

## Zhang Yu - CEO, Aeon Therapeutics, China

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*Dr. Zhang Yu, CEO of Aeon Therapeutics, shares the unique journey that motivated him to establish Aeon Therapeutics, as a joint venture of Chinese VcanBio and US-based Eureka Therapeutics, to commercialize Eureka's assets in China and to tackle one of the biggest challenges facing the global CAR-T industry: the difficulty of treating solid tumors.*

### **Dr. Zhang, could you start by sharing the motivation behind the establishment of Aeon Therapeutics?**

Aeon Therapeutics was founded in March 2017 in Zhangjiang Hi-Tech Park in Shanghai. But the exact genesis of the company is rather interesting, as Aeon is actually a joint venture (JV) between a Chinese cell and gene therapy listed company, VcanBio (600645, SH), and a San Francisco-based CAR-T therapy biotech, Eureka Therapeutics.

I myself joined VcanBio in 2014 after a long period of study and work in Germany and Europe. At that time, as a service provider, VcanBio was working with many local and international companies in China. By 2015, I was overseeing the R&D department where we had two stem cell drugs in the process of filing for IND with the National Medical Products Administration (NMPA). Later that year, the Shanghai Stock Exchange (SSE) Main board started thriving, so the company relocated me to the investment department to focus on business development and investor relations. However, less

than six months later, the markets fell rapidly and VcanBio decided it was too risky to continue playing on the Main Board. Alternatively, we established a biotech investment fund where we met Eureka Therapeutics.

Initially, we were discussing Series C financing for Eureka Therapeutics. However, in 2016, there was a significant regulatory change in China after the Wei Zexi incident: a 21-year-old student who died after receiving a DC-CIK experimental treatment for synovial sarcoma which he had discovered in an online promoted result on the Chinese search engine Baidu. Previously, companies were allowed to provide autologous T-cell therapies to patients as a commercial medical technical service. However, the government decided to change this and go through the same regulatory and clinical pathways as a bio-pharmaceutical drug. On top of this change, foreign companies had never been allowed to invest directly in the cell and gene therapy sector in China.

As a result, VcanBio and Eureka Therapeutics decided to establish a JV, Aeon Therapeutics, which would focus on commercializing Eureka's assets on solid tumors in China.

### **Could you introduce the assets from Eureka Therapeutics you are bringing to China?**

We are developing a pipeline of novel cancer therapeutics targeting intracellular and cell-surface targets.

Usually, the CAR T-cells recognize and attack cancer antigens present on the surface of tumors. However, many cancer targets, particularly those expressed specifically by solid tumors, are primarily expressed intracellularly by peptide-MHC complexes. Developing drugs that can target these antigens is extremely challenging because these peptides are very small, the length of around eight to 12 amino acids, and they are also embedded within the peptide-MHC alpha and beta chain. Therefore, these intracellular-targeting antigens are normally considered 'undruggable'. However, with our technology, we have been able to develop CAR-T therapies to target peptide-MHC-I complexes inside the cells. This also means that IP is not easily copied, given the high technical hurdles for competitors.

Our first product is an extremely innovative anti-AFP ( $\alpha$ -fetoprotein) CAR-T therapy for hepatocellular carcinoma (HCC). For instance, initial data presented in September 2018 demonstrated a favorable safety profile with no observed cytokine release syndrome or drug-related neurotoxicity.

In our pipeline, we also have other products including: NY-ESO-1 for multiple solid tumors, including sarcoma and lung cancer; and dual targeting CD19/CD22 products for B cell malignancies.

All of these products have been developed on Eureka's proprietary platforms. The first is our ARTEMIS™ platform, which was created to mimic the natural biology of T-cells to fight cancer, with the intention of creating safer and potentially more effective T-cell therapies. For instance, through this platform, we have the ability to design therapies with the potential to greatly reduce or eliminate cytokine release syndrome (CRS) and other life-threatening cytokine-related toxicities that have been observed with other CAR-Ts.

The second is our proprietary E-ALPHA® antibody discovery platform, which comprises a highly diverse fully human antibody phage library of over 10 billion clones with unique antibody sequences and a robust workflow that is designed to enable us to develop highly specific antibodies against target antigens, including peptide-MHC complexes and cell surface proteins.

### **Solid tumors are arguably one of the hardest areas for CAR-T therapy. Why did Aeon Therapeutics choose to focus on this area first?**

When we started Aeon Therapeutics, we had a long discussion with Dr. Liu about how we could differentiate ourselves. From a practical perspective, Eureka had already out-licensed their first liquid tumor therapy to Juno Therapeutics, and Juno was recording great data. In addition, we also know that liquid tumors are already an extremely crowded space, seeing that most CAR-T companies choose to focus on this area. Therefore, we decided to work on solid tumors to set ourselves apart from our competition. We are one of the first companies to work on this anti-AFP target successfully.

In addition, given our limited resources as a new biotech, we started by focusing on only one indication. We picked HCC because liver cancer is a significant area of unmet need in China. Liver cancer is a major cause of death in China, and globally, over 50 percent of new liver cancer cases as well as deaths from liver cancer come from China. As a Chinese biotech, we also wanted to focus on a China-specific cancer indication.

### **As a JV between Chinese and American cell and gene therapy companies, what advantages does Aeon Therapeutics have in terms of product and clinical development?**

The overall strategy is to leverage on both countries' clinical and regulatory systems synergistically to accelerate the clinical development of Eureka's assets.

In China, you currently have two regulatory pathways for the clinical development of cell and gene therapies: the usual IND and clinical trial pathway, as well as investigator-initiated studies. For investigator-initiated studies, you can apply to individual hospitals for approval from their ethics committees to undertake studies with small patient numbers with the aim of obtaining preliminary safety and efficacy data. This is akin to the Institutional Review Board (IRB) system in the US. Once you have a proof-of-concept, you can begin the standard clinical trials.

This is what Aeon Therapeutics has done with our first product, the anti-AFP ( $\alpha$ -fetoprotein) CAR-T therapy for hepatocellular carcinoma (HCC). We did our investigator-initiated study in China with around 20 patients to obtain preliminary safety and efficacy data - which we then used to file for IND with the US FDA (through Eureka Therapeutics). We received IND approval from the US FDA in January 2019, and we have enrolled our first patient just last month. Having that preliminary data from Chinese patients allowed us to fast-track our IND application in the US.

The next step is to file for IND in China. Having a successful US FDA IND will help us immensely in this regard because the NMPA is still not as mature as the US FDA. This product is a highly innovative first-in-class and first-in-human product, which makes it riskier and more complex for regulators to evaluate. The NMPA has made significant advances in terms of aligning with global regulatory bodies but cell and gene therapies are still a very new field globally, so there is a learning curve. If we are able to use data from US clinical trials in our China IND application, it would significantly strengthen our application.

This is essentially the strategy we will take with our first-in-class and novel products. For our liquid tumor products with more established pathways, we will go through the standard clinical trials route.

### **How challenging was it to oversee the technology transfer from the US to China?**

This was a major priority for us. Cell and gene therapy is an extremely complex area and unlike pharmaceutical drugs, there tends to be a lot of process-specific know-how and manual expertise required. Therefore, for the first couple of patients, we brought in Eureka employees to work while our employees observed. This was another reason we wanted to establish a JV so that our teams could obtain the expertise and technology more easily.

In addition, to reduce the chances of human error and increase the overall reliability, efficiency and quality of our manufacturing processes, we have implemented an automated system to handle the overall process. When we did the investigator-initiated proof of concept study in China, we had different groups, and each were monitored by three employees: two to execute the process and one to document. As you can imagine, if we had to expand this system to larger-scale trials, we would need to hire a very large working team. Therefore, we decided to automate the process so that we only need one person to supervise and maintain the machines for more than three patients at this time. So far, this strategy is working well for us.

### **How will Aeon Therapeutics build up its commercial operations?**

For our solid tumor products, we will develop them to the commercial stage, while for our liquid tumor products, we will license them out to local companies. For liquid tumor products, we are happy that Eureka already has a good track record in this area, having out-licensed BCMA CAR-T (JCAR125) to Juno for multiple myeloma, with extremely promising results in their US trial.

Aeon Therapeutics is currently present in two Chinese cities: Beijing, our HQ where we focus on commercial collaborations, business development and regulatory and clinical functions; and Wuhan, where we are currently building a large GMP facility.

We have chosen Wuhan as our manufacturing base because of two key factors. Firstly, Wuhan is conveniently located in the middle of China, accessible by highspeed train within four hours from major Chinese cities like Beijing, Shanghai, Xi'An, Chongqing, Shenzhen and Guangzhou. For cell and gene therapy products that rely on cold chain logistics and speedy delivery times, highspeed train is the most reliable means of transportation. Conveniently, our manufacturing facility is in the center of China. Secondly, Wuhan has a large talent pool suitable for our needs. It has the largest number of undergraduate students in the country, and most universities have biology or medical departments. The living costs are also far lower compared to Shanghai or Beijing.

### **Quite a few biotech CEOs have mentioned the talent crunch, particularly for the C-suite. How challenging is this issue for Aeon Therapeutics?**

I think there are three roles that are extremely difficult to fill in the Chinese biotech industry right now: CEO, CMO (Chief Medical Officer) and CFO. The requirements for the ideal CEO are really very high: either a doctorate or a medical degree, relevant background in product and clinical

development for the specific therapeutic areas, as well as well-qualified experience in management, business development and financing.

The CMO position is also important because Chinese biotechs are increasingly looking to work on novel first-in-class drugs. A good CMO is needed to help with clinical applications to analyze and manage unpredictable effects, liaise with KOLs and design the right methods to observe efficacy and safety. Finally, since most Chinese biotechs eventually want to IPO, having a CFO is important to ensure that their financial procedures are all compliant.

**Finally, as you mentioned, you did not initially set out to become the CEO of a biotech company. What have you learnt on this journey so far?**

It has been a great learning process. I have sat on both sides of the table: investor and biotech company. As a biotech CEO, a main priority is to look for investors because we need to keep our operations running. At earlier fundraising rounds, you are usually speaking to investors who are unfamiliar with the biotech industry. This means that you need to explain who you are and what you do very clearly. Once you advance to later rounds, the investors are more experienced, so they expect more information from you. Therefore, it is important to be able to present Aeon Therapeutics appropriately to different types of investors.

The second aspect is R&D. We are a clinical-stage company, so R&D takes a lot of my time and energy. This is even more critical when you work with first-in-class and first-in-human products. There are new patient reports every day and when necessary, you have to meet KOLs and physicians to discuss how to deal with the reports.

The third aspect is management. Aeon Therapeutics is still relatively small with only around 40 people focusing on the clinical translation and IND filing of one product. Of course, as the company grows, the management of people will become more important. Recruitment is also a huge topic. We are growing our pipeline, so we need more human resources to support our operations.

Finally, we are also looking at developing further dialogue with government stakeholders and regulatory authorities to open more regulatory pathways for cell and gene therapies. The current system is very beneficial, but I think more can be done to improve the environment. For instance, right now, the GMP requirements for Phase I clinical trials are even stricter than those in the US. If this relaxes somewhat, in line with international standards as the industry matures, it would support the continued growth and innovation of the Chinese cell and gene therapy industry.

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