John Luk â?? Chairman & Founder, Arbele

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Arbele is a clinical stage biotech centred on an innovative T-Cell Engager approach to gastrointestinal cancers. Chairman and founder John Luk explains the prevalence of these cancers in China, the companyâ??s challenging clinical trials journey, and the pursuit of breakthrough and fast-track designations in the US and an IND in China for its lead candidate. He also discusses Arbeleâ??s aim to finalize Series B funding by the end of the year and its ongoing discussions with potential partners.

Having spent time in the US and worked with two major pharma companies in Shanghai, what motivated you to launch your own venture?

I have always had a very clear vision: to save cancer patientsâ?? lives through the invention of novel therapies. Big Pharma often focuses on making profits, which is understandable since they are businesses, but this approach leaves gaps in certain regions. For example, in China, liver and stomach cancer are significant burdens but, because of the low potential rate of return, therapies that address these diseases are often deprioritized by multinational pharma companies.

We initiated our venture with the goal of developing first-in-class drugs for rare disease indications, we want to fill that gap and help patients in need. Gastric cancer is highly prevalent in Asia, specifically in China, but with significant disparity, it is considered an orphan indication in the US due to its low incidence rate. Others such as oesophageal and pancreatic cancer are also not very

common in the US, affecting fewer than 250,000 people. What is fortunate for us is that orphan indications allow us to pursue fast-track, accelerated approval processes after completing phase two/pivotal trials. Recently, a T-cell engager for a subtype of lung cancer was approved a month ahead of schedule under priority review, breakthrough designation and orphan drug designation, which is very encouraging for us as we employ a similar mechanism of action. This approach is applicable not only to lung cancer but also to colon and other gastrointestinal cancers, as well as women-centric ovarian and cervical cancers.

How important is identifying the right targets when working on solid tumours?

Very important. For instance, p53 is an excellent cancer target but is considered undruggable because it does not possess typical drug target features and thus designing small molecules to target p53 is exceptionally challenging. So, for solid cancers, including gastrointestinal (GI) cancers, success largely depends on the tumour-associated antigen. Recently, a drug developed by Amgen targeting DLL3, part of the Notch pathway, was approved. DLL3 is a unique target in some types of lung cancer but not in normal tissues. Our initial strategy focus is on the prevalence of gastric and bile-duct cancers in Asia, aiming for FDA approval and fast-track designation, and then expanding to other indications in the future.

Was a T-Cell Engager approach part of your strategy from the beginning?

Initially, we explored CAR-T therapy, which I found to be ground-breaking even before my time at J&J as it demonstrated robust efficacy in treating cancers. During my tenure at Hong Kong University (HKU), I discovered Cadherin-17 as a specific marker for the GI tract and hence filed a patent for it as both a diagnostic and therapeutic target.

When I founded my company, I licensed this patent exclusively and globally from HKU. Everything has to be global. Fragmenting the market is not feasible. Although they are different, CAR-T and bispecific T-cell engagers are in fact based on similar mechanisms. CAR-T involves modifying the patientâ??s T-cells and re-infusing them, which was not viable in Hong Kong due to regulatory constraints at that time.

Having initially prioritised CAR-T, the shift to focusing on T-cell engagers, which work like typical biologics, was a wise decision. Unlike CAR-T, which is personalised and costly, T-cell engagers provide a lower barrier to market access and cost. In the US, CAR-T treatments can cost nearly a million dollars, while in China, it could be around USD 300,000 to UD 500,000.

How has Arbeleâ??s clinical trials footprint evolved, how many people are involved in your Phase I trials and what endpoints are you looking for?

Our journey with clinical trials has been quite challenging due to the innovative nature of our work. When we consulted with the FDA back in 2019, there was no success case for T-cell engagers in solid tumours, so there were no specific guidelines available. They did, however, caution us about the potential safety issues, particularly the risk of cytokine release storms, which is a known severe adverse side effect as seen in T-cell engagers that were initially approved for blood cancers.

Therefore, we had to proceed with extreme caution, starting with an ultra-low doses and escalate gradually, with intervals of four to eight weeks between doses, to ensure patient safety. Our primary goal is to prove the drugâ??s safety and the absence of off-target side effects. In our ongoing Ph1 study, we have observed no mortality and no severe adverse events. Specifically, we have not seen any grade four adverse effects, and only one instance of a grade three, with the majority being grade one or grade two. We have had over 20 patients participate in the trial thus far. Given the positive safety profile, it looks very promising to be a first-in-class and first-in-human treatment.

Are these trials being conducted in Hong Kong?

We are conducting trials in both Hong Kong and Australia. Interestingly, the recruitment of patients has been slightly better in Hong Kong, which could be attributed to various factors including the cancer types, the size of the hospital and its reputation, as well as the number of available trials for patients. That said, in Hong Kong, there is limited experience with first-in-human trials since they are often accustomed to Phase III large-scale clinical trials conducted by Big Pharma. We have had to provide guidance and instructions to the Contract Research Organisations (CROs) involved, recruiting patients globally but conducting trials locally in Hong Kong and Australia.

Considering this is likely to be a first-in-class treatment, are the patients in the trials receiving it as a sixth-line treatment, similar to CAR-T therapy?

These patients are very sick, with a projected survival of only three to six months and without any treatment. They have already undergone multiple lines of therapy. Our challenge is to treat these severely ill patients while ensuring the safety of our drugs. Our trials have been reviewed by two independent international safety committees, which include a diverse mix of experts (all based in the USA) in biostatistics, pharmacokinetics (PK), and oncology, providing a comprehensive assessment of our clinical data. Both of these committees have given us a green light, indicating our treatment is safe for use. These are independent validations that ensure our trial meets the highest safety standards.

I have friends and relatives with stage four colon cancer who face limited options. Surgery and radiation are not viable, leaving chemotherapy or targeted therapy as their last options. Many patients are reluctant to undergo chemotherapy due to the severe side effects and the likelihood of tumour recurrence. As for targeted therapies, only five to ten percent of patients test positive for the specific targets needed and can undergo the treatment. Immunotherapy also requires specific tumour burden and microsatellite instability (MSI) status to qualify for treatments like PD-1 or PD-L1 inhibitors.

Our T-cell engagers have a much broader applicability. For colon cancer, nearly 100 percent of patients are positive for CDH17 cancer-specific target, eliminating the need for extensive testing or screening. For gastric cancer, about 60 percent of patients qualify, and for pancreatic cancer, the figure is around 40 to 60 percent. This means our drugs can potentially treat a very high percentage of the patient population, making them a versatile and promising option.

You have also developed something called Tiberias technology. Could you elaborate on what this innovation represents?

What we refer to as Tiberias is actually a technology called TIBTECH. During our Pre-Investigational New Drug (PIND) review with the FDA, they asked us to develop a companion diagnostic kit. Companion diagnostics are essential for targeted therapies as they help identify suitable patients for treatment. Because treatment can be very costly, calculating the cost-benefit ratio is crucial. So, the FDA requested a companion diagnostic to select the right patients for the treatment.

We have since established a platform to develop the companion diagnostic test using tumour samples, biopsies, or tissues. This platform is fully operational. All patients in our phase one clinical trial have provided tumour samples to determine if they are CDH17 positive. They are eligible for the trial if they test positive.

And are you monetising this platform?

We are currently in the process of getting registrations and learning the commercial aspects. We have also developed an independent blood test in collaboration with hospitals in Hong Kong, Guangzhou, and Shanghai. We have received government grants to develop the prototype and conduct initial validations. We aim to officially launch it later this year. This platform could be a significant commercialization opportunity for the company. While this platform used to be part of Arbele, it is now an independent entity called Tiberias. We are adept at spinning off innovations while still focusing on commercialization.

The company is also expanding operations to Guangzhou, what is the rationale behind this move, especially when regulatory and clinical aspects are still misaligned between Hong Kong and the Greater Bay Area (GBA) territories?

Yes, despite challenges with alignment across the Greater Bay Area, it was a strategic decision to establish a presence there, even during the difficult COVID-19 period in 2020. We secured incubators in the BioIsland area of Guangzhou, where we have two companies: Tiberias Tech, focusing on diagnostics, and Caleb Bio for therapeutics. Caleb Biomedical will also help facilitate and advance our clinical trials in China.

While regulatory systems are currently misaligned, there are ongoing efforts to harmonize regulations within the Greater Bay Area. This could lead to more streamlined processes and reduced bureaucratic hurdles in the near future. We want to be one of the early adopters of this change.

Last year, a listed Mainland China company with global presence, expressed interest in partnering with us on potential registrations and marketing for our ARB202 T-cell engager. We believe that increasing our presence in GBA will create more strategic opportunities and synergies for the company and the biotech community there.

What are the next inflection points for your company in terms of clinical development, financing, and partnerships?

It is a multifaceted and multidimensional process. Our immediate focus is on securing breakthrough therapy or fast-track designations for our lead candidate cabotamig (ARB202). We have already demonstrated safety and tolerability in our phase one trial, we are currently analysing this data to refine our clinical protocols for pivotal phase two trials. Our goal is to file for breakthrough

designation with the FDA and pursue fast-track approval concurrently. Simultaneously, we are preparing to file an Investigational New Drug Application (IND) for National Medical Products Administration (NMPA) approval in China. We will then be able to expand our studies to the US and China. This approach ensures we are well-positioned in both major markets for commercialization.

Your strategy seems quite resource intensive. How are you progressing with fundraising?

We have successfully completed Series A and are now in the process of raising Series B, targeting USD 100 million, We aim to finalize this round by the end of this year. Additionally, we are actively seeking interim funding opportunities to support our ongoing initiatives. Strategic financial planning is crucial as we expand our operations and advance our clinical trials.

Regarding partnerships, we are in continuous discussions with potential partners, particularly major pharmaceutical companies. It is noteworthy that even one patient demonstrating partial regression in our ARB202 study can attract these companies to the negotiation table. These discussions have been ongoing since our last buyout, reflecting strong interest and the potential for lucrative collaborations.

It seems like you are at a critical juncture right now, especially leading up to the end of the year. Is it correct to say that the decisions you make during this period will significantly impact the future trajectory of the company?

These next few months are indeed crucial for us. While discussions about a potential phase III trial, asset sale, or IPO may come later, our immediate focus is on securing the right partnerships and maintaining control over our assets, particularly for the China market. Recently, we received a term sheet offer from a major pharmaceutical company in China. We insisted on retaining only the China rights, which led to some intense negotiation. This decision is informed by our past experiences where selling China rights can impact other partnerships especially those with multinational corporations. We have learnt that retaining control over our key assets in strategic markets is vital for our long-term growth and partnership opportunities. So, it has been a valuable learning process for us. We are navigating these negotiations carefully to ensure we align with our strategic goals and secure the best possible outcomes for the company.

You have more of a scientific background than a managerial one. How do you envision the leadership of the company evolving? Are you actively seeking a CEO, or are you grooming someone within the team?

Yes. I often view myself as more of a scientist than a manager. However, I am always on the lookout for bright talents to join our team, and when they do, I aim to nurture them to potentially take on leadership roles in the future, including that of CEO. Currently, we have around 30 team members, which feels like an ideal size for us. When recruiting individuals, I consider their potential to take over C-suite positions within two or three years. My mindset is always about grooming successors; either I get promoted to a higher level or, if I am not performing well, I am ready to step aside and let someone else take the helm. There is no fear in handing over the reins when the time is right.

Arbele is a rare example of Hong Kong homegrown biotechs. With the government trying hard to nurture a biotech ecosystem, what recommendations would you like to share for better supporting scientists and entrepreneurs in translating scientific breakthroughs into products?

Hong Kongâ??s government has already made significant investments in universities, which is commendable. However, I believe they should also direct funds towards companies like ours. By investing directly in biotech companies, the government can support flagship programmes that showcase Hong Kongâ??s potential for innovation. Unlike investments in universities, which can take a decade or more to yield returns, funding or investing in biotech companies can generate quicker returns. Our company has grown organically, starting from zero to now having over 100 patents and progressing through clinical trials. If a Big Pharma partner invests billions in our product, it would be a testament to Hong Kongâ??s capabilities.

To better support scientists and entrepreneurs, the government should establish vehicles to facilitate such investments rather than relying solely on venture capital that often prioritizes quick returns. Sovereign funds, similar to those in Singapore or the Middle East, could be an effective avenue for this. Such funds align national priorities with economic growth and innovation, providing long term support for the biotech sector.

What message would you like to convey to our audience to capture their interest in your company?

Our company offers a unique value proposition with a strong scientific foundation. We develop first-in-class medicines targeting a novel cancer target that addresses a significant portion of all cancers, particularly gastrointestinal cancers, which represent a third of all cancer cases. More importantly, we prioritize patient-centric care with the goal of not just extending survival but achieving cancer-free survival for three to five years or even longer. Our innovative T-cell engagers, which operate with a mechanism similar to vaccine memory, hold promising potential in eradicating tumours and preventing cancer progression. What truly sets us apart is our team of senior executives with extensive experience in Big Pharma, ensuring a meticulous approach to drug development and a steadfast focus on patient benefit. Our dedication to developing ground-breaking therapies and improving patient outcomes is what drives us forward. We invite you to join us on this exciting journey as we strive to make a significant impact in the fight against cancer.

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