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As China's pharmaceutical landscape expands into innovative biologics, SPH Biotherapeutics (HK) – an R&D affiliate of Shanghai Pharma – is advancing a dual-targeting CAR-T platform with early clinical results beneficial in paediatric leukaemia. Based in Hong Kong, the company combines research autonomy with manufacturing scale in Shanghai, while piloting new models for hospital-integrated production and cross-border collaboration. Grounded in pragmatism and scientific focus, its approach reflects both international ambition and local adaptability. As Dr. Hua Zhang puts it, "For anyone seeking a place where world-class science and a balanced lifestyle can coexist, Hong Kong offers a uniquely compelling proposition."

How did your collaboration with Shanghai Pharma begin, and what prompted the company's move into cell and gene therapy?

After returning to China from the US in the summer of 2018, I was approached by Shanghai Pharma Group, the country's second-largest pharmaceutical company and a member of the Fortune Global 500. At the time, the group had a well-established presence in commercialisation, logistics, and the production of traditional Chinese medicines and generic chemical drugs, yet had not ventured into the field of biomedicine. With the international biopharmaceutical landscape rapidly evolving – particularly following the 2017 approval of Novartis' tisagenlecleucel, the first CAR-T therapy – the

company’s leadership recognised the need to build in-house innovation capabilities and explore this emerging frontier.

I was invited to lead the scientific arm of a newly envisioned subsidiary, working alongside a CEO responsible for business operations, who was a classmate and roommate in their medical school time. Together, we founded SPH Biotherapeutics (HK), a research and development affiliate of Shanghai Pharma focused on genetically engineered T-cell therapies, including CAR-T and T-cell receptor-engineered T-cell (TCR-T) platforms. Starting entirely from scratch with no team, infrastructure, or proprietary technology, we brought and presented a promising business plan to the Hong Kong Science & Technology Park, which ultimately granted us approval with regard to my past twenty-year experience in the National Institutes of Health (NIH).

Why was Hong Kong chosen as the base for SPH Biotherapeutics (HK) despite the option of operating from Mainland China?

The decision to establish our base in Hong Kong was driven primarily by personal considerations. Although I was born in Shanghai, I spent a significant portion of my professional life in the US and developed a deep appreciation for both Western and Chinese cultures. Hong Kong offered a natural intersection of these worlds, an environment where I felt both comfortable and inspired. Beyond the cultural dimension, the city presented several strategic advantages: it is a global financial and logistics hub with an open economic system, unrestricted currency exchange, free flow of information with no hindrance or censorship, and seamless capital movement. Its international connectivity, including visa-free entry for US passport holders, further enhanced its appeal. While Mainland China may offer a more flexible regulatory framework for clinical research, the overall ecosystem in Hong Kong combined with its global outlook made it an ideal launchpad for building a forward-looking biotechnology company.

What scientific approach underpins your lead dual-targeting CAR-T programme, and how did it progress from concept to clinical readiness?

SPH Biotherapeutics (HK) was established to spearhead the development of cutting-edge cell therapies, with our lead programme focused on a dual-targeting CAR-T therapy for paediatric acute lymphoblastic leukaemia (ALL). From the outset, we adopted a bicistronic design to engineer two distinct CARs – targeting CD19 and CD22 antigens – within a single T-cell, rather than using a

tandem construct. Although this approach held significant theoretical promise, it presented a major technical obstacle: the two CARs were initially expressed at unbalanced levels, compromising therapeutic efficacy. Over the course of six to eight months, our team undertook extensive molecular optimisation, carefully adjusting the modular architecture of each CAR to achieve stable and harmonised co-expression. This breakthrough provided the basis for clinical translation.

Recognising the need to move beyond the laboratory, we established a dedicated manufacturing facility in Shanghai, equipped to produce both the viral vectors and the engineered cells supporting early-stage human studies. The city's robust medical infrastructure enabled us to collaborate with Shanghai Children's Medical Centre on an exploratory evaluation of our CD19/CD22 construct. Between January 2022 and April 2024, a total of 358 paediatric patients with relapsed or refractory ALL, most of whom were in late-stage, treatment-exhausted conditions, received our therapy. While the study was not conducted under full regulatory oversight, all manufacturing followed procedures equivalent to GMP, and the primary aim was to assess safety and therapeutic potential in a clinical context.

The results were highly encouraging: the one-year event-free survival rate reached approximately 76 percent, with an overall survival rate of 93 percent. These outcomes were presented at the American Society of Haematology (ASH) Annual Meeting last year and received strong recognition from both the scientific community and the media, underscoring the potential of our dual-targeting strategy in addressing a critical unmet medical need.

What clinical value does a dual-targeting CD19/CD22 CAR-T therapy offer compared to single-antigen constructs, and what have initial outcomes shown?

The rationale for developing a dual-targeting CAR-T therapy combining CD19 and CD22 stemmed from a critical limitation observed with CD19-only constructs. Relapse frequently occurs within six months of treatment due to antigen loss, whereby leukaemic cells escape immune detection by ceasing to express CD19. By incorporating CD22 as a second antigen target, our optimised bicistronic construct was designed to mitigate this vulnerability and extend the durability of response.

While regulatory bodies such as the European Medicines Agency (EMA) and the US FDA require up to 15 years of follow-up data for paediatric cell therapies, our programme has thus far generated three years of post-treatment data. Relapse was still observed in approximately 17 per cent of patients, an outcome that, although not uncommon in this indication, prompted further analysis.

In several cases, relapse was associated with the emergence of CD19/CD22 double-negative clones or insufficient T-cell persistence, potentially due to limitations in the patients' own cellular fitness. However, most of these cases were successfully managed through a second infusion of previously preserved CAR-T cell products, leading to complete responses and confirmed negative minimal residual disease. Although these findings are preliminary, they strongly suggest that dual-targeting CAR-T approaches may offer both enhanced initial efficacy and a viable pathway for retreatment, representing a significant therapeutic advancement for relapsed or refractory paediatric ALL.

What are the next steps toward regulatory approval for your lead programme, and how are you positioning the therapy globally?

Our lead CD19/CD22 CAR-T therapy is currently undergoing Phase I clinical evaluation to establish a safe and effective dosing protocol. This will be followed by a Phase II trial involving approximately 100 patients across five sites, using the recommended dose identified during Phase I to further assess efficacy and safety in a broader population. The outcome of this study will form the basis for a Biologics License Application, with a view to obtaining conditional marketing authorisation.

While China remains the primary development base, our vision for this therapy is global in scope. We filed for international patent protection two years ago, and the approval process is now well advanced. This will enable us to pursue regulatory pathways in the US and Europe. Encouragingly, following the presentation of our data at the ASH Annual Meeting, we received strong interest from clinical partners in Southeast Asia, particularly in Singapore and Thailand, who are now exploring local applications of the platform. In parallel, we are advancing a second clinical programme using the same CD19/CD22 construct under a separate Investigational New Drug (IND) application for adult patients with non-Hodgkin lymphoma (NHL). This expansion reflects our strategic commitment to building a versatile therapeutic platform capable of addressing both paediatric and adult haematological malignancies across multiple markets.

Given the availability of approved CAR-T therapies, why are you pursuing adult non-Hodgkin lymphoma as a second indication?

Although approved CAR-T therapies from Novartis and Kite Pharma already serve adult B-cell lymphoma patients, we believe our dual-targeting CD19/CD22 construct can offer meaningful clinical and commercial advantages. From a therapeutic perspective, targeting two antigens rather

than one may reduce relapse rates caused by antigen escape and improve overall durability of response, an area where single-target therapies still face limitations. Strategically, adult non-Hodgkin lymphoma represents a significantly larger market than paediatric ALL, and we see a strong potential to reach more patients.

Furthermore, we are conducting research and development using domestically produced instruments, reagents, and manufacturing platforms, which allows us to reduce production costs substantially. Whereas existing CAR-T therapies can cost upwards of USD 400,000 per treatment, we believe our approach could halve that figure. Even in China, where local CAR-T products are priced around CNY 1.2 million (approximately USD 165,000 – 170,000), access remains limited due to affordability constraints and the absence of a comprehensive reimbursement framework.

Our believe is that market penetration has been modest, not due to lack of clinical demand, but because most patients are unable to pay out-of-pocket. In the long term, we are optimistic that improvements in national insurance coverage and broader economic growth will create the conditions for wider adoption of advanced therapies such as ours.

How did you build a specialised team for advanced cell and gene therapy in Hong Kong's emerging biotech ecosystem?

Establishing a specialised team for cell and gene therapy in Hong Kong required careful consideration, particularly given the limited depth of local experience in this emerging field. That said, the city offers a strong academic foundation, supported by a number of internationally ranked institutions – including The University of Hong Kong (HKU), The Chinese University of Hong Kong (CUHK), The Hong Kong Polytechnic University (PolyU), and The Hong Kong University of Science and Technology (HKUST) – which produce a steady stream of high-calibre scientific graduates.

Upon arriving, I focused on local recruitment, and while the candidates were intellectually capable and highly motivated, few had direct exposure to transgene T-cell technologies, which were still relatively new to the region at the time. We therefore invested significantly in training, and I was amazed to see how quickly the team adapted, most members became technically proficient within such a short time. Today, the team operates with exceptional efficiency and supports a pipeline of approximately ten active targets, covering both haematologic malignancies and solid tumours, reflecting the depth and agility we have built from the ground up.

How do you manage regulatory and operational responsibilities across Hong Kong and Mainland China, and what advantages does this structure offer?

Our “R&D in HK and clinical translation in Shanghai” operating model draws a clear distinction between functions performed in Hong Kong and those managed from Mainland China, enabling us to pursue innovation with agility while remaining fully compliant with regulatory expectations. In Hong Kong, our activities are focused exclusively on research and early-stage development. We are not subject to local regulatory oversight for advanced therapy medicinal products, which allows us to move swiftly without procedural bottlenecks. All clinical development, manufacturing, and regulatory submissions are coordinated through Shanghai Pharma’ specialised regulatory and clinical affairs teams, which possess extensive experience and institutional capacity to guide therapies through the approval process. Manufacturing is also centralised in Shanghai, supported by dedicated quality assurance and quality control infrastructure. This division of labour has proven highly effective, allowing our Hong Kong-based team to operate with singular focus on discovery and preclinical development while leveraging the regulatory maturity and manufacturing scale of our parent organisation in China.

While Hong Kong’s biomedical ecosystem still lags behind more established life sciences hubs in terms of supply chain depth and production scale, it offers distinct advantages that support our innovation goals. The city provides open access to global knowledge resources and scientific literature, unrestricted procurement of international equipment and reagents, and a seamless digital infrastructure, all of which are difficult to replicate in the mainland due to internet restrictions and cross-border regulatory hurdles. Although conducting R&D in Hong Kong is comparatively more expensive, we are currently insulated from financial pressures thanks to strong backing from our parent company.

That said, we are actively exploring a potential spin-off and eventual IPO, which would enable us to secure independent financing and sustain long-term growth as the scale of our pipeline increases. Our Hong Kong team remains lean, highly efficient, and focused on innovation, while manufacturing and regulatory execution continue to be anchored in Shanghai. This dual-site structure, combining the intellectual openness of Hong Kong with the operational strength of Mainland China, has served us well, and remains integral to the advancement of our ten active development programmes across paediatric and adult haematological malignancies, as well as solid tumours.

What personal reflections or final message would you like to share about your experience living and working in Hong Kong?

After seven years in Hong Kong, I can confidently say that the city offers an outstanding environment for both scientific innovation and quality of life. From a professional standpoint, its open access to international research resources, lack of restrictions on global procurement, and efficient infrastructure make it an ideal location for agile, R&D-led operations. Unlike in other jurisdictions, where access to information or materials may be constrained, Hong Kong's openness facilitates seamless collaboration and exploration.

On a personal level, the city is safe, highly convenient, and surprisingly tranquil once you step outside the central districts. The public transportation system is highly efficient and extensive, and it is not uncommon to work late into the evening and still feel completely secure. During the cooler months, from November to March, I particularly enjoy going many scenic hiking trails, with Hong Kong's blend of beautiful mountains and coastal views offering a refreshing contrast to the intensity of laboratory work. While the summer heat and humidity can be challenging, they are part of the city's character and do little to diminish its broader appeal.

For anyone seeking a place where world-class science and a balanced lifestyle can coexist, I believe Hong Kong offers a uniquely compelling proposition.

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