Chengbin Wu – CEO, EpimAb Biotherapeutics, China (2019)

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Dr Chengbin Wu, founder and CEO of EpimAb Biotherapeutics, introduces their exciting and proprietary bispecific antibody-generating platform, Fabs-In-Tandem Immunoglobulin (FIT-Ig®) and its ability to discover and generate novel and differentiated bispecific antibodies to meet unmet medical needs in China; shares the progress of their first program, EMB01, a EGFR-cMet bispecific antibody that just started its Phase I/II trial in February 2019; and gives his perspective on the importance of discipline to an early-stage biotech CEO.

Chengbin, congratulations on the progression of EMB01, your EGFR-cMet bispecific antibody as I understand dosing has just started in a Phase I/II trial last month. Can you tell us more about this program?

We are very excited about EMB01 because this is the first program based on our proprietary bispecific antibody platform, Fabs-In-Tandem Immunoglobulin (FIT-Ig®), that is entering the clinic. Firstly, this serves a very important purpose for technology validation, completing the cycle from early discovery to process development to manufacturing to clinical stage. In addition to that, it is also a very exciting molecule in and of itself because it is designed to target very specific market needs in China and other Asian markets. Up to 60 percent of various populations in this region have non-small cell lung cancer (NSCLC) with the EGFR mutation, and they receive conventional

small molecule targeted therapies, including third-generation therapies like AstraZeneca's Tagrisso®.

The main challenge for these patients is that after six to nine months, many of them will develop resistance to these targeted therapies, either from new EGFR kinase domain mutations or through overexpression or amplification of cMet.

To counter this, we developed this EGFR-cMet bispecific antibody to tackle the issue from the root. Our molecule EMB01 can bind to both EGFR and cMet receptors on the cell surface to cause simultaneous co-degradation of the two receptors. As both receptors are completely destroyed, there is very little risk of resistance developing. Our *in vivo* pharmacological studies using patient-derived tumor models have seen very phenomenal efficacies across multiple cancer types, from lung cancer to liver cancer to gastric cancer. Mechanistically, this is a very powerful molecule that can tackle the resistance problem at the root, and at the same time, from the commercial standpoint, this molecule also has huge potential across multiple indications.

As both a platform and a product company, what is the current strategy for EpimAb's development over the next few years?

For EMB01, we are interested to bring this molecule all the way to market in China ourselves, and to partner with multinational companies for global development. At that moment, the focus is on conducting Phase I trials in both China and the US ourselves. Once we have reached clinical proof of concept (PoC), we will be open to all kinds of collaborations.

As a biotech company, our technology platform is also very important and it is one of our strategic priorities to collaborate based on this platform. Our current focus is on oncology and within this therapeutic area, there are many mechanisms you can try to accomplish with bispecific antibodies. This is one of the biggest advantages of bispecifics. There is almost no limit in terms of the number of 'mix-and-match' combinations of target mechanisms, and the goal is to find a meaningful combination that generates synergistic effects. EMB01 is a perfect example of this: combination therapy with an EGFR and a cMet antibody will not possess the co-degradation mechanism that our bispecific has.

There is still a lot of potential in bispecifics, whether it is to improve on existing therapies, to extend these mechanisms into solid tumors, or to further optimize and reduce toxicities. Outside of this mechanism, there are even more opportunities. We want to discover more of such unique and

synergistic bispecific antibodies.

EpimAb is not the only biotech company in China to have its own discovery platform. What differentiates FIT-Ig from other platforms?

The field is definitely very crowded. Especially within the bispecific technology field, many companies claim to have a technology platform to generate such antibodies. But we need to look at the quality of these platforms, how much resources and money the companies have invested in their platforms, and of course, whether these platforms have helped the companies generate large licensing deals, as we have with UK-based Kymab and Innovent Biologics in China. Those definitely help differentiate our FIT-Ig platform from the rest. In addition to licensing our technology, we are also utilizing our FIT-Ig platform to develop our own pipeline of novel bispecific antibodies. This focus on innovation further differentiates FIT-Ig from other antibody platforms.

Bispecific antibodies are engineered from two different monoclonal antibodies combining their key features into one molecule. Most commercially available bispecific technologies rely on significant modifications of the basic structural elements of an antibody, which can completely change the overall stability or enhance immunogenicity. Our proprietary FIT-Ig technology re-arranges the DNA sequences of two monoclonal antibodies into three constructs and then co-expresses them in mammalian cells, which brings a number of advantages such as expression in good quantities and easy one-step purification, as well as a comparable *in vivo* pharmacokinetic profile to monoclonal antibodies after intravenous or subcutaneous administration.

Our lead candidate, EMB01 is a bispecific antibody based on the FIT-Ig format that binds to the EGFR receptor and the cMET receptor. Following discovery and candidate selection, we advanced EMB01 from cell line development to IND filing in 15 months, a time requirement similar to standard antibodies, proving the efficiency of our platform.

Our in-house capabilities are most focused on biology because when it comes to the unique mechanisms associated with bispecifics, the understanding of the biological mechanisms is really critical. Half of our in-house expertise lie in biology: *in vitro* and *in vivo* biology mechanisms, cell signaling and so on. Our technology platform has been established now but we want to continue to invest and develop it further, to further improve the knowhow and to streamline the process and so on. That will come hand-in-hand with discovering more molecules. To move from setting up the technology platform to actually discovering innovative compounds is a big jump, and you need both solid technology and a solid understand of biology.

The local Chinese industry has a history of working with generics and biosimilars, which is a matter of following other people's concepts of the molecules, or what we call 'reverse-engineering'! We are working to change this focus on generics and biosimilars by utilizing our FIT-Ig platform to develop novel therapeutics and further differentiate ourselves to have a competitive advantage. We do not want to do another PD-1 or PD-L1 molecule, for instance.

Secondly, to avoid being copied, you need to work in difficult areas. You need to be facing technical hurdles and barriers to entry; if you work in an 'easy' area, then everyone else will be able to follow or copy what you do! Our FIT-Ig platform certainly allows us to do this because copying a bispecific is non-trivial and far more difficult than making a standard antibody.

Finally, the last point when it comes to differentiating ourselves is to address a huge unmet medical need. The market does not need another PD-1. The market needs a product like our EMB01 that really addresses the needs of this TKI-resistant population, who have run out of treatment options! This is why we think our EMB01 is a really meaningful program, and on top of that, it helps to validate and differentiate our FIT-Ig platform.

Another recent piece of exciting news is the appointment of Dr. Bin Peng as Chief Medical Officer. How does this support EpimAb's development?

We are certainly very excited to bring him onboard and he brings a rare caliber of talent and profile, given his previous expertise with the cMet small molecule compound in China and other Novartis flagships like Gleevec®, with his most recent role being the Global Head of Translational Clinical Oncology (China) at the Shanghai Novartis Institutes for BioMedical Research (NIBR). He knows this mechanism and the field extremely well, and therefore he also understands the problem of resistance development. When I showed him our EMB01 data, it really intrigued him and that paved the way for discussions to bring him onboard EpimAb. Top people are always looking for exciting and groundbreaking programs and platforms to work on, so his joining EpimAb really validates the work that we are doing.

Personally, I have worked in many different types of companies. When I first returned to Shanghai in 2010, I joined a local CRO, Shanghai ChemPartner, where I helped to establish their biologics organization, before moving on to Hong Kong-listed Chinese pharma company, 3SBIO, which mainly focuses on biosimilar development. Previously in the US, I had worked in Abbott. Therefore, I have seen different corporate organizations and also built up a strong network. Hiring innovative discovery talents is not an issue because of that network.

However, today, our compounds are entering the clinical stage. This is why I needed Dr. Bin to come onboard to establish our clinical capabilities and to implement a strong clinical program. I wanted to find the best person to lead our clinical team and then give him the space to establish his own organization within EpimAb.

At EpimAb, we try to take a stepwise approach to our growth and development. We hire people only as required when our programs progress to certain stages. We are not trying to grow a 200-plus people organization immediately! We apply the same principle to all areas of our development, from CMC and manufacturing capabilities to financing.

Looking forward, what other priorities do you have for EpimAb at the moment?

Back to EMB01, the first molecule for any biotech company is always very exciting. We are aiming to receive breakthrough therapy designation from the US FDA, given that this is an area with no current treatment options. We want to quickly advance this program through the Phase 1/2 clinical trial and expect to have final results by the end of 2021. With positive signals, that could then be our registration trial. If we receive this, it could be feasible to launch EMB01 on the market within three years!

Both our second and third programs are in immuno-oncology. The second, a dual checkpoint inhibitor is already in CMC development and we are aiming for IND filing in early-2020. The third is in cell line development with a T-cell engaging mechanism. We hope to advance both into the clinic around 2020. We have already received a lot of interest in all three programs from other pharma companies and we look forward to potential collaborations and partnerships.

It is also time for us to develop some level of inhouse manufacturing capacity and we have already secured a building in Suzhou bioBay to establish our process development and pilot manufacturing facility. This will help us quickly move programs from the discovery to clinical stages. This is especially critical for innovative programs involving unique molecular designs that are difficult to outsource CMOs. FIT-Ig is a very unique technology platform so we want to continue building our in-house expertise, which will expedite the CMC process for the next few molecules in the pipeline. You need your own in-house manufacturing expertise.

On a more personal note, having worked in many companies leading significant R&D programs, this is your first role as CEO. What lessons have you learnt?

My main takeaway is that you have to be really disciplined in what you do. I am a scientist by background and I like to do many different things! I am so excited about our FIT-Ig platform because there are so many things we can do with it. The technology is not limited to oncology, it can be used also for immunology, neuroscience, metabolic diseases and so on. But as the CEO of EpimAb, I must maintain our focus on oncology because this is also the competitive advantage for an early start-up company. There are some companies working across multiple therapeutic areas but I do not like this approach.

At EpimAb, I want to focus on an area where we have the edge. I want us to quickly generate the data and products to become competitive. So in all related decision-making processes, I always remind myself to be disciplined.

This is also why we are so open to collaboration on our platform. We want to work with other companies to discover new compounds for other areas like inflammation and autoimmune diseases, where I also see huge potential. This way, we do not lose our focus but we maximize the potential of our platform!

The Chinese biotech industry is still in its early stages. To have sustainable long-term growth, we need companies with original discoveries and innovations, which is why you see that most of the biotech CEOs are bona fide scientists with drug discovery backgrounds, who are best positioned to discover novel compounds. Of course, as the industry matures, different business models will emerge. Of course, at the end of the day, people are the fundamental blocks of collaboration. You want to work with people that share the same standards, business concepts and values as yourself. That is key to success.

If I could share with the global pharma industry, a new generation of biotech companies are emerging in China. We are eager to collaborate – with Chinese companies, with foreign companies, in China, and globally! I hope everyone is aware of our growth and stay open-minded to working with us, be it on products, technology platforms or co-development strategies.

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