



I-Mab Biopharma
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I-Mab Biopharma: going global with innovative biologics

With its two-pronged approach, I-Mab Biopharma is developing biological therapeutics indicated for cancer and autoimmune diseases for the Chinese market and for the rest of the world.

China, with a population of more than 1.4 billion people, is the world's second-largest pharmaceutical market, valued at nearly \$600 billion. Yet despite the medical need for new medicines in this huge market, most Chinese pharmaceutical companies have historically focused on producing generic drugs, active pharmaceutical ingredients, and traditional Chinese medicines.

I-Mab Biopharma ('I-Mab'), headquartered in Shanghai, is different. From its inception in 2015, the company has been focused exclusively on discovering and developing innovative biologics, including monoclonal antibodies (mAbs), fusion proteins and bispecific antibodies that have either first-in-class or best-in-class potential for cancer and autoimmune diseases. I-Mab also stands out from many other traditional Chinese pharmaceutical companies with its global vision, and its commitment to bringing innovative drug candidates to global markets.

Recently, the incidence and mortality of cancer in China have been higher than in the US and globally. Yet many new biologics approved for cancer and autoimmune diseases in the US and Europe are not currently available in China. At the same time, the Chinese biologics market is growing faster than the global biologics market, and is estimated to reach RMB 1.3 trillion/\$190 billion in sales revenues by 2030.

I-Mab was founded amidst waves of change sweeping China around 2015, especially reforms in China's health care and regulatory environment and the shifting dynamics of capital markets in the country. These developments, combined with breakthroughs in oncology and autoimmune disease medicines, a growing biologics market, and an increasingly large talent pool within China, created a great opportunity to launch an innovative, global drug discovery and development company.

I-Mab's focus on oncology and autoimmune conditions is driven by two factors. The first is the unmet medical need for new therapeutics in these areas in China and globally. The second is that these therapeutic areas draw on the scientific strengths of the company in immunology. For autoimmune diseases, the goal is to discover new pathways to downregulate or inhibit an over-heated immune response with the potential for better safety and efficacy than current treatments. In oncology, the vision is to harness the power of the immune system to eradicate tumor cells, going beyond the current programmed cell death 1/programmed cell death 1 ligand 1 (PD-1/PDL-1) therapies. Overall, immuno-oncology accounts for three-quarters of I-Mab's research

and development (R&D) activities, and immune-inflammation comprises the remaining one-quarter.

I-Mab was initially formed with just a small group of people with extensive pharmaceutical and academic experience. Moving swiftly since then, in the past three years alone the company has raised almost \$400 million in cash from equity financing to grow and innovate. Today I-Mab employs approximately 170 staff, with offices in Beijing and the US, in addition to its headquarters in Shanghai. Collectively, I-Mab has R&D capabilities covering discovery through to chemistry, manufacturing and controls (CMC) and clinical development, as well as business development functions. I-Mab also plans to begin construction of a commercial biologics manufacturing facility in Hangzhou, China, by the end of 2019.

Despite the high bar for developing first-in-class and best-in-class drugs, I-Mab now has more than ten innovative drug candidates or investigational drugs in its pipeline, and is currently running three phase 1 clinical trials in the US, and a further three trials, mostly phase 2 or 3, in China. I-Mab anticipates its first product launch in 2021–2022, for the anti-CD38 monoclonal antibody TJ202, which is currently in a phase 3 trial and a registrational trial in parallel in Greater China for multiple myeloma (Fig. 1).

A tale of two portfolios

The successful development of first-in-class drugs is a dream of many pharmaceutical companies, but is an inherently risky pursuit with historically low success rates. I-Mab balances the risks of pursuing a first-in-class strategy with a simultaneous focus on creating innovative drug candidates with best-in-class potential that draw on the lessons learned by others with molecules in similar classes.

I-Mab complements this balancing of risk at the pipeline level with a unique business model and a risk-controlled portfolio strategy that comprises two elements: a lower-risk, fast-to-market China portfolio, and a higher-risk, fast-to-proof-of-concept global portfolio (Fig. 2).

China portfolio. The fast-to-market China portfolio is built around in-licensed investigational drugs that have demonstrated a favorable clinical safety profile and preliminary efficacy data in phase 1 or 2 trials in the US, Europe, or elsewhere. I-Mab only selects candidates with the potential to become first-in-class or best-in-class therapeutics for urgent unmet medical needs in China. Then, through in-house R&D and drawing on I-Mab's deep knowledge and past experiences of the requirements for drug approval

by the National Medical Products Administration (NMPA), the company builds additional data packages for late-stage clinical trials to support product registration. I-Mab's direct access to Chinese clinical trial networks, combined with its insights into the Chinese regulatory environment, guides investigational drugs through this complex terrain.

The China portfolio today comprises five investigational drugs that are either in, or ready to enter, phase 2 and 3 clinical trials in Greater China.

The most advanced investigational drug, the anti-CD38 mAb TJ202, is being evaluated in two product registration trials for refractory or relapsed multiple myeloma—one assessing TJ202 as a monotherapy, and the other assessing the drug as a combination therapy with lenalidomide. TJ202, originally developed by Germany-based MorphoSys AG, has demonstrated advantages over other treatments and good clinical safety and efficacy data in European trials. The investigational drug was in-licensed by I-Mab to address unmet medical needs and commercial opportunities in China for the treatment of multiple myeloma and autoimmune diseases such as systemic lupus erythematosus (SLE). I-Mab plans to submit a New Drug Application (NDA) for TJ202 as a monotherapy for multiple myeloma in 2021, with an NDA as a combination therapy to follow. Beyond multiple myeloma, I-Mab believes that TJ202 has even greater potential for the treatment of SLE, and the company plans to file an Investigational New Drug (IND) application in late 2019.

Enoblituzumab, the latest addition to I-Mab's China portfolio, is a humanized antibody directed at B7-H3, a member of the B7 family of T cell checkpoint regulators, which is widely expressed across multiple tumor types and plays a key role in the regulation of immune responses against cancers. As the only conventional B7-H3 antibody in clinical development worldwide, enoblituzumab has the potential to be a first-in-class anticancer immunotherapy for a variety of solid tumors that overexpress B7-H3. Enoblituzumab was originally developed by MacroGenics, and in multiple clinical trials conducted by the company has shown a favorable safety profile and preliminary clinical efficacy when combined with pembrolizumab in recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) and non-small-cell lung cancer. I-Mab has recently in-licensed the Greater China rights to this investigational drug with a plan to conduct a registrational trial in China, pending approval by the NMPA, in patients with recurrent or metastatic SCCHN. Further clinical development with MacroGenics is expected for other cancer indications in China and globally.

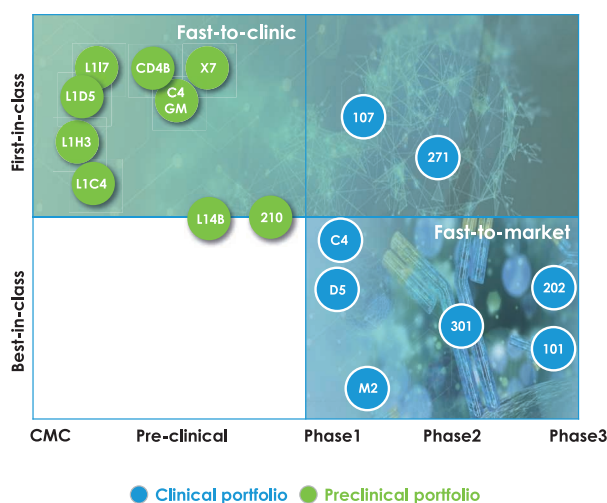


Fig. 1 | Candidates in development. I-Mab Biopharma's portfolio of therapeutics spans both sides of the clinical development process. CMC, chemistry, manufacturing and controls; PoC, proof of concept.

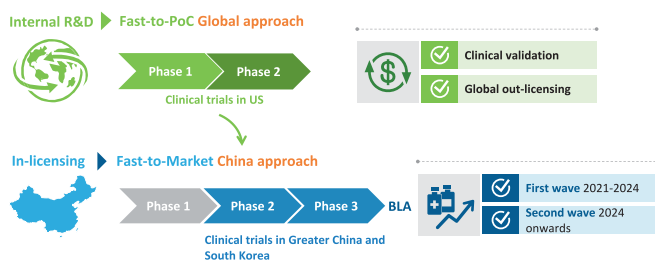


Fig. 2 | Visualization of the strategy behind I-Mab Biopharma. BLA, biologics license application; PoC, proof of concept; R&D, research and development.

Global portfolio. Whereas the goal of the China portfolio is to bring in-licensed products to the Chinese market as quickly as possible, the global portfolio focuses on demonstrating proof of concept, safety, and preliminary efficacy of I-Mab's internally developed innovative biologic drug candidates. The strategy is to clinically validate these candidates in the US, where I-Mab can take advantage of the US Food and Drug Administration's streamlined regulatory system for innovative drugs, which includes a clearly defined and predictable timeline toward approval. Once clinically validated, the further clinical development of these candidates is pursued in China, where I-Mab has access to huge patient pools, extensive clinical trial networks, collaborations with leading hospitals, and a regulatory pathway that allows the fast-track approval of drugs that are supported by solid clinical data generated in the US.

I-Mab typically out-licenses the global rights to internally generated candidates once they have been clinically validated in the US, while retaining the right for further development and commercialization in Greater China. With this approach, I-Mab intends to get new, innovative medicines to Chinese patients faster than, or at the same time as, these drugs receive global market approval.

The global portfolio contains biologics with first-in-class or best-in-class potential that fall into two molecular classes: mAbs and bispecific antibodies.

I-Mab currently has three mAbs in phase 1 trials in the US (TJC4 and TJC5 for multiple cancer indications, and TJM2 for rheumatoid arthritis and other autoimmune diseases), and two mAbs—TJX7 for autoimmune diseases—are at the CMC stage, with INDs and the initiation of phase 1 trials in the US expected in 2020.

TJC4 is a prime example of I-Mab's in-house innovation. As a fully human mAb targeting CD47, TJC4 has the potential to stand out from other clinical-stage CD47 antibodies. Blocking CD47 activates tumor-engulfing macrophages, an important cancer-fighting mechanism. But current efforts to develop CD47 antibodies by several companies have been hampered by hematologic side effects such as anemia owing to their inherent binding to human red blood cells (RBCs). TJC4 is a rare antibody originally selected, by design, to avoid or minimize binding to RBCs while maintaining high tumor-killing potency. TJC4 is being evaluated in a phase 1 clinical trial in patients with cancer in the US, and no anemia has been observed in the first cohort of patients so far.

Bispecific antibody-engineering technology

In recent years, bispecific antibodies—which integrate two therapeutic molecules, two antibodies or one antibody with a cytokine, by molecular engineering into one single superior therapy—have

become an important pathway to safer, more efficacious cancer treatments. Bispecific antibodies, however, are more challenging to develop than traditional mAbs. Recognizing this, I-Mab has created a proprietary technology to engineer these promising molecules.

Relying on cutting-edge immunology and this proprietary antibody-engineering technology, I-Mab has created a panel of seven bispecific antibodies with first-in-class potential. Five of these are built around I-Mab's PD-L1 antibody, which acts as a backbone to which a second antibody or cytokine function can be added. TJ-L14B contains a 4-1BB agonist antibody, TJ-L117 an interleukin-7, TJ-L1H3 a B7-H3 antibody, TJ-L1D5 a CD73 antibody, and TJ-L1C4 a CD47 antibody—all of which have been shown to act synergistically with the PD-L1 backbone in preclinical assays and animal cancer models. I-Mab has also engineered a bispecific antibody that links I-Mab's anti-CD47 mAb TJC4 to granulocyte-macrophage colony-stimulating factor (TJ-C4GM) for the treatment of solid tumors, and another that combines I-Mab's proprietary Claudin-18.2 antibody with a 4-1BB antibody for the treatment of gastric cancers. Proof of concept for all I-Mab's bispecific antibodies has been validated in *in vitro* and *in vivo* studies, providing a solid scientific basis for validation in patients with cancer.

What's next for I-Mab?

I-Mab is committed to being a fully integrated, end-to-end global biopharmaceutical company with the capabilities to take candidates from discovery through good manufacturing practice (GMP) manufacturing, preclinical and clinical development, right up to commercialization. To make this a reality, I-Mab plans to rapidly advance the China portfolio to NDA approval, and expects all the clinical assets in the China portfolio to undergo phase 2, 3, or registration trials in 2020, with NDAs to the NMPA being filed in sequence between 2021 and 2024. I-Mab will initially partner with a specialty pharmaceutical company with commercial experience and infrastructure in China to jointly market these products.

Regarding the global portfolio, the goal is to rapidly advance candidates into early-stage clinical validation. I-Mab plans to advance the three mAbs currently in phase 1 trials in the US into phase 2, and to initiate new US clinical trials for TJ210 and TJX7 and the first few bispecific antibodies by the end of 2020 or early 2021. As part of this effort, I-Mab is expanding its clinical team based in Maryland, US, and is also setting up a translational medicine group with a biomarker laboratory in the US. Looking to the future, Jingwu Zang, founder and chairman of I-Mab, is as excited as ever. "We are keen to talk to investors and potential partners about possibilities for working together on our inspiring mission to bring transformational medicines through innovation to patients in China and the rest of the world."

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