Cell and gene therapy in China
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Since 2010, we have seen a number of advanced therapy medicinal product (ATMP) approvals and product launches. These ATMPs, in particular cell and gene therapy (CGT), helped to bring new hope for patients and their families who were suffering from indications – such as cancer and rare diseases – where there is a high unmet medical need.

China is making excellent progress in CGT development and the clinical trial activities in China for CGT have grown significantly in the past few years. After having produced a chimeric antigen receptor T cells (CAR-T) therapy with 94% response rate in myeloma patients in 2017 and setting up a 50-50 collaboration with Janssen, Legend Biotech, a China-based, biotech company successfully completed its US IPO in early 2020.

Other local companies have also taken the path of collaborating with large global biopharma firms, including Suzhou Innovent Bio, which formed an R&D collaboration with Roche. Innovent will use Roche’s technologies for both discovery and development, giving Roche an option to eventually license each product for ex-China development and commercialization.

And progress is moving forward even during the global COVID-19 pandemic. JW Therapeutics – a joint venture established by WuXi AppTec and Juno Therapeutics – completed a US$100m Series B round of financing in June 2020. JW Therapeutics’ lead product, a CAR-T therapy, started Phase II trials in China.

The current regulatory requirement in China is less stringent than in the US, requiring permission only from the internal hospital ethics committees. This presents a double-edged sword since it is less cumbersome to navigate complex regulatory processes and get ATMPs into clinical trials, but it may also lead to questionable products being introduced into the pipeline if there is not appropriate hospital-level oversight. In addition to the upward-trending clinical trial activities, capital is being invested and collaborations are being formed between multinational companies and their Chinese counterparts in the CGT space. For instance, Merck KGaA collaborates with GenScript to develop and establish a globally recognized CGT manufacturing service in China.

In the following pages, we focus on sharing the current key market and regulatory dynamics.

In China, the number of CGT clinical trials, found in clinictrials.gov, have grown significantly, as shown in Figure 1, and most of the trials are CAR-T. Within the active trials for CAR-T, approximately 75% of those are in hematological or “blood tumors,” the technology is now shifting to solid tumors. The remaining 25% are spread among various malignant tumor treatments, such as cancer of the gastrointestinal (GI) tract, liver, lungs and breast.

**Figure 1.** CGT clinical trials commenced in China (2014–19), as found on the FDA clinical trials website (www.clinicaltrials.gov)
Many of the clinical trials in China are initiated by the ~100 biopharma and biotech companies, with a few leading the pack. Table 1 below shows some of the top CGT companies in China along with their corresponding targets and current trial status. Most recently, Fosun Kite has filed for new drug application (NDA) of its leading product, FKC876, an anti-CD19 CAR-T, to the National Medical Products Administration (NMPA). Nanjing Legend Bio, a subsidiary of GenScript Biotech and Johnson & Johnson’s collaborator, initiated a Phase 2 clinical trial in 2019 for its LCAR-B38M in China and globally. Similarly, in 2019, Hrain Biotechnology commenced Phase 1 clinical trials in China for its three CAR-T products, and CARsgen Therapeutics received clearance for conducting Phase 1 clinical trials in China and in the US, respectively, for hepatocellular carcinoma (target: Glypican-3 (GPC3)) and multiple myeloma (CT053; target: BCMA). In addition, CARsgen was granted RMAT designation by the U.S. Food and Drug Administration (FDA) for relapsed/refractory multiple myeloma (rrMM) for its CT053. Besides CAR-T, China is also quite dynamic in the development of gene therapy; notability, CureGenetics based out of Suzhou is developing a range of treatment products, and it has entered global strategic collaborations with Thermo Fisher Scientific in 2017.

Table 1. Leading CGT companies in China, focusing on CAR-T

<table>
<thead>
<tr>
<th>Company</th>
<th>Site</th>
<th>Founded year</th>
<th>Ongoing CDE registered clinical trials</th>
<th>Site space (m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosun Kite Biotechnology Co., Ltd</td>
<td>Shanghai</td>
<td>2017</td>
<td>DLBCL/ PMBCL CD19 NDA</td>
<td>10,000</td>
</tr>
<tr>
<td>Nanjing Legend Biotechnology Co., Ltd</td>
<td>Nanjing, Jiangsu</td>
<td>2014</td>
<td>MM BCMA Ph2</td>
<td>150,000</td>
</tr>
<tr>
<td>Hrain Biotechnology Co., Ltd</td>
<td>Shanghai</td>
<td>2015</td>
<td>DLBCL / FL CD19 Ph1</td>
<td>3,000</td>
</tr>
<tr>
<td>CARsgen Therapeutics Co., Ltd</td>
<td>Shanghai</td>
<td>2014</td>
<td>Solid tumor GPC3 MM BCMA Ph1</td>
<td>7,600</td>
</tr>
<tr>
<td>HuaDao CAR-Tcell</td>
<td>Shanghai</td>
<td>2017</td>
<td>ALL CD19 Ph1</td>
<td>15,000</td>
</tr>
<tr>
<td>JW Therapeutics (Shanghai) Co., Ltd</td>
<td>Suzhou, Jiangsu</td>
<td>2016</td>
<td>NHL CD19 Ph2</td>
<td>Unknown</td>
</tr>
<tr>
<td>Chongqing Precision Biotech Co., Ltd</td>
<td>Chongqing</td>
<td>2016</td>
<td>ALL CD19 Ph1</td>
<td>15,000</td>
</tr>
<tr>
<td>Galaxy Biomedical Investment Co., Ltd.</td>
<td>Chengdu, Sichuan</td>
<td>2016</td>
<td>B-Lymphoma CD19 Ph1</td>
<td>Unknown</td>
</tr>
<tr>
<td>Shanghai Cell Therapy Group Co., Ltd.</td>
<td>Shanghai</td>
<td>2014</td>
<td>DLBCL CD19 Ph1</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Sources: Yaozh database, company websites, literature research, EY-Parthenon analysis

There are also quite a few hospitals in China sponsoring CAR-T clinical trials, including four hospitals in China that have double-digit trials sponsored, as indicated on clinicaltrial.gov: Shenzhen Geno-Immune Medical Institute, Beijing Boren Hospital, Chinese PLA General Hospital (in Beijing) and Southwest Hospital (in Chengdu, Sichuan). In addition to these top four, there are dozens of other hospitals in China sponsoring CAR-T trials.
Observations in China: R&D trends

Global CAR-T R&D at present is particularly focused on a few central priorities:

1. The attempt to develop “universal” CAR-T.
2. Efforts to improve CAR-T cell production efficiency.
3. Expansion into solid tumor treatments.

CAR-T R&D in China is closely aligned with these global priorities. For example, Chinese companies such as the Suzhou-based biotech Gracell Biotechnologies are focusing on the challenge of universal CAR-T. Traditionally, CAR-T cell therapies have been autologous – meaning the T cell donor and recipient are the same person. This allows therapies to avoid immune rejection, but it also leads to complicated bidirectional logistics pathways and challenges when it comes to therapeutic scale-up.

To ameliorate this, companies such as Gracell are investigating the possibility of “universal,” allogeneic (different donor and recipient with unidirectional logistics chain) CAR-T cell therapies, using CAR-T cells that are modified to evade the immune system of the recipient. Gracell has initiated a Chinese clinical trial of allogenic CAR-Ts for acute lymphocytic leukemia (ALL), using its TruUCAR Technology, based on lymphocytes obtained from healthy donors and modified with CRISPR gene editing to avoid graft versus host disease (GvHD) as well as rejection. Gracell is also using its patented FasT CAR solution to reduce the CAR-T cell production from weeks down to days.

Chinese companies are also, for example, making efforts to optimize CAR-T-inclusive treatment protocols in the country. This has resulted in a move toward protocols which use CAR-T in combination with other treatments (for example, combo therapy with anti-PD-1 monoclonal antibodies to boost CAR-T cell persistence), dual target CAR-T treatment (e.g., two separate CAR-Ts of different targets, such as CD19 and CD22 or BCMA and CD19), and sequential CAR-T treatments, all intends to induced sustained remission of tumors.

In addition to speaking with the leading biotechs, we have also conducted several interviews with key opinion leaders (KOLs) and physicians in the leading hematology departments of major hospitals in China to understand the current view of CAR-T by the medical community with respect to: a) the positioning of CAR-T vis-a-vis current treatment options, b) the treatment cycle and timeline of CAR-T and c) the clinical perception of CAR-T. Currently, CAR-T is perceived as the last line of defense in the Chinese medical community and can be a complementary option to allogeneic hematopoietic stem cell transplantation (Allo-HSCT).

**Figure 2. Positioning of CAR-T therapy in the current treatment paradigm**

<table>
<thead>
<tr>
<th>Treatment perspective</th>
<th>Treatment flow</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Last line of treatment option in the near term</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Complementary therapy in combination with HSCT</strong></td>
<td></td>
</tr>
<tr>
<td><strong>In the initial stage, physicians may only adopt the approved therapy for last line treatment, considering its efficacy data limitation and high cost</strong></td>
<td></td>
</tr>
<tr>
<td><strong>But it has the potential to be promoted in the mid to long-term when its efficacy has been proved through real world evidence</strong></td>
<td></td>
</tr>
<tr>
<td><strong>1st line</strong></td>
<td><strong>2nd-3rd line</strong></td>
</tr>
<tr>
<td>Targeted drug + chemotherapy</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Relapse</td>
<td>Relapse/ refractory</td>
</tr>
<tr>
<td><strong>For B-cell lymphoma and leukemia treatment. CAR-T can be administered as complementary therapy before Allo-HSCT to improve efficacy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Conversely, CAR-T therapy could also be administered to relapse patients after Allo-HSCT has been conducted</strong></td>
<td></td>
</tr>
</tbody>
</table>

Note: Allo-HSCT=allogeneic hematopoietic stem cell transplantation
Sources: expert interview, EY-Parthenon analysis
Cell and gene therapy in China

Cell and gene therapy in China

Figure 2 shows how CAR-T therapies are positioned with respect to current treatment options for hematological cancers. CAR-T is used as the last line of treatment after patients have failed chemotherapy and targeted therapies, or as a complementary treatment with Allo-HSCT, either before or after Allo-HSCT to improve clinical outcomes.

Recent product launches (Yescarta and Kymriah) in the US and EU have shown that CAR-T cell therapies are commanding premium pricing; due to health economic reasons most payers are shifting to value-based payment strategies to adapt to the high cost of ATMP and curative therapies. In China, it is expected that the patient is to pay fully out-of-pocket or potentially via commercial insurance in the foreseeable future. Value-based pricing is one of the topics being discussed; however, it is not expected to be implemented in the near future.

Typical CAR-T treatment in China takes approximately one month, with post-treatment monitoring counted separately. Figure 3 shows the typical CAR-T treatment in China by key steps. Patient eligibility screening takes about one to two weeks with specific criteria set. The CAR-T cell creation and cell production step takes another one to two weeks before CAR-T cells are infused back into the patient. There are preparation steps required, e.g., chemotherapy and resting, before CAR-T cells can be infused; as such, the CAR-T cell infusion step takes about one week. Once the treatment is complete, patients are closely monitored initially at once per month intervals, and then gradually extended to semi-annually as the conditions stabilized.

The general perception from the medical community EY interviewed in China toward CAR-T therapeutics is quite positive. The overall confidence level toward CAR-T therapies from physicians who have clinical trial experience related to CAR-T trials is

Figure 3. CAR-T treatment cycle in China

Patient eligibility → Cell collection → CAR-T creation and production

Pre screening

Example of criteria, i.e., not a hepatitis B
Patient, ECOG score is less than two points (can walk), etc.

Tests

Bloodtest, PET-CT
Bone marrow puncture, etc.

Pre-treatment eligibility assessment

Lymphocyte collection

CAR-T creation and expansion

Conditioning therapy

Patient undergoes conditioning chemotherapy during this period

Note: 1) CRS: cytokine release syndrome
Sources: Expert interviews; literature research; EY-Parthenon analysis

*Eastern Cooperative Oncology Group (ECOG) score describes a patient's level of functioning in terms of their ability to care for themselves, daily activity and physical ability.
high; high treatment response rates have been observed from those CAR-T trials. In addition, the treatment response results of locally developed CAR-T therapies are regarded to be in line with global clinical trial results although there is no conclusion of better response results due to the lack of head-to-head comparison clinical trials.

Besides the positive perceptions, there are also concerns with post-CAR-T infusion cytokine release syndrome (CRS) handling capability in China. CRS grading and handling require the experiences of the physicians and the nurses in charge, where training is provided by the sponsoring companies are needed. It is also important to take the CRS factor into consideration for patient eligibility and CAR-T infusion preparation. Furthermore, as with all ATMPs, therapeutic heterogeneity is observed between companies and specific types of cells are observed, due to variations in process and end product.

Acknowledging that intellectual property (IP) is crucial for CGT development, and to understand the importance of IP, we have conducted various interviews and discussions with multinational and Chinese biopharmaceutical and biotech companies, law firms, Chinese associations and government stakeholders on the IP environment in China and expectations/trends going forward. What we found is that the Chinese Government is making significant effort in the past few decades, as shown in Figure 3, in strengthening the China IP environment, and that effort is aligned with the Chinese Government’s overall national strategy to foster innovation in China. The latest is a Notification released by the China National Intellectual Property Administration in March 2020 that calls for revision of Patent Law to enhance the protection of IPs and increase the enforcement of penalizing patent
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Mar 1984
• The first Patent Law was passed by the 6th National People's Congress (NPC)
• However, application did NOT extend for drugs and substances obtained using chemical methods

Jan 1992
• The US and China signed a Intellectual Property Rights Memorandum Of Understanding (MOU)
• This MOU allowed the patent application for all chemical invention, including drugs and agro-chemical substances, and the coverage included product and process

Sep 1992
• To reconcile the disparity between the Patent Law and MOU, the 7th NPC revised (the first revision) the Patent Law to allow patent applications for drugs and substances obtained using chemical methods
• The revised Patent Law also stipulate the condition (for public common interests) for compulsory licensing of patent

Aug 2000
• Post joining WTO and abiding to Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs), the 9th NPC revised (the second revision) again the Patent Law, which modified the condition of compulsory licensing of patent along with other articles
• This version made the Patent Law more aligned to the international (e.g., US and EU) standards

Oct 2002
• The release of Drug Administration Law (Pilot) stipulated the disclosure of the patent situation for the drug being submitted for regulatory approval with NMPA (National Medical Products Administration), this is the first time such request and linkage of patent with drug approval application

Dec 2008
• The 11th NPC revised the Patent Law (the third revision) added the articles on patent infringement from the regulatory perspectives
• This version also added new condition for compulsory licensing of patent: for public health reasons

May 2017
• China State Council released the "Regarding the strengthening of review and approval reform for facilitating innovation for drug and medical devices (Opinion)"
• The Opinion suggested the establishment of patent linkage system, patent term restoration, and clinical trial data protection
• This Opinion, however, is for guidance and no formal establishment regarding patent linkage system

Mar 2020
• China National Intellectual Property Administration released a policy notification on pushing the revision of the Patent Law to enhance the protection of drug IPs, establishment of publicly releasing data of counterfeit drugs and biologics, and expanding of collaborations with overseas countries among others
• The notification also calls for more stringent on enforcement of IP infringement, including establishment of National IP data center, increasing of penalty, among others

Sources: Lit research; EY-Parthenon analysis

Figure 3. China regulation and policy guidelines relating to drug intellectual property

infringement along with other specific milestones to be achieved in the coming couple years. This is a positive for those multinational pharmaceutical companies looking to enter the Chinese CGT market but may have some concerns with the IP environment in China.

Anticipating the future growth of CGT, big pharmaceutical companies have started to form collaborations and engage in M&A with biotechs. Similarly, multinational pharmaceutical companies have established their presence in China CGT via collaborations with Chinese local players, as shown in Table 2, to capture the CGT growth prospects in China, in particular in CAR-T therapeutics.

Going forward, more collaborations between multinational pharma and Chinese local players are expected,
especially when the CAR-T products of the leading Chinese biotechs in Table 1 have entered late clinical trial stages. These biotechs offer not only clinical-stage CAR-T products but also potential access to a large and growing Chinese market. Most of these companies are founded by scientists and could benefit from the commercial capability of multinational pharmaceutical companies and their global presence for commercialization of their CAR-T in China and globally, which benefits all parties and those seeking medical care.

We also expect China to continue seeing more research and clinical development activities in CGT, expanding from the current CAR-T dominant space to more diversified modalities. There has been a general attitude shift toward innovation in the China bio and pharma space, and there is also favorable government policy support, increasing capital flux and more talents returning from the US and EU. While some of these biotechs would eventually grow to become a fully integrated biopharmaceutical company, the majority can benefit from teaming with multinational pharmaceutical companies.

### Table 2. Selected collaborations between multinational and Chinese companies in CGT

<table>
<thead>
<tr>
<th>MNC pharma</th>
<th>Chinese company</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Licensing</td>
<td>Xian Janssen/Johnson and Johnson</td>
<td>GenScript</td>
</tr>
<tr>
<td></td>
<td>Novartis</td>
<td>CBMG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ GenScript grants Janssen a global license to develop and commercialize lcar-b38m</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ Janssen will record global net sales outside greater China</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ CBMG is responsible for the manufacture and supply of Novartis CAR-T drug Kymriah in China</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ Novartis will receive royalty free intellectual property rights to some CBMG CAR-T technologies worldwide</td>
</tr>
<tr>
<td>Collaboration agreement</td>
<td>Merck &amp; Co</td>
<td>GenScript</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ Cooperate to build a Chinese plasmid and virus production platform in line with global standards</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ Merck provides GenScript with a full range of training and consulting services, ranging from lab development to process design for large-scale GMP production, plant facility concept design, and quality management system</td>
</tr>
<tr>
<td>Joint venture</td>
<td>Kite Pharma</td>
<td>Shanghai Fosun Pharmaceutical (Group) Co., Ltd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ The Chinese-foreign joint venture: Fosun Kite Biotechnology was established in 2017 in Shanghai China, with Fosun and Kite Pharma each holding 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ Fosun Kite is dedicated to the advancement of innovative cell therapy and its industrialization in China to benefit patients</td>
</tr>
</tbody>
</table>

Sources: Literature research; EY-Parthenon analysis
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