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Dr Shuqian Jing, founder, Chairman and CEO of Gmax Biopharm, an innovative biotech company headquartered in Hangzhou, shares how his experiences at global biopharma companies like BMS and Amgen inspired him to create his own biotech company; Gmax's focus on G protein-coupled receptor (GPCR) therapeutic antibodies; the exciting pipeline the company has in metabolic and cardiovascular diseases and cancer; as well as their highly productive and unique antibody technology platform.

Dr Jing, could you introduce your background and your motivation for establishing Gmax Biopharm to our international audience?

I completed my PhD at Salk Institute for Biological Studies in San Diego, California, after which I moved to BMS. Nearly three years later, I joined Amgen in 1993 and stayed until the end of 2007. Initially, I planned to start a biotech company either in Thousand Oaks or in San Francisco, but the 2008 global financial crisis made that dream impossible since it would have been difficult to raise money to establish a biotech with nothing but some ideas in that climate. For the next few years, I travelled between USA and China, working mainly with universities and research institutes. By chance, I met some people here in Hangzhou who were very interested in working with me, and they decided to invest a significant amount of money at that time, CNY 50 million (USD 7.3 million), in our programs.

Gmax was established in 2010. The name "Gmax" reflects our focus on G protein-coupled receptor (GPCR) therapeutic antibodies. After multiple years of hard work, our team has been quite successful in identifying over 10 different GPCR targets and discovering eight monoclonal antibody drug candidates. Most of these GPCR targets are within the areas of metabolic and cardiovascular diseases, and therefore, the therapeutic focus of our company is naturally in these two areas.

In terms of metabolic diseases, we look specifically at diabetes, obesity, non-alcoholic steatohepatitis (NASH) and liver fibrosis. These are all significant chronic diseases, particularly in China and USA. In cardiovascular diseases, we focus on a couple of them, mainly pulmonary arterial hypertension (PAH), a rare and terrible disease.

If we succeed in any single one of these areas, Gmax will become a very successful biotech company.

What are the flagship projects you are currently working on?

We currently have three clinical programs: one for Type 2 diabetes, one for obesity, and one for PAH. The first, GMA-102, for Type 2 diabetes, is very unique because it is a humanized anti-GLP-1R monoclonal antibody carrying a GLP-1 fragment. The presence of the antibody changes the whole binding mechanism and essentially makes the molecule much more tolerable to the patient with lower toxicity. Comparing it to the newest products on the market, including dulaglutide from Eli Lilly, our data shows that the maximum tolerated dose is three times higher. In addition, our molecule is also much longer-lasting. In our Phase II clinical studies, the elimination half-life of the molecule exceeded 230 hours! The longest elimination half-life of an existing product on the market is Novo Nordisk's semaglutide at about 160 hours, and dulaglutide's elimination half-life is between 80 to 95 hours. With the dual advantages of lower toxicity and longer half-life, we are very excited about our molecule and expect that our molecule will show greater efficacy than existing products on the

market. The longer half-life also means that we might be able to dose patients weekly or even bi-weekly for diabetes.

The second program, GMA 105, is for obesity, which could potentially be the first long-lasting GLP-1 for obesity.

The third clinical program, GMA 301, is an endothelin receptor antagonist (ERA) antibody for PAH. Currently, there are only three existing ERA therapies for PAH globally. Initially, we wanted to identify an antibody that could cross-interact with rodent and human receptors, this would have helped us to do our pre-clinical studies more cost-efficiently in rodents instead of non-human primates. Unfortunately, we were not successful in identifying such an antibody after a long period of trying. So we eventually decided to use the antibody that only recognizes the receptors of human and non-human primates. For that purpose, we generated two different monkey models, and one is hypoxia-induced while the other is chemical-induced. These have given us a lot of information about this molecule. Based on our monkey studies and Phase IA studies in healthy volunteer in Australia, we believe that this molecule has very low toxicity. For instance, we dosed the monkeys twice a week at dosages of 25 mg/kg to 250 mg/kg, and the tox reports given by both Chinese and USA-based pathologists showed no meaningful tox response! In our Phase IA trial in Australia, we dosed healthy volunteers from 75 mg to 1,000 mg and still saw virtually no tox response. In addition, the antibodies last a very long time in human, between 500 to 570 hours (in our phase IA study), which means that we could dose patients once a month.

At the moment, we are filing for Phase IB studies in China and USA, to collect more data on the molecule's potency and efficacy, and we hope to expand to a multi-country, multi-centre trial soon. At the meantime, we are also planning a pediatric PAH trial. We have already received Orphan Drug Designation by the US FDA and we are very excited about this molecule becoming a significant breakthrough. For PAH, there are three critical parameters of determining how quickly the disease progresses: right ventricular pressure, pulmonary arterial remodelling and right ventricular hypertrophy. Most people die within three years because they get a hypertrophic right ventricle and eventually right heart failure and death. Across all three parameters, our molecule works much better than the existing drugs, even at relatively low doses of 300 mg.

We hope that our Phase IB studies might progress well enough to allow the European Medicines Agency (EMA) and the US FDA to give the molecule Breakthrough Therapy designation, which would fast-track this molecule's clinical development. That would mean that we could expect to launch this molecule on global markets in 2022 or 2023!

One of Gmax's research areas focuses on antibodies. Can you elaborate more on this?

Currently, bifunctional molecules are becoming more and more popular, especially bispecific antibodies. This gave us an inspiration. We have already discovered a group of unique antibodies. Moving forward, if we can modify our antibodies by adding more functional motifs, we could convert them into a bifunctional or trifunctional or even quadrifunctional molecule. Through our investigations, we developed our own technical platform that we call a "bibody" platform. Bibodies are different from bispecific antibodies because of their more flexible structure. For instance, so far all existing bi-specific antibodies are dual-antagonists mostly being used in cancer therapy, while bibodies can work on different signaling pathways and different parts of a human body. Bibodies can be a dual-agonist, dual-antagonist or even a combination of antagonist-agonist! Furthermore, from an engineering viewpoint, bibodies can be manufactured similarly as normal

antibodies because we are not making huge changes to the fundamental antibody structure.

From our antibody platform, we have already made a huge number of constructs for indications in both metabolic and cardiovascular areas, for instance T2DM, obesity, NASH, liver and lung fibrosis, PAH, and heart failure, etc. We also started a couple of very interesting oncology programs. The first is in ovarian cancer, the most deadly disease in women for which there is still no good drug available globally. Looking back, we noticed that Abbott had conducted a small-molecule endothelin receptor antagonist (ERA) trial, which had failed for several reasons. Upon analysis, we believe that we identified some of the reasons for the failure. Firstly, in ovarian cancer, only 20 to 30 percent of patients overexpress ETA – this is similar to the proportion of patients with breast cancer that overexpress HER2. Therefore, patient stratification is a very important part of the clinical trial design. Secondly, the ETA itself can only be used as a GPS to identify cancer cells, it cannot kill the cancer cells directly, which means another head needs to be added to the ERA antibody. We have found over 1,200 monoclonal antibodies against this target through our platform. We used one of these antibodies as the core structure and linked an anti-CD3 motif to it to form a antibody. This antibody can bind and activate CD3-expressing T-cells and engage the activated T-cells with ETA-overexpressed cancer cells.

We are applying the same principle to developing a treatment for melanoma. Here, we know that the ETB is overexpressed, but we still work on identifying the percentage.

Therefore, antibodies are a very interesting customizable therapeutic antibody structure and we have a larger number of them in our early development pipeline, mainly clustered around the CMC stage. We hope to produce enough materials to push these compounds into pre-clinical and clinical stages soon.

What has been your clinical development strategy?

As a general strategy, we decided to start all clinical trials in Australia and New Zealand because of the favourable clinical environment. The regulations are more conducive, the speed is faster (around two to three months faster than the US), and the cost is relatively lower. Australia also has a number of well-established Phase I clinical trial centers. Through our work with them, we have established good relationships and now they are very familiar with our needs.

This has been made even more beneficial because China recently reformed its drug review and approval processes to accept global clinical data so we would not need to repeat all the clinical trials in China. For our current clinical programs, for instance, we are only doing a bridging study in China, and for our first molecule for Type 2 diabetes, we hope to finish this before the end of 2019 so that we can start Phase IIb studies soon. For Phase IIb studies, we are deciding if we will also conduct them in Europe and/or the USA.

With such a rich portfolio and asset library, what kind of collaborations are you interested in pursuing?

Now we are looking to establish a presence in Europe, probably Belgium as we have a few potential partners there, to start the IND filing and orphan drug application for our PAH drug in the EU. In general, our management team is more familiar with the European and US markets, but we are certainly not going to neglect the China market.

For our PAH program, for instance, as an orphan drug, it requires comparatively less resources for development, so we are inclined to look at global development and commercialization. For other programs in diabetes and obesity, it would be more difficult to conduct large-scale global trials so we would tend to concentrate on China and perhaps the U.S. markets first. Of course, if we meet potential partners, we are very open to global co-development, co-marketing or other kinds of collaboration.

Overall, we have many exciting programs at all stages of development for which we are looking for good potential partners. We have around 90 people at the moment, so we are working with rather limited resources, even though we have so many exciting molecules and programs that we want to work on. With external help and support, we hope to work faster to help our drugs reach patients globally more quickly.

On a more personal note, having worked at BMS and Amgen in the U.S., how do you feel these experiences have contributed to your current role as CEO of Gmax Biopharm?

My experience with BMS and Amgen gave me great insights and experience into biotech R&D. I had very productive years with both companies: at BMS, for instance, in two years and eight months, I published three *Cell* papers. At Amgen, in the first nine years, I worked in early discovery and published another 20 to 30 papers, including another *Cell* paper. After that, I spent the following six years in development and filed over 40 patents. I have been through the entire drug discovery and development process.

From the bigger picture, I joined BMS in 1990 and Amgen in 1993. This was the period that the biotech industry was booming in the US. Not only did I watch these two biotech companies grow, I was a part of their growth and development. I experienced the biotech boom in the US. Having started my own company, this experience gives me more confidence about the entire process. Even though I cannot do everything myself, I know what needs to be done, and how to develop and execute on the correct strategic plan. Not many people have had this experience or this opportunity.

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