THE DEVELOPMENT OF CHIMERIC ANTIGEN RECEPTOR-T CELL THERAPY IN CHINA

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INTRODUCTION

- Chimeric antigen receptor (CAR)-T cell therapy represents a major advancement in personalized cancer treatment. In this strategy, T cells are genetically engineered to express a synthetic receptor that binds a tumour antigen. CAR-T cells are then expanded for clinical use and infused back into the patient's body to attack and destroy chemotherapy-resistant cancer[1].
- Significant clinical advantages have been showed in the cancer patients treated with CAR-T cell therapy, especially for CD-19 positive hematologic malignancies.
- Two CAR-T cell therapies were approved recently in Europe and United State :
  - Kymriah® (Tisagenlecleucel): approved for the treatment of B-cell acute lymphoblastic leukemia (ALL) and Diffuse large B-cell lymphoma (DLBCL).
  - Yescarta® (Axicabtagene ciloleucel): approved for the treatment of DLBCL and primary mediastinal large B-cell lymphoma (PMBCL).
- In the past years, China had the largest number of clinical trials now being conducted in the worldwide, and the number of relevant publications increased substantially. Therefore, China is considered as one of the most active players in the development of CAR-T cell therapies[2].

OBJECTIVE

- This study aimed to describe the current regulatory environment of CAR-T cell therapies in China.
- The CAR-T cell therapies in development in China were investigated to identify the CAR-T cell therapies expected to reach the China market in the near future.

METHOD

- China drug regulatory authority official websites, mainly National Medical Products Administration (NMPA)[3] and National Health Commission (NHC)[4] were browsed, complemented by a literature review to include the articles discussing the relevant regulations for the CAR-T cell therapy in China.
- The official website for the China Drug Evaluation Centre (CDE)[5] was searched to identify the CAR-T cell therapies currently approved for the initiation of clinical trials in China.

RESULTS

- Although substantial achievements in stem cell field were witnessed, China was often criticized by the international community for the loose and inconsistent regulation of stem cell related therapy (including CAR-T cell therapy):
  - The regulation of cellular-related therapies experienced several changes from regulated as biological products, to medical technology, to self-managed technology, and finally as biological products again (Figure 1).
  - It was confusing for developers to decide which regulation should apply to CAR-T cell therapies given the inconsistences between different regulations.

Figure 1. History of regulation applied to CAR-T cell therapies in China

2003-2006: Guidelines for Human Gene Therapy Research and its products[6]
- Stem cell-based products were first categorized as biological drugs, which were regulated by the State Food and Drug Administration (SFDA). The review and approval of new drugs were based on the provision of drug registration.

2009-2011: Regulation on the clinical application of medical technology[7]
- Cell & gene therapies were classified as category 3 medical technologies, associated with highest risk, ethical issues, and have not yet scientifically proven its therapeutic value. Under such regulation, approval from a technical audit board was required before a cellular therapy product could be used.

2015: Allowance of self-managed application of stem cell therapy
- The clinical application of stem cell or immune-cell therapies as medical technology was rescinded, and medical institution were allowed to self-management of the application of these treatments.

2016: Suspension of clinical applications without regulatory approval[8]
- After the striking death of Zexi Wei, who received one controversial cell-based immunotherapies for the treatment of synovial sarcoma, all the clinical application of unapproved cell therapies were suspended.

2017: Guideline on the research and review process of cellular product
- Cellular products were regulated as biological products again. This document could be deemed as the primary regulatory document of cellular product in China.

2019: Administrative regulation for the clinical application of New biomedical technologies (Draft for comments)[9]
- Clinical research for biomedical technologies cannot be carried out unless the government have approved it. Biomedical technologies classified as high risk were now subject to the direct management of NHC, while biomedical technologies classified as low risk were under the regulation of provincial Ministry of Health.

- This year, a risk based regulation for biomedical technologies was proposed in the 'Administrative regulation for the clinical application of new biomedical technologies (2019)'. CAR-T cell therapies met the definition of high-risk biomedical technology that were under the direct regulation of NHC.
- A series of flexible regulation approaches in order to encourage the development of innovative therapies (including CAR-T cell therapies) were proposed[10] (Table 1).

Table 1. Regulation or initiatives for the innovative therapies development

Strategies for encouraging the development of CAR-T cell therapies	
Review and approval	• Allowance of non-registered clinical data for market authorization application as long as the data reliability, integrity and traceability were justified; • Acceptance of overseas clinical trial data for market authorization application. • Implementation of priority review and approval pathway for innovative drugs with unmet clinical needs.
National initiatives	• Biotechnology (including cell and gene therapy) was defined as "strategic emerging industry" in the "Made in China 2025" and "13th five-year plan", which means that China government will give priority to its development through financial supporting programs or investment in infrastructure and overseas talent recruitment.

- The first CAR-T cell therapy approved for initiation of clinical trials was LCAR-B38M CAR-T cell therapy developed by the Nanjing Legend Biotech in 2017.
- A total of 16 clinical trials applications for CAR-T cell therapies were accepted by China CDE until July 2019.
  - Among them, 12 were CD-19 targeted CAR-T, 3 were BCMA targeted CAR-T and 1 was GPC-3 targeted CAR-T.
- A tendency of worldwide collaborations between international pharmaceutical giants and China biotech companies has been witnessed with purpose to achieve a cooperative business model for an even faster development of CAR-T cell therapies (Figure 2).

Figure 2. International collaborations between China biotechs and foreign companies

Legend biotech, China + Janssen (December 2017)[11]
- Entered into a worldwide collaboration and license agreement between two companies to jointly develop and commercialize LCAR-B38M in multiple myeloma.
- Janssen will make an upfront payment of $350 million that will be recorded in the fourth quarter and additional payments based upon the achievement of certain development, regulatory and sales milestones.

Fosun Pharma, China + Kite pharma = FOSUNKITE (January 2017) [12]
- Establish a Sino-foreign cooperative enterprise in China under the cooperation agreement through its wholly-owned subsidiary to introduce KTE-C19.
- Fosun Pharma intends to contribute US$20 million and Kite Pharma contributes with the right to exclusive use of its products and proprietary technology at the value of US$20 million. Each of them owns 50% equity interests in the cooperative enterprise.

Wuxi AppTec, China + Juno = JW Biotechnology (April 2016)[13]
- The mission is to build China's leading cell therapy company by leveraging Juno's world-class CAR together with WuXi AppTec's R&D and manufacturing platform and local expertise to develop novel cell-based immunotherapies for patients with hematologic and solid organ cancers
- Juno and WuXi AppTec have equal initial ownership in JW Biotechnology

- Despite the fact that China has the world's largest number of clinical trials of CAR-T cell therapies currently being conducted, there are still some challenges in terms of both regulatory and technical aspects that need to be overcome:
  - Clinical trials: the overall patient sample size and study centre number were quite limited. studies were generally not well-designed and the drug dosage used in the clinical trials were not fully explained[14].
  - Research institution: within around 98 research institutions involved in the basic stem cell research in China, the structure of faculty's professional titles and education degree was unsatisfactory: less than a quarter of institution faculty held either M.D. or Ph.D. degree[15].
  - Regulation: ambiguity existed regarding whether CAR-T cell therapies should be regulated as medical technology or biomedical product. This possibly leaded to the increased number of unapproved applications of CAR-T cell therapies in clinical trials in China.

CONCLUSIONS

- A supportive regulatory environment for the development of CAR-T cell therapies was created in China. With the benefits of such encouraging initiatives and collaborative business model established with international pharmaceutical companies, promising CAR-T cell therapies are expected to reach to Chinese patients in the upcoming years.
- Efforts are still awaited to improve the quality of clinical trials as well as the speciality of research personnel involved in the CAR-T research. Clarification on the application of the different regulations/guidelines are needed to increase regulation consistency.

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