William (Wei) Cao â?? Founder, Chairman & CEO, Gracell, China

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William Wei Cao, chairman and CEO of Gracell, shares the fascinating journey that inspired him to establish Gracell in Shanghai to tackle the four big challenges facing the global CAR-T industry; the four novel technology platforms Gracell is working on that are already drawing significant investor and Big Pharma interest; and the mission of Gracell to deliver affordable and accessible CAR-T therapies to meet global patient needs through non-exclusive collaborations.

William, could you share the inspiration behind your establishment of Gracell, which is in fact your second CAR-T company in China?

As you mention, Gracell is my second CAR-T company. I was also the co-founder and CEO of Cellular Biomedicine Group (CBMG) but I decided to leave in 2016 to relocate back to California with my family, to fulfil an earlier promise I had made to them. By that point, it was two years after CBMG had listed on NASDAQ so I felt the company was in good hands. Therefore, I became a US-based investor to look for investment projects that might be of interest to the Chinese market.

Two things quickly changed my mind again. Firstly, working in the investment world â?? the working style and the angles you take â?? was very different to what I was used to, which was raising small companies into sizable companies, i.e. helping them grow up, with a strong focus on the R&D side of the business. Secondly, the CAR-T industry is still in its infancy and I realized there were still many imperfections with the technology. I thought I could still contribute to the advancement of CAR-T.

Through my role as a biotech investor, I evaluated a handful of pitches and ideas, during which I became acquainted with world-class scientists. I received an invaluable bird eyeâ??s view of the global CAR-T industry, seeing all the latest technologies and â??toysâ?? being developed. CBMGâ??s NASDAQ IPO also provided me with some financial resources to fund Gracellâ??s establishment. I, therefore, was able to start to seed different projects, which were technology platforms that I found most interesting.

In the meantime, I also spoke to my family and friends, including many industry leaders in China as well as globally, who were very supportive. Many of my industry colleagues assured me that they would invest in any company I established! I also started to recruit my core leadership team.

Finally, in May 2017, we registered Gracell here in Shanghaiâ??s Caohejing Hi-Tech Park. The name is a portmanteau of the words â??Graceâ?? and â??Cellâ??. I did not set out to establish a company at the beginning but it turned out to be a logical progression of the past couple of years.

There are many CAR-T companies emerging. What would you define as the core mission of Gracell?

In my experience, good, talented people must be inspired by a higher goal. Gracellâ??s mission is to develop first-in-class CAR-T therapies to serve patient needs globally. Having assembled a top-notch team with strong interdisciplinary capabilities and experience across immunology, gene-editing, stem cells and so on, we brainstormed on the current industry landscape and put together a blueprint for Gracellâ??s development.

Today, we see that there are four core problems â?? pain points â?? for the CAR-T industry globally. If we can resolve even just one of them, then Gracell would have achieved something incredibly meaningful.

The first obstacle is the significant cost of CAR-T therapies. In the US, we are looking at a price tag of USD 400,000 â?? 475,000 just for the CAR-T drug itself, and adding the associated medical services can take the whole cost up to USD 1 million. This is exorbitant, even for US patients. In the biotech industry, sometimes there is a gap between scientific breakthroughs and real market needs.

In the US, the healthcare system is bloated at 25 percent of GDP. In China, the national GDP is already half of the US, and healthcare spending is only six percent. The public healthcare system simply cannot afford to fund therapies costing USD 1 million per patient! Not even CNY 1 million (USD 150,000) is feasible in developing markets like China. We have done some market research in a number of first- and second-tier cities and we estimate that the maximum price for patients to bear out-of-pocket is CNY 400,000 (USD 60,000). Therefore, we think cost is the first pain point of the industry.

The second obstacle is the length of the process. For instance, the â??vein to veinâ?? time (time from when cells are extracted to when they are infused back into the patient) for CAR-T products approved in USA is around 30 to 50 days. Considering how fast a disease like acute B-cell lymphoblastic leukaemia (B-ALL) progresses, that is a very long time for patients to wait. Then you have to factor in potential failures with the manufacturing processes.

The third obstacle is patient relapse. So far, figures suggest that after six to 12 months, up to 50 percent of patients, including those in complete remission, will relapse.

The last obstacle is that thus far, CAR-Tâ??s efficacy in solid tumours has been pretty low. This is a huge area of unmet need; the market size of solid tumours is ten times that of blood cancers.

Therefore, Gracellâ??s focus now is to work on four platforms to resolve these four core â?? the cost, the manufacturing process, the relapse rate, and the efficacy in solid tumours â?? problems in the global CAR-T industry.

Could you outline your flagship platforms and how they could tackle the four issues you highlighted?

The first is our novel FasT-CAR platform, which seeks to deal with both the high cost and the length of the manufacturing process. At the moment, the industry average manufacturing time is around two weeks. Our technology allows for manufacturing to be done overnight â?? the shortest in the industry so far.

I must emphasize that this achievement was made not through increased labour hours or cutting corners or simply â??working fasterâ??. There are certain steps in the process you simply cannot push unless you innovate. Here we benefited from our strong interdisciplinary teams, who had expertise in gene delivery technology and stem cells that they utilized to maintain the youth of the T-cells while uploading sufficient target genes to the T-cells. We also made a number of other adjustments, such as changing the culture conditions, and so on. Even I was surprised when my team first announced to me that they had shortened the time to overnight! I thought reducing it to a week would have been a great improvement.

So far, we have evaluated nine young adult B-ALL patients treated with CD19-targeted FasT CARâ??T product, and eight of them entered complete remission. The data points are very impressive. For instance, in terms of potency, FasT-CAR is 20 to 40 times more potent than conventional CAR-T! This reduces the cost of goods even further.

The second is our universal CAR-T or what we call the â??off-the-shelfâ?? CAR-T. This is something that other companies are already exploring, with Cellectis being the pioneering company with this technology. After Kite Pharma was acquired by Gilead Sciences, the then-CEO and CMO both left to establish Allogene Therapeutics to also explore this area. Shortly after, they IPOed on NASDAQ with a valuation of USD 3.6 billion. That reflects the high industry expectations of this technology!

The concept is straightforward: to make CAR-T therapies from healthy donor cells and manufacture hundreds of thousands of doses that can be stored for use when needed. This would simplify production immensely and also reduce costs. Needless to say, this has proved much easier said than done. We are working in this area because we believe that the current technology is rather imperfect, requiring the use of a very toxic immuno-suppressive drug to condition patients, in order to prevent rejection of the CAR-T therapy by the host immune system. This is very undesirable because it leaves the patients susceptible to infections.

What we want to do is to enable the CAR T-cells themselves to resist the attack from the host immune cells. Therefore, we â??fitâ?? the T-cell with two GPS systems: one to track and kill the target cancer cells, and the other to defend itself against the host immune cells â?? both sword and shield! It is a beautifully simple concept. So far, we have tested it in animals and *in vitro* and it has worked beautifully, so we are very excited to take this further.

What about the other two technology platforms Gracell is also working on? Could you briefly introduce them?

Our third platform tackles the disease relapse issue. At that moment, only three indications have been successfully treated by CAR-T: Non-Hodgkin lymphoma, acute B-cell leukaemia and multiple myeloma. The average relapse rate is 30 to 40 percent of the patients who have achieved complete remission (CR). The problem is that the target antigen disappears after a while, so the T-cells can no longer find the cancer cells, which have either mutated or been internalized. But cancer cells have multiple antigens and markers. We decided to pack two GPS into the T-cell, called Dual CARs T cells to target two different tumour antigens â?? because it is very unlikely that both will disappear at the same time â?? and also to add a suicide switch to kill the T-cell if we need to. We are already testing this technology in patients and we have studies running for all three blood cancers.

Finally, the fourth platform targets solid tumours. We have selected some very toxic, aggressive cancers like pancreatic cancer and ovarian cancer. This is a very challenging and far more ambitious project than the other three I just mentioned, so we have positioned this as lower priority internally

and our aim here is to see what kind of progress we make here.

What is interesting is that, as you mentioned, you returned from California to establish Gracell in China. What made Suzhou and Shanghai better locations than California for such a biotech startup?

Indeed, some people were very surprised to hear that I found California not exciting enough for me and I wanted to return to China! The main reason is that Gracell would be able to leverage the vast medical resources and fast-tracked clinical research system available here. At the moment, we have six programs in Clinical Research stage through the hospitalâ??s scientific and ethics committee (EC) system. The equivalent of this in the US is the Institutional Review Board (IRB) system, but the timelines are much shorter in China.

As you know, the gene-editing scandal with the rogue Chinese researcher became an international scandal recently. This is unfortunate because it gives the world a negative impression of Chinese science and research that I want to correct. The IRB system is very important for CAR-T development because using animal models for testing CAR-T is simply not accurate. This is understood by the global industry and regulators. Animal models used in CAR-T studies are immuno-compromised animals to prevent host rejection of the CAR T-cells. Even if you use humanized animal models, the environment is still artificial and the readouts do not reflect the human body. It will not tell you anything about the right dosage levels or any potential rejection issues. This is why it is so important to test in humans â?? of course, only after the safety profile of the therapy is well-established.

In addition, such studies also give patients â?? many of whom have run out of options â?? a chance to try new therapies. For Gracell, we work with the best Grade A hospitals in China and we follow all the right processes. In addition, we also offer patients the option to undergo the conventional CAR-T treatment should they not benefit from novel CAR-T therapies.

Clearly, Gracell has a very clear blueprint for success in terms of developing its novel breakthrough CAR-T technologies. What are some headwinds you see for the company?

There are certainly many! Firstly, on the regulatory side, we are in a fast-growing and fast-changing industry and there have been many regulatory reforms. The National Medical Products Administration (NMPA) has hired three US FDA veterans to sit in key positions. So far, the overall direction of the reforms has been to promote innovative drug development and launch while discouraging the appearance of â??me tooâ?? and copycat drugs, which is great. However, as a biotech company, it means we must stay abreast of such developments. The costs of clinical studies and trials are also increasing, partly as a result.

US-China tensions is another potential area of worry. In many areas, basic research in the US is still more advanced than in China. Their weak spot is more in the speed of translation from research ideas to commercial products, so there is a lot of potential for mutually beneficial collaboration. I hope there will continue to be a free exchange of ideas and technologies between the two countries, which will ultimately benefit patients.

Finally, talent recruitment is another challenge. We want the best of the best. Competition for talent is fierce at the moment in China. I know the industry quite well so I have an extensive network but it can still be difficult to bring the right calibre of talent in. For instance, we are currently searching for a

Chief Medical Officer. While our requirements are straightforward, they seem to be rather stringent and probably there is only a handful of potential candidates globally! For instance, we are looking for a bilingual person with a medical degree, at least ten years of clinical trials experience in oncology in the US or the EU-5 countries, and currently holding a position of senior director or higher in MNCs. We cannot compromise on this since the Chief Medical Officer is someone that must present the core science and innovation of Gracell to the global industry.

Having been a biotech entrepreneur, worked across different sectors and functions and also in investment, do you have any advice for the new generation of biotech entrepreneurs in China?

> Gracellâ??s mission is to make drugs accessible to ordinary patients. Many of the patients we see now in our clinical studies are not well-off. This mission is what keeps you going through the ups and downs of biotech entrepreneurship.

Everyone probably has the same list but with different priorities. For me, the first is your mission and vision. Gracellâ??s mission is to make drugs accessible to ordinary patients. Many of the patients we see now in our clinical studies are not well-off. This mission is what keeps you going through the ups and downs of biotech entrepreneurship.

Then second comes the team. For many biotech entrepreneurs, especially first-time entrepreneurs, they focus too much on technology, since without innovative technology or IP, you cannot advance. But with the right mission and the right team, you can make advancement, or acquire technology. This is the model that successful Chinese biotech companies â??such as Innovent, Zai Lab, CStone â?? have taken.

The third is the technology platform. The Chinese environment is far more open than before. If you are talking about a â??me tooâ?? product or technology, that is a big problem.

Finally, we can talk about money. The origin of money is important. It is best to work with reputable institutional investors that share your vision for the company so they can bring in additional resources. Working with individual investors can be a little difficult because they have a shorter attention span and are less tolerant of market dynamics or fluctuations.

A final message on behalf of Gracell to the global industry?

Gracell was established in China for one purpose: to utilize the medical resources and the Chinese IRB system to quickly advance the development of our four technology platforms. Without clinical data, you cannot attract the attention of investors and MNC pharmas.

We may be based in China but our vision is global. With four different innovative CAR-T platforms progressing very well, starting from H2 2019, we will have multiple presentations monthly at international conferences, all with meaningful data about each of our programs. Through this, we hope to attract potential partners and opportunities for collaboration.

Our plan is to continue to develop our technology platforms, as well as develop products based on these platforms, while also enabling other companies to use these platforms. There are so many diseases and unmet medical needs, one company cannot cater to all of them. This is why we hope to have non-exclusive partnerships with other pharma companies â?? in order to benefit the most

patients, in China and globally.

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