Chengbin Wu â?? CEO & Founder, EpimAb Biotherapeutics

In a biotech company, itâ??s essential to explore different avenues initially, but once you identify what works best, focus your efforts there to create more value

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EpimAb Biotherapeuticsâ?? Chengbin Wu explains why the expansion of bispecifics into solid tumors and autoimmune diseases marks a major therapeutic turning point. He outlines how, through rational antibody engineering and unique molecule formats, EpimAb has differentiated itself with safer, more effective therapies than its competitors, as well as how the company is prioritising partnerships with multinational pharma and US-based VCs to accelerate clinical development.

MSDâ??s recent USD 1.3 billion acquisition of Curon Biopharmaceuticalâ??s bispecific antibody therapy highlights the growing interest in the field; as EpimAb has been on this journey for a decade, what do you think has fueled the recent rise in demand for bispecific antibodies?

The bispecific field has indeed seen significant growth over the past five years, largely due to some key breakthroughs in drug development. One of the most important advancements has been the expansion from liquid tumors into solid tumors. This is crucial because the solid tumor market is much larger, but it is also far more challenging to penetrate. However, we have started to see a lot of progress in this area with bispecifics.

One notable example of progress is Amgenâ??s success with their DLL3xCD3 molecule for small cell lung cancer. This was probably the first T cell engager (TCE) bispecific to make meaningful headway into the solid tumor space. This achievement is likely to pave the way for developing other targets within solid tumors.

Recently, we have also witnessed bispecifics, particularly TCE engager molecules, making strides from oncology into autoimmune diseases. This is a significant development because it leverages similar mechanisms and targets but applies them to entirely different scenarios. For certain autoimmune diseases, monoclonal antibodies have reached a point where new drug development has plateaued. However, bispecifics, especially in the context of TCEs and B cell depletion mechanisms, have shown promise across various autoimmune indications. This breakthrough has opened up a new avenue for future drug development, with autoimmune diseases representing a vast market with over ten different indications where these approaches could be applied.

These two breakthroughs of expanding into solid tumors and moving from oncology to autoimmune diseases are creating significant opportunities for further exploring innovation in the bispecific area with our pipeline.

Despite the possibilities, bispecific antibodies seem to have taken longer to gain traction amongst big pharma with the only few examples you just mentioned. Why do you think this adoption is just starting to take off now?

There are a few key reasons why the bispecific space has taken longer to gain momentum. First, it comes down to the development of the technology itself. Early on, for instance, Amgenâ??s first-generation molecule used a single-chain format that had several limitations, including a short half-life, significant cytokine release, and some neurotoxicity. These issues were largely due to the immaturity of the technology at the time. As the technology has advanced and matured, many of these obstacles have been overcome. This has led to the emergence of more refined products with better efficacy, greater convenience, and improved safety profiles.

Another critical factor has been the challenge of managing the CD3 molecule. Engaging T cells can lead to tumor-independent T cell activation and a subsequent release of cytokines, which were major hurdles in the early days of bispecific development. Many programs were terminated because of severe side effects like cytokine release syndrome, neurotoxicities, and ICANs, all associated with T cell activation. Initially, developers used CD3 antibodies with affinities that were too high. While this increased potency, it also led to a narrow therapeutic window due to the side effects, forcing dose escalation to stop before reaching optimal levels, causing many programs to be discontinued.

Over time, significant efforts in both discovery and translational research have improved our understanding of how to manage CD3 affinities effectively. Researchers have learned how to construct bispecifics with the optimal CD3 affinity for T cell engagement, as well as how to design the constructâ??s architecture to maximize therapeutic responses by optimizing the distance between binding sites. This accumulated knowledge has played a major role in the recent surge of interest in bispecifics.

Furthermore, until recently, using TCEs outside of oncology was considered too risky. Even just five years ago, suggesting the use of a TCE for autoimmune diseases would have been seen as reckless. However, as physicians have gained more clinical experience and learned how to manage issues like cytokine release syndrome more effectively, the medical community has become more comfortable using these therapies in non-oncology settings. This growing expertise, both in the lab and in clinical practice, has been instrumental in opening up new avenues for bispecifics,

contributing to the current boom in the field.

Could you share the journey of EpimAb? How did you navigate the challenges during the early stages of clinical development. What key insights have you gained through this process?

Our journey began with the development of our first TCE molecule targeting multiple myeloma. We focused on a BCMAxCD3 molecule, staying within the oncology field. When we started, several other programs were already in Phase 1 trials, so we were not the first to explore this space. However, what stood out to us was the safety profile of our molecule. It was remarkably safe compared to others at the time. Amgen, for instance, faced significant neurotoxicity issues, and Pfizer had to temporarily halt their program due to toxicities. Clearly, side effects were a major challenge, even for BCMAxCD3 therapies.

In our case, when we observed our moleculeâ??s performance, we noticed minimal cytokine release both *in vitro* and *in vivo*. We even conducted monkey studies at a high dose of 45 milligrams per kilogramâ??a very high dose for TCEsâ??and still observed only a small amount of IL-6 release. This indicated that we had a particularly safe molecule. With this differentiation in safety, we decided to move forward into clinical trials, despite not being first-in-class.

Additionally, our molecule featured a unique 2Ã?2 format, with two binding sites for CD3 and two for BCMA. This design was different from other BCMA molecules and offered an advantage in binding more strongly to tumor cells, potentially improving tumor cell killing. With these factors in mind, we believed we had a strong case for differentiating ourselves in terms of both safety and efficacy as we progressed into clinical development.

This journey taught us the importance of rational antibody engineering. We developed a unique CD3 molecule with low cytokine release and combined it with our bispecific format. We then validated this approach during the translational phase, particularly focusing on safety and minimizing cytokine release. Remarkably, our clinical data almost perfectly matched our predictions, which was incredibly satisfying.

That experience underscored the importance of redesigning molecules in a thoughtful, rational way to mitigate risks before entering clinical trials. It is crucial to fully understand how your molecule functions, how it differs from others, and what its strengths are before advancing into clinical development. This thorough understanding is key to successful and safe drug development.

Can you highlight some of the most promising molecules in EpimAbâ??s pipeline?

One of our most promising molecules is EMB-06. We completed the full Phase 1 study for this molecule last year, conducting trials in both China and Australia with about 40 patients â?? roughly 60% in Australia and 40% in China. The study involved dose escalation from 2 mg to 300 mg across ten different dose cohorts. Most of the patients were in the second or third line of treatment, and many were triple-refractory, meaning they did not respond to first-line treatments or CD38 antibody treatments. Some were also in advanced stages, such as stage 2 or 3.

When we reached the efficacious dose level, starting at 120 mg and then moving to 200 mg and 300 mg, we observed an overall response rate (ORR) of 92%, with 11 out of 12 patients responding. This efficacy is comparable to CAR-T therapies, which also show response rates in the 90% range,

making these results very impressive. In terms of safety, at the 120 mg dose cohort, all four patients responded positively. Across all cohorts, we had about 30 patients and observed cytokine release syndrome (CRS) in only two cases, both of which were grade 1. This gives us a CRS rate of around 20%, which is significantly lower than the 60-80% seen with other molecules.

These results have generated considerable excitement, not just because of the strong efficacy and safety profile in multiple myeloma patients, but also due to the extensive biomarker analysis we conducted. We observed strong depletion of B cells in the periphery, which has caught the attention of the autoimmune field. There is significant interest in molecules that can effectively deplete both B cells and plasma cells, and EMB-06 has shown it can do this.

In September 2024 we announced a collaboration with the US biotech Vignette Bio to take EMB-06 into Phase 2 trials and beyond for various autoimmune indications. Under this agreement, Vignette will develop and commercialise EMB-06 outside of Greater China (mainland China, Hong Kong, Macau and Taiwan), while EpimAb shall retain the rights to EMB-06 in Greater China. EpimAb will receive total upfront considerations of USD 60 million in cash and equity of Vignette and will be eligible to receive up to USD 575 million development, regulatory and commercial milestones, plus royalties on net sales.

Additionally, in our pipeline, we have another T-cell engager targeting ROR1 and CD3, which is highly innovative and could be among the first in class. This molecule is geared toward solid tumor treatment. ROR1 is expressed in several solid tumors, including breast and lung cancers. While some companies are developing antibody-drug conjugates (ADCs) for this target, we believe a T-cell engager is better suited because the expression level of ROR1 is not very high. ADCs work best with targets that have high expression levels, like HER2, to ensure enough of the payload is internalized to kill the cancer. If the target is not abundantly expressed, ADCs may not be effective.

This ROR1xCD3 project is currently in Phase 1 dose escalation. For now, we are developing this program internally at EpimAb, as we are with most of our pipeline, except for EMB-06, which we mentioned earlier.

EpimAb recently appointed a new Chief Medical Officer following the retirement of their predecessor after a five-year tenure. How challenging is it to find someone who can seamlessly integrate into and understand the complexities of this research area?

There is indeed a significant shortage of talent in China when it comes to finding a qualified Chief Medical Officer, particularly for innovative drug development. The history of such work in China is relatively short with most of the focus being on biosimilars. It was not until around 2015 that real biotech and innovative drug development truly began to take off here, which means we have less than a decade of experience in this space. As a result, we do not yet have a deep talent pool of medical professionals who fully understand how to conduct trials for innovative drugs.

Dr. Bin Peng, our first CMO, brought a wealth of experience when he joined us after retiring from Novartis at age 65. He had been involved in the early development of key treatments for KIT-positive GIST and Philadelphia chromosome-positive chronic myeloid leukemia at Novartis, so he had a deep understanding of evaluating safety profiles and achieving clinical proof of concept in terms of efficacy.

The challenges were significant, particularly in our first program entering the culturable lung cancer space. Oncology trials, especially Phase 1, are complex because you are working with patient populations, not just healthy volunteers. You need to establish safety profiles while also quickly

identifying efficacy signals.

Finding someone with the right experience and understanding of innovative drug development took time. We did not have a replacement lined up when Dr. Peng retired, and it took several months to find Dr. Yonghong Zhu, our new CMO. We are thrilled to have him on board because he brings a unique combination of scientific and medical expertise. He has a medical background as well as a Ph.D., and he has experience in both discovery research and clinical development from his time in the U.S., transitioning between different companies. His comprehensive understanding from discovery through translational research to clinical development is vital for a company like ours.

Almirall recently signed a deal to use EpimAbâ??s platform for developing bispecifics in immunology, even though they already had a deal with another company using a similar platform. Can you tell us more about this partnership?

Almirall is keen on innovating by developing new concepts and molecules within the bispecific structure, and they see this approach as a cost-effective way to generate new products. Licensing existing technologies can be quite expensive, so they have invested in internal discovery efforts in this direction.

They approached us after evaluating several different bispecific technology platforms, and our Fabs-In-Tandem (FIT) Immunoglobulin platform stood out for them. According to their feedback, our platform excelled in the structure and targets they wanted to pursue. It was easy to work with and produced excellent data during the discovery phase.

One major concern for companies unfamiliar with bispecifics is manufacturing feasibility. If a platform does not allow for a commercially viable manufacturing process, it can hinder the development of the product, regardless of the promising data. Early-stage programs often get terminated because they cannot generate a stable or commercially viable process. This is why ensuring drug-like properties and manufacturing feasibility is crucial from the beginning.

At EpimAb, we do not have in-house manufacturing, but we collaborate extensively with CDMOs. We have already developed a robust process for our FIT platform that works well in terms of manufacturing.

As for the partnership with Almirall, they have licensed certain target pairs to work on eye diseases, which is a non-oncology area and does not conflict with our core focus. While they have not disclosed specific targets, we know their focus is on immunology. The program is progressing well, and one of the strengths of our FIT platform is its user-friendliness. It is easy to adopt and requires minimal antibody engineering experience, allowing Almirall to integrate it efficiently without straining our internal resources.

How active are you seeking partnerships today and what kinds of collaborations are you seeking to reach?

We are actively seeking more partnerships, and we focus on two main types of collaborations. The first type involves multinational pharma or biotech companies with strong expertise in clinical development, especially in therapeutic areas that align well with the profile of our drug products. These partners are ideal because they can help move our molecules quickly into the clinic, ensuring that development progresses efficiently.

The second type of partnership we are looking for involves US-based venture capital (VC) companies that are interested in incubating or developing new companies in the US. In these collaborations, we might retain the rights to develop the product in China while the VC-backed company focuses on the US market. This co-development approach allows the VC to fund the project to a point where its value significantly increases, making it more attractive for a later-stage partnership with a big pharma company.

Big pharma companies can be cautious, especially in oncology, where they often want to see extensive data before committing. They might wait until a product reaches a later stage, like phase two, before getting involved, which requires significant additional funding. This is where VCs play a crucial role, helping to bridge that gap and advance the program to a stage where big pharma becomes interested.

When big pharma sees a promising product with clear differentiation and a well-defined strategy, they are not hesitant to make substantial investments. We have seen deals in the range of USD 800 million upfront, with total deal values exceeding USD one billion. Therefore, having a clearly differentiated product and strategy is key to attracting the right partners.

Looking ahead, what do you see as the key inflection points for EpimAb over the next few years?

In the short term, a key inflection point for us is advancing our first program to Phase 2 proof of concept. This program, EGFRxcMET, is being developed for GI cancers like metastatic colorectal cancer (CRC), a significant market in China with high unmet needs. Current immunotherapies, like PD-1 inhibitors, are not effective for CRC, and there are few targeted therapies available. We are eager to see how our program performs in Phase 2, as we have already observed promising results in Phase 1B, though with a limited patient group. Phase 2 will provide more data with a larger patient population, and we hope to see strong responses.

Another major focus is our ROR1xCD3, which is a first-in-class TCE. We are currently in the middle of dose escalations for this drug. By the end of this year or early next year, we anticipate reaching an effective dose level and observing some efficacy. This will help us understand the best indications and patient profiles for Phase 2. Achieving early clinical proof of concept for ROR1xCD3 will be a significant milestone and add considerable value to the company. For any TCEs, reaching this milestone with innovative targets will be highly valuable.

Looking ahead, the company will need capital to progress. Currently, it appears that securing business development deals might be easier than raising financing. Our focus is to advance our molecules to the next stage of development, creating more value for the company. This progress will then facilitate discussions about financing or partnership deals. Big Pharma typically looks for data that supports milestones, such as Phase 2 POC, when considering deals.

At present, our priority is to advance both our clinical and innovative preclinical programs. We aim to move these innovative programs into the clinic and generate data. All these efforts are focused on creating value for the company. Patience is essential as we take one step at a time. If we secure BD deals that provide additional cash, it will be beneficial, giving us more time to create value for the company over time.

As a first-time founder and CEO, what key lessons have you learned on this entrepreneurial journey?

Creating a company and using technology I invented to develop drugs has been an incredibly fascinating and rewarding experience. Watching the molecules we created using our technology reach patients has been very fulfilling.

One of the most important lessons I have learned is the value of feedbackâ??understanding what works and what does not. Over the past few years, it has been crucial to learn from our experiences with various programs, target combinations, and mechanisms. Identifying which targets, combinations, and mechanisms work best with our technology has been a key part of this process. This accumulated know-how helps us in developing future molecules.

For example, EMB-06 has proven to be very effective. It is the first product we have developed that has reached a strong clinical proof of concept, with a 92% overall response rate in multiple myeloma. From this experience, I have found that the TCE mechanism is highly effective for our FIT-Ig platform. This approach seems to be a reliable strategy, and we plan to replicate and build upon this success, not only in oncology but also in autoimmune diseases.

In a biotech company, it is essential to determine what works and what does not. Initially, it is wise to explore different avenues to minimize risk. However, once you identify what is most effective, it is important to focus your efforts there and strive to create more value in that area.

Is there a final message you would like to share with our global audience on behalf of EpimAb?

At EpimAb, we have a diverse range of technologies in the bispecific and multispecific space. We are always open to collaborating with other companies and exploring innovative areas, such as T-cell receptors. Our technology performs well in this area as well.

We have numerous innovative preclinical programs and assets, and we are interested in collaborating at any stage of development. Whether it is at the preclinical stage or during clinical development, we are eager to engage in discussions and explore potential partnerships.

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