Liang Schweizer – CEO & CSO, HiFiBiO Therapeutics

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17.02.2021

Tags: China, France, USA, Biotech, HiFiBiO, Strategy, Immunology, Oncology

Dr Liang Schweizer introduces immunotherapy-focused biotech HiFiBiO Therapeutics, the main advantages of the company's unique single-cell technology platform, its open innovation approach, experience with capital markets, and advice for other biotech leaders.

Liang, could you briefly introduce HiFiBiO Therapeutics, which was established in 2017?

HiFiBiO Therapeutics is an emerging multinational company mobilizing the human immune system to combat cancer and autoimmune disease. Our vision is to pioneer curative immunotherapies for each and every patient by unlocking the power of the immune system enabled by a sustainable pipeline of biotherapeutics. Two of our key differentiators are, firstly, our cutting-edge single-cell technology, and secondly, our open innovation approach. We are currently operating in China, the US and France.

Single-cell technology is our founding core platform, and we apply it from target identification and drug discovery to patient stratification, which differentiates ourselves from the rest of the industry.

The name HiFiBiO actually came from initial discussions among the founding team. We were thinking of how to describe the unique discoveries made within this field with the motivation to understand biology better and more accurately at the single-cell level, i.e., having a high fidelity understanding of biology. High Fidelity was then shortened to HiFi. Separately, there was also some nostalgia attached because the name reminded some of us of hifi sound systems!

What are the main advantages of this single-cell technology platform?

Having worked in the pharma industry for many years, specifically in drug discovery and development, I am aware that one of the persistent challenges the industry faces is identifying an effective target. Even after the target has been identified, how do we develop good drugs? Furthermore, good drugs do not necessarily translate into clinical success, so we also need to position the drug within the right patient populations. These are problems all drug developers in the industry encounter.

One of our single-cell capabilities – through our CelliGO™ platform – is to provide innovative solutions by allowing B-cell deep immune profiling, functional screening, and sequencing-based antibody discovery.

- Millions of cells can be analyzed per experiment with 5000+ droplets per second
- Agnostic with respect to species and source of cells
- Flexible in-droplet assay types; Ability to profile secreted antibodies
- Barcoded single-cell sequencing maintains native antibody heavy chain and light chain pairing
- Rapid turnaround time from screening to sequence

We also developed a concept called DIS™ (Drug Intelligence Science) where we take patient samples that have been or will be treated by the drugs, and link phenotypes of treatment-sensitive versus treatment-resistant samples, with intrinsic signatures that can predict whether patients will be sensitive or resistant to treatment. We use machine learning algorithms at the single cell level to predict this, and then validate the identified biomarker in a clinical setting, typically during Phase 1B or Phase 2A trials. This is very novel since this approach has not been performed in the clinical setting. We believe the DIS approach will enhance the possibilities of success in drug development and reduce clinical trial costs.

Why has HiFiBiO chosen to focus on cancer and autoimmune diseases?

Firstly, the traditional bulk analysis method is well-established and suited for diseases that are more homogenous, but cancer and some types of autoimmune diseases are well-known for being heterogeneous, i.e., you cannot look at the average of a mixed cell population to understand the biology, you have to look at the single-cell level.

Secondly, the majority of our team including myself has personally been involved in oncology and immuno-oncology for a long time. I am also a co-inventor of several IO clinical drug candidates. We wanted to leverage our internal expertise in this area.

Therefore, the company has selected immune modulation as a specific area of biology where we wanted to build our capabilities. This applies to cancer and autoimmune diseases, but it can also apply to other therapeutic areas that relate to immune modulation. For instance, last year, we also initiated a program to identify neutralizing antibodies against COVID-19, which took us into the infectious disease area due to the exceptional circumstances of the global pandemic. This was another area where our single B-cell cloning technology was well-positioned to deliver value. As a result, we actually managed to file our IND within just six months, which is the shortest time period from the start of a project to IND filing I have ever seen in my career.

With such a novel antibody discovery platform, will HiFiBiO focus on the discovery side and pursue commercial options for your clinical candidates, or will you be looking to build up your clinical capabilities as well?

We will be pursuing a mixed strategy. We have started building our clinical capabilities, which center around oncology, but we are certainly open to expanding our focus to other areas.

However, given that we have such a strong discovery engine and a rich pipeline, we will not be able to advance all programs into development by ourselves at this stage as a biotech startup, so we are always on the lookout for potential partners. We already have a number of discussions ongoing for some of our assets. We currently have teams in the US, China and France, so we have been looking to see which assets suit which market.

To take an example, for our COVID-19 antibody, initially we focused on China because it was first affected by the virus and there were so many patients at that time, but the situation developed fairly quickly and it is now Europe and the US that are being overwhelmed. For that reason, we have started our work in China and filed our IND first with the US FDA. Now we are conducting our Phase 1 in the US. In the meantime, we are also actively discussing with potential partners to advance this further globally and regionally to develop or commercialize this program. We already have one collaboration with Pharmsynthez and the Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry RAS (IBCh) in Russia.

We are very excited about this COVID-19 neutralizing antibody because we think it has the potential to be a best-in-class therapy. It is ultra-safe and engineered with minimal risk of antibody-dependent enhancement (ADE), and an extended half-life, with antibody protection expected to last from nine months to a year.

For our flagship program, HFB3010, a novel fully human IgG1 class OX-40 agonistic antibody, we are looking to drive it internally. We aim to establish proof-of-concept (POC) of our DIS™ system, to validate our approach. As you know, after the success of the checkpoint inhibitors, the industry started to explore agonists but so far, the outcomes have been disappointing. We think our single cell platform will make a big difference for the clinical outcomes.

Our hypothesis is that these agonists can only be effective if positioned well within the right cancer indications and the right patient populations. We think certain T-cell clonal types can only be activated in certain tumor types. Therefore, we are using our single-cell technology to look at specific T-cell clonal types. We hope we can successfully develop agonists using our three-level DIS™ approach, meaning, by selecting the right indication, picking the right biomarker, and validating that biomarker in the right patient populations within a clinical setting. Using this approach, we could possibly push the drug response rate above the current benchmark of around 30 percent to 50 percent or even higher.

We are now actively driving this innovative DIS approach by leveraging our unique single-cell technology, with these high-quality and amazing agonist molecules that we have developed. This year, we will have two IND filings for HFB301001 and HFB200301 in the US, and we hope to be one of the first companies in the world to deliver the desired positive clinical outcomes for immune agonists.

Can you tell us more about your open innovation approach?

Open innovation is one of our differentiators. Even for Big Pharma companies, there was a great need to collaborate with external academics and biotechs. There are limited resources available and it is unrealistic to do everything on our own. Once we come up with novel ideas around target science or discovery technologies, we like to find the best partners globally to work with.

Of course, we understand Big Pharma partners could bring strong commercial capabilities and a global network, but regional or local partners offer local expertise and experience. Even Big Pharma has limited reach compared with our Russian partner within Russia, for instance. This is

also one of the main reasons we have established R&D sites across three continents.

Many Chinese biotechs have US affiliates but we also have presence in France because two of our scientific cofounders actually work at the *École Supérieure de Chimie Industrielle*s (ESPCI) in Paris. We are still working with them closely. Our Paris team focuses on developing our single-cell technology platform, and our collaborations with ESPCI and the Curie Institute, for instance, really help us advance our technology development.

Our US team is based in Boston and connects well with the top institutions and hospitals in the area, including Harvard University, Dana-Farber Cancer Institute and so on. The US has the best drug discovery and development capabilities in the world, and Boston is at the heart of this. Some of our collaborators are just down the road from us in Cambridge, so that facilitates our existing research collaboration.

One of the most important aspects of our work in China is the collaborations with CROs, and there is a lot of supporting infrastructure for preclinical and clinical operations. We have also noticed that there are some very promising young scientists in China, both overseas returnees and local talents, and I think increasingly in the future, there will be a lot of potential for innovative technology and therapies to be developed by them.

How do you assess the cost of talent in China in relation to the maturity of the capabilities so far?

China evolves so fast. We have witnessed dramatic changes over recent years. If we just look at today's situation, I would say that salaries for bench scientists are still lower compared to the US or Europe. Where China is lacking is in terms of experienced drug hunters, so it is quite common to see that people with just a few years of experience are being pushed to senior levels in Chinese companies. In my personal view, there is a higher chance that this group of people may be overtitled or overpaid, but that is also just a result of market dynamics. As the Chinese market matures, this situation will also improve.

HiFiBiO has raised over USD 100 million so far. How have your experiences with the capital markets in the US, Europe and China been?

Most of our funding has been Asia-based, although as an international company, many of our funders also have international presence. We have also participation from US-based strategic investors. In general, it is very helpful that there is a lot of support for the biotech industry in China, and Asian investors have become significantly more active over the past two decades.

There has also been a change of mindset. Earlier on, companies would look at investors only as sources of capital but now they recognize that investors can provide a network and industry guidance and so on.

An interesting, related point is the board composition of biotechs in the US versus China. I am a member of the CEO Roundtable group in Boston, and I have noticed that US biotechs have boards comprising experienced industry professionals that have previously discovered drugs. This is still rare in Asia, and I can see both pros and cons of that. The pro is that it means the board is able to think out of the box and keep an open mind when it comes to new technology platforms and paradigms. This helps with innovative research. The con is that sometimes it can be difficult to explain the drug development process to people that have not personally experienced it. Drug discovery is a lot harder than outsiders think. If someone has never conducted a scientific experiment before, they might not understand that science is intrinsically through trial and error. Experiments are not successful all the time.

I do not have a lot of direct experience with European capital markets but from observation, I think there is less of an appetite for risk there – biotech is inherently risky – and it is also more regulated, which makes starting new companies a little more challenging. In addition, I suspect that many European funders are actually investing their capital into US or Asian funds.

In 2020, you were awarded three prizes in France, US and China: the top female founder in France from BusinessFinancing.co.uk; the Extraordinary Women Advancing Healthcare Award by The Commonwealth Institute in Boston, and the Top Ten Female Founders from the Hangzhou government in China. Looking at your journey as a women leader and scientist, what challenges have you faced and what advice would you give to future generations?

Early in my career, I never felt that I encountered challenges just because I was a woman. I used to feel that if I just did my best, I would have opportunities and be able to succeed. But as I advanced higher and higher in my career, I noticed that there were fewer and fewer women around me, and now in the C-suite, this is very clear.

What has been interesting for me to see is that despite different cultural beliefs in the US and China regarding women – for instance, the culture in China is still quite male-dominant, particularly in the rural areas, with parents usually preferring to have boys, while this is not so much the case in the US – both countries still face challenges when it comes to promoting women leadership. In China, somewhat paradoxically, we also have a famous saying that women hold up half the sky, which emphasizes the importance of women within society. We are also taught, growing up, that we can do as much as men, so that may also be why I grew up so assertive. Yet both countries still have significant inequities regarding women in leadership positions.

The first piece of advice I would give is to believe in yourself. Although the word 'forceful' is sometimes seen a bit negatively, especially in relation to women, I do believe that women should be more confident and assertive. Across many societies, women are still today conditioned to be nice and easygoing, and to sacrifice their careers for their families. I was fortunate not to face the last challenge because I have a very supportive husband over the past three decades. Nevertheless, I have worked hard to speak up when needed and to express my opinions very clearly. If we keep doubting ourselves, we might yield too easily when we are discouraged by others.

The second piece of advice is to be persistent and persuasive. It is important not to give up. In addition, women also have to communicate and influence others to see their perspectives.

To wrap up the interview, the Chinese biotech sector has grown so fast in the past few years. For many of them, their ultimate aspiration is to become a global biopharma company with presence overseas. HiFiBiO has had a head start with building a multinational presence so what insights can you share with your fellow CEOs regarding the kinds of difficulties they may expect to face?

I think the most important thing is to understand that being international is not as simple as setting up an office in a foreign country and hiring some local talents there. You have to really invest, adapt and integrate your operations into the local ecosystem so that the existing local stakeholders see you as a part of the ecosystem. In Boston, HiFiBiO is seen as a US company. In Paris, we are seen as a French company. In Hangzhou, we are seen as a Chinese company. This is because we have integrated very well, and this is also how I was able to win these prizes last year on behalf of our local operations in all three countries.

Secondly – and this is also part of integrating locally – it is critical to have international standards so you can fit in. When you work on high-quality science, you will earn the respect of your peers no matter where you are.

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