancer Center, which is very unique because they have always been very selective about the companies and molecules they choose to work with. This important five-year collaboration, established this year as well, involves five of our molecules, which is remarkable. Four of them are apoptosis- targeted and the remaining one is our third-generation BCL-ABL inhibitor HQP1351.

We also have a great partnership with another Chinese biotech company, Genor Biopharma, to conduct combination trials with their PD-L1 candidate – the first Chinese-developed PD-1 drug approved for the Chinese market. We hope that this will also be a very productive collaboration. This partnership will also help us gain experience with combination therapies, which would also support potential cooperation with Big Pharma companies in the future.

One of the biggest challenges for the innovative pharma industry in China today is talent. How has Ascentage tackled this in the past ten years?

As the Chinese pharma industry strives for innovative drug development, there are two great needs for talent: on the R&D side and on the clinical side. I spoke at a Drug Information Association (DIA) meeting a few years ago about the severe lack of qualified Chief Medical Officers (CMOs) in China. For a company like Ascentage doing novel drug development, every single molecule we advance into the clinic is new. The Chief Medical Officer needs to be qualified and experienced enough to handle any potential issues from the very first day.

I like to use an aviation analogy. CMOs are the pilots that have to oversee the design, management and running of clinical trials at a company. Even if you raise the funding to buy a new fleet of aircraft, the planes will not fly without the pilots. Furthermore, a pilot cannot be hired and put to work the next day. They require extensive training and experience, tens of thousands of flight hours, so to speak.

For Ascentage, the majority of our management team have either trained or worked in the US or other mature markets like Japan, with over 20 years of industry experience. At the same time, we also invest significantly in our employees to train and support them. Today, while Ascentage is only ten years' old, we actually have a number of employees that have been with us for over ten years because they were working with us before that, at the Shanghai R&D center of our previous US company. The very first scientist we hired in 2006 is still with us today.

We have built a culture at Ascentage that is science- and data-driven, driven by open professionalism and mutual support. In China, companies sometimes struggle with managing so-called 'intellectuals' (□□□□) because they have their own ideas. At Ascentage, we welcome intellectual ideas and contributions, we do not impose top-down hierarchy. For instance, we address each other by our first names, not by our titles.

Currently, we have over 400 employees, the majority of which are smart, educated and self-motivated. This corporate culture helps our overall productivity and reduces staff turnover.

Finally, we also invest in the future pipeline of talent by hiring and training local graduates. China has a great pool of talented graduates who are young and energetic. As an industry, we must invest in them for the future development of the ecosystem.

On a more personal note, what is your dream for Ascentage?

For me personally, it has been a very long journey. I first went to the US in 1986 as a life sciences research assistant. In those years, you could only go to the US if you had a funded position like a research assistantship or a teaching assistantship, which meant your tuition was waived and you could receive a small stipend. I remember when I left China, I only had a one-way ticket to the US! None of us had any idea where the future would take us. But we were fortunate to go to the US during the beginning of the biotech boom in the 1980s. In that sense, I and my fellow students were at the forefront of the industry. I accumulated a lot of experience and knowhow over the following decades.

Coming to China, the regulatory environment has improved significantly since 2015, most critically in terms of the shortened regulatory review timelines and the improved reimbursement mechanisms. At the same time, the pharma industry in China is growing more innovative and international. Today, we are the world's second-largest pharma market. I hope that in a decade or two, China will also become the world's second-most innovative pharma market, with Chinese companies ranking in the top 10 or 20 most innovative or largest pharma companies globally.

As for Ascentage, we hope that in a few more years, we will deliver on our aspirations to launch not just one but several drugs on the market in China as well as globally. Our dream has always been to become an innovative global biotech company.

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