Yan Tan – CEO, Xbiome, China

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17.06.2020

Tags: China, Xbiome, Biotech, Artificial Intelligence

Yan Tan, CEO of Xbiome, the first AI-based microbiome drug development company in China, outlines the rationale behind the firm's founding, what makes its technology platform unique, and the challenges of attaining funding for cutting-edge innovation.

Yan, could you start by introducing yourself and the motivation for establishing Xbiome in 2017?

I completed my undergraduate studies at Peking University in China before moving to Boston University to start my PhD in bioinformatics. While doing my PhD, I had the opportunity to join a laboratory group at the Broad Institute, where I eventually completed my PhD in bioinformatics and computational biology. I was fortunate to have two advisors at the Institute, a mathematician and an immunologist, so I was exposed to a lot of different areas of research, including metagenomics. During that time, I started to play around with tools like machine learning and AI in the area of gut microbiome research.

After I completed my PhD, I joined an enterprise Big Data company called Tamr, founded by computer scientist Dr Michael Stonebraker, who won the Turing Award in 2014 (the equivalent of a Nobel Prize in computer science). Tamr helped companies across many different industries to makes sense of the data they have collected. During the year or so I was with Tamr, I used different technological tools to develop in-house analytics, helping pharma companies like Novartis

to integrate their databases so that the data could be used and analyzed more efficiently for drug discovery and development.

Shortly after, I joined a start-up VC fund, FREES Fund, in Beijing. I was interested in this opportunity because it gave me the chance to return and work in China. It also became a platform for me to gain a broader view of how the start-up and VC environment worked in China. I spent 1.5 years there working on technology transfer as well as investment in early-stage start-ups, focusing on companies in biotech and big data and AI-based drug development companies. By 2017, I realized that there was no biotech company focusing on the microbiome drug development field in China.

The gut microbiome research area is extremely new, and scientific activity really began only in 2008 with the establishment of the Human Microbiome Project by US and European scientists. Looking at the example of the Human Genome Project, we can see that that project led to a huge boom in the genomics field with a lot of business opportunities for companies. Shenzhen-based BGI, for instance, is now one of the largest genome sequencing companies in the world. Pharma companies have also started to use gene sequencing and newer Big Data approaches to facilitate drug discovery and development. However, in the aftermath of the Human Microbiome Project, researchers and companies had developed in the US and Europe but not in China.

I, therefore, saw a great opportunity to develop and grow a microbiome company in China. I spoke to a number of different stakeholders across hospitals, industry and academia in both China and the US, and by November 2017, I had formed the right team with the right expertise, as well as raised the initial funding, to establish Xbiome.

As the first AI-based microbiome drug development company in China, could you share what makes your drug development platform unique?

When we established Xbiome, I approached some of my former colleagues at the Broad Institute as well as companies in the US to learn from their approaches but we soon discovered that this area is really extremely new, particularly when it comes to using the microbiome to develop therapeutics. We could not even find a CRO in China to meet our needs. As a result, for the past two years, we have been focused on developing our own in-house capabilities.

To explain briefly, a number of different approaches and methodology have been developed to study the relationship between human gut microbiota and other parts of the body. There are a number of different challenges when it comes to studying gut microbiota. Traditionally, researchers

used to study each microbial species as an isolated unit. However, most microbial species cannot be successfully isolated. A new field of research called metagenomics seeks to study a collection – known as a consortium – of different microbial species taken from samples directly extracted from natural environments. Due to the presence of many different strains of microbes, a lot of work is required to assemble, handle and clean this 'mixed' data so that it becomes usable. We, therefore, had to build our own AI-based metagenomics platform, develop our own databases and build our own modelling capabilities – all within the China context.

We also had to build our own 'culturomics' platform, which is complementary to our AI platform. We describe it as our link between the digital and the physical fields of our work. Metagenomics analysis allows us to infer what strains or combinations of microbial species could have therapeutic effects on specific diseases but that knowledge only becomes useful for drug development if we can isolate and culture these strains for production. We are working with Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences to leverage their laboratory facilities.

We also had to develop our own *in vitro* assays to screen for potentially useful microbial consorta as well as build our own *in vivo* animal models.

Based on all these platforms and in-house capabilities, we have developed a couple of fecal microbiota transplantation (FMT) capsule products for the treatment of autism and graft versus host disease (GvHD). These are currently in investigator-initiated trials (IIT) in humans in China and we expect to use that data to file for US IND later this year, with Phase IB trials expected to start next year.

The field of microbiome studies is still very new globally. What are some of the challenges when it comes to working with such cutting-edge science?

Generally speaking, the mission for this new area is to establish causality and gather evidence for the mechanism of action for the efficacy of such treatments. In my view, there are two major challenges here. Firstly, compared to the development of small and large molecule drugs, not enough assays have been developed to assess the functionality of potential treatments. Functional assay screening for drug target identification is very mature in small and large molecule drug development, and most of the popular drug targets have been studied fairly extensively. Secondly, most of the assays that we do have are based on microbial consortia, which produce a huge amount of complex data, so a lot of different computational approaches and methods have to be used to analyze the data. This makes it harder for us to identify the mechanism of action. We have

to leverage sophisticated data analysis tools to strengthen the evidence demonstrating the therapeutic effects of certain microbial consortia.

In AI and machine learning, there is a concept called ‘the curse of dimensionality’. It refers to data sets with too many features or variables. Specifically in our case, we are dealing with data sets with very high dimensions but a relatively small sample size, since it is difficult to procure clinical samples. We, therefore, need to apply modern AI approaches like network analysis and knowledge graph inference methods to reduce the dimensionality of our data in order to facilitate predictive modelling. What is positive is that AI technology is developing continuously. New algorithms or methods developed by Big Tech companies or academic researchers and programmers will also benefit the advancement of AI medicine.

At the same time, we continue to try to collect as much data as possible. We decided to start with human-first clinical trials to gather as much human data as possible, e.g. cohort data with healthy subjects, data of patients receiving FMT capsules as treatment, etc. At the beginning, we decided to acquire as many clinical samples as possible of different types – blood, stool, tissue, etc. – so that we could identify which therapeutic indications showed the most promise for FMT capsules.

We are also collaborating with other academic and research institutes in China to advance the basic science of gut microbiome research. In autism, for example, a lot of research has been done recently in terms of developing useful mice models for Tier-3 autism (the most severe level) for *in vivo* studies as well as developing functional *in vitro* assays for microbial screening. This is very important work because autism is quite a heterogeneous neurodevelopmental disorder that is still not well-understood. The diagnostic criteria for autism are behavioral so we need to have accurate mice models and the correct assays to establish mechanism of action and clinical efficacy.

Last year, you raised a total of USD 24 million across three fundraising rounds. How do you evaluate the current investor sentiment in your particular area?

We consider ourselves very lucky. Despite being a relatively new company, in 2019, we raised the most money in our field in China. We are really one of the frontrunners in this field of research in China and possibly regionally, even globally. Our investors were and are strong supporters of our vision and R&D.

Speaking about the general investor sentiment regarding the gut microbiota area, I think we are still at an early stage in China. A couple of years ago, not many people even believed in this area of

research. Now, more papers have been published and companies in the US and Europe have made advancements, so there is a little more interest but investors here are still largely adopting a ‘wait-and-see’ approach. I believe most of them are still waiting for a couple of key milestones: firstly, a single strain or consortia demonstrate significant efficacy in a Phase II study; secondly, a FMT-capsule drug approved by the US FDA (we expect one or two such approvals as soon as 2021 or even later this year); and thirdly, such a drug being successfully commercialized in these markets. Such events will boost the entry of more capital into this area.

Xbiome has good supporters in China and along with our own development, we also aim to educate the market and ecosystem here about the importance and the potential of gut microbiome research. Overall, we are very optimistic that this will become a very hot investment area in the next couple of years.

What do you see as the benefits of being based in Shenzhen?

The Shenzhen government has a very open and supportive approach to business, particularly start-ups. It is extremely easy to build a business here, and there are many government policies that attract talents not only from other cities in China but also from overseas. The government has also invested extensively in scientific and research facilities and laboratories, so start-ups like Xbiome have affordable access to great infrastructure. Finally, there is a strong start-up culture here. There have been a lot of success stories from Shenzhen and the average age of the population here is very young, so the atmosphere here is very entrepreneurial and energetic, which is great for a young start-up like us.

A final message for our international audience?

Xbiome’s vision is to leverage emerging AI technologies to advance scientific frontiers in exciting areas such as microbiome to treat diseases globally. We are an international company and our team has a very international background. We want to open our platforms to potential collaborators all around the world, and we are very open to different collaboration opportunities including clinical and commercial co-development as well as the in-licensing of later-stage assets from global companies for the China market.

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