CONSIDERATION OF A SUSTAINABLE CELL AND GENE THERAPY ECOSYSTEM
— THE CASE OF CAR-T CELL THERAPY —

Takako Kato
Industry Innovation Dept., Technology & Innovation Studies Div.
Mitsui & Co. Global Strategic Studies Institute

SUMMARY

- Substantial growth is expected for the market for cell and gene therapy products, which includes CAR-T cell therapies. Because the medical treatment process involving the use of living cells and other such elements is very complicated and expensive, a new ecosystem is needed for full-scale market penetration of such therapies.

- In the West, where the social implementation of CAR-T cell therapy is one step ahead of other countries, high value-added services, such as supply chain management (SCM) using digital technology, cold chain logistics, specialty pharmacies, and cell processing centers (CPCs), are emerging.

- These new services are expected to organically connect various stakeholders, such as patients, governments, scientific societies, academia, medical institutions, insurers, and pharmaceutical companies, to promote the formation of a “cell and gene therapy ecosystem” for the sustainable and stable supply of advanced cell and gene therapy products.

BACKGROUND TO THE CELL AND GENE THERAPY PRODUCTS DEVELOPMENT AND CURRENT SITUATION

Currently, the scale of the global pharmaceutical market is over JPY 100 trillion (approximately USD 953.8 billion) and the development of pharmaceuticals for treating illnesses defined as “unmet medical needs,” which refer to diseases that cannot be satisfactorily treated with existing treatments, is advancing. According to a report by the Center for Research and Development Strategy (CRDS) of the Japan Science and Technology Agency (Figure 1), in the context of the modern history of pharmaceuticals, the 20th century was considered the golden age of small molecule drugs, while the 21st century to the present has been viewed as that of

Figure 1: History of pharmaceuticals (since 1900)

Source: Japanese-language report by the Center for Research and Development Strategy (CRDS), Japan Science and Technology Agency, on the trends and outlook for next-generation medicines and basic technologies, and R&D strategies to be promoted (Jitsuedai/yaku kiban gijutsu no doko to tenbo, suihi/shi subeki kensyu kaigatsu seiritsu).
antibody drugs. Going forward, the development of cell and gene therapy products, which include regenerative medicine, cell therapies, and gene therapies, is expected to gain impetus along with that for nucleic acid medicines, digital medicines, microbiome medicine and phage therapies, in the interest of providing patients with more sophisticated and advanced treatments as well as radical treatments. In particular, patients have high expectations for the social implementation of cell and gene therapy products (processed cells and tissues, and products for gene therapies; they are classified as shown in Figure 2. In Japan, the technology related to these products, therapies or medicines is generally called as “Regenerative Medicine Products”). In Japan as well, an accelerated drug approval program for cell and gene therapies was adopted in 2014 ahead of other countries, and this has been helping to commercialize products and shape the industry.

According to a study by the Alliance for Regenerative Medicine, the world’s largest industry group in the field of cell and gene therapy products, 1,028 clinical trials were being conducted worldwide as of the end of 2018, and among these, trials for cancer-targeting products accounted for 598, or more than half (58%). The group has also forecast that 10-20 products will be released to the market by 2025.

In this field, pharmaceutical companies are actively pursuing large-scale M&As in a bid to expand their development pipelines by acquiring the seeds of innovation at the R&D stage, and to absorb know-how for the development of treatments using cells. GILEAD Sciences (US) bought Kite Pharma (US) for USD 11.9 billion in 2017; Novartis (Switzerland) acquired AveXis (US) for USD 8.7 billion in 2018; and in 2019, industry realignment picked up further momentum with Astellas Pharma’s (Japan) purchase of Audentes Therapeutics (US) for approximately USD 3 billion, and Bristol-Myers Squibb’s (US) acquisition of Celgene (US) for USD 74 billion.

EXAMPLE OF A CELL AND GENE THERAPY PRODUCT: CAR-T CELL THERAPY

What is CAR-T cell therapy?

In the field of cell and gene therapy products, CAR-T cell therapy (Chimeric Antigen Receptor T-cell Therapy), the development of which is the objective of the abovementioned M&As by both GILEAD Sciences and Bristol-Myers Squibb, is attracting attention as a breakthrough treatment for some types of leukemia and other diseases. A report related to this therapy states that when standard treatment becomes ineffective for children with acute lymphoblastic leukemia, many of them are likely to die within one year. However, a marvelously high long-term survival rate of about 70% was reported for patients with acute lymphoblastic leukemia who received CD19 CAR-T cell therapy¹ (Naoki Hosen, “Shin Shuyō Men'eki-gaku” [New Immuno Oncology], Jikken Igaku

Because of this finding and other reports, patients have high expectations of the therapy’s strong efficacy for some relapsed and refractory leukemia cases.

CAR-T cell therapy is a type of treatment in which T cells (a type of immune cell in the blood) are first collected from the patient’s body and processed. The processing mainly involves the introduction of a gene that enhances the ability to capture and attack cancer cells into the T cells. These modified and powered-up T cells are then returned to the patient’s body, where they carry out treatment of the disease in vivo (Figure 3). Because this treatment requires a completely customized operation using the patient's own T cells, pharmaceutical companies are proceeding with social implementation cautiously by working with only a limited number of medical institutions.

In the West, approval for CAR-T therapies for the treatment of hematologic cancers and lymphomas has been granted for Kymriah, manufactured by Novartis (Switzerland), and Yescarta, manufactured by Gilead Sciences (US) (Figure 4). In Japan, Kymriah was approved in 2019, but the public focus is rather on its high price of JPY 33,493,407 per patient. Currently, approximately 400 clinical trials for next-generation CAR-T cell therapies and other such treatments are underway inside and outside Japan, targeting not only blood cancers, such as leukemia, but also solid cancers (“Gan to men’eki CAR-T ryōhō’ ketsueki gan no jisseki to ta gan syu e no kitai” [Cancer and Immunity: Results of CAR-T cell therapy for treating blood cancers and prospects for other cancers], December 2018, Gan+[Cancer+], Editorial Supervisor, Professor Emeritus Keiya Ozawa, School of Medicine, Jichi Medical University). In addition, according to the US market research firm Frost & Sullivan, global sales of CAR-T cell therapies are expected to reach USD 3.9 billion in 2022, and pharmaceutical companies are likely to become even more enterprising in this field in the future.
New treatment process and supply chain

The treatment process for CAR-T cell therapy is complicated because it involves the use of live cells, and the supply chain is also markedly different from those for conventional small molecule drugs or antibody drugs (Figure 5). For conventional small molecule drugs and antibody drugs, hospitals procure those by placing orders with pharmaceutical wholesalers and necessary drugs will be delivered accordingly.

Figure 5: Comparison of supply chains for small molecule drugs/antibody drugs and cell and gene therapy products (in the example of CAR-T cell therapies)

<table>
<thead>
<tr>
<th>Small molecule drugs &amp; antibody drugs</th>
<th>Cell and gene therapy products (Example: CAR-T cell therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place order with a drug wholesaler</td>
<td>Place order with a pharmaceutical company or specialty drug wholesaler</td>
</tr>
<tr>
<td>Compile patient treatment process and schedule</td>
<td></td>
</tr>
<tr>
<td>Collect cells from the patient (apheresis)</td>
<td></td>
</tr>
<tr>
<td>Freeze or refrigerate the patient's cell sample</td>
<td></td>
</tr>
<tr>
<td>Ultra-low/low temperature transport</td>
<td></td>
</tr>
<tr>
<td>Manufacturing at Cell Processing Center (procedures for processing and culturing cells)</td>
<td></td>
</tr>
<tr>
<td>Ultra low temperature transport</td>
<td></td>
</tr>
<tr>
<td>Evaluation for shipment</td>
<td></td>
</tr>
<tr>
<td>Delivery of product to the hospital from the drug wholesaler</td>
<td>Deliver to hospital</td>
</tr>
<tr>
<td>Administer to patient</td>
<td>Administer to patient</td>
</tr>
<tr>
<td>Register patient treatment data (disease registry system)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Prepared by MGSSI

In contrast, for CAR-T cell therapy, the process up to the actual implementation of the treatment is very complex. In addition to a doctor’s diagnosis of a patient and order of the product with a pharmaceutical company or specialty wholesaler of cell and gene therapy products, the collaborative efforts of multiple other professionals are needed to handle subsequent procedures. Those procedures include the compilation of the treatment process and schedule for the patient, collection (apheresis) of cells from the patient’s body, preparation and freezing of collected cells, ultra-low/low-temperature transportation of cells to a manufacturing site called cell processing center (CPC), quality evaluation to determine suitability for dispatch, final product delivery to hospitals, administration to the patient who has undergone pretreatment, and registration of patient treatment data in the disease registry system. Looking into the more detailed process, there are other strict requirements for these procedures, including to ensure the quality of the patient’s unique and irreplaceable cells, the freezing and refrigeration requirements differ depending on the product (Kymriah requires frozen transportation to and from the CPC, while Yescarta requires refrigerated transportation to the CPC and frozen transportation for the return trip), and timelines for delivering products to hospitals need to be managed by the minute. As such, each procedure must be managed meticulously.

Challenges for wider adoption in Japan

Since Kymriah was first launched in the US in 2017 and then in Europe in 2018 ahead of the other parts of the world, the West have already seen progress on discussions on building supply chains and establishing international standards. Meanwhile, in Japan, despite the market release in 2019, a supply chain for the smooth provision of CAR-T cell therapy is still in the developmental stage. Specific issues include the uneven and insufficient distribution of CPCs (as of December 2019, Japanese medical system relies on overseas CPCs, which entails a waiting time of one to two months, including transportation), development of a supply chain management system to ensure traceability of patient samples and to coordinate multiple professionals, adjustments to meet the requirements of international cold chain logistics established by overseas regulators.
and industry associations, creation of a new system for paying medical expenses, and development of specialized human resources, such as cell culture specialists. In the future, it is expected that the high price of the therapy and healthcare insurance reimbursement will also become agenda for discussion.

COMPANIES’ DEVELOPMENTS FOR NEW SERVICES TO SUPPORT THE STABLE SUPPLY OF CAR-T CELL THERAPY

In the West, where the social implementation of CAR-T cell therapy is ahead of other regions, the markets are seeing the emergence of high value-added services and operations, such as supply chain management using digital technology, high-end cold chain logistics, specialty pharmacies, and cell processing and manufacturing by CPCs on a contract basis.

1. Supply chain management (SCM) services utilizing digital technology

New services for providing pharmaceutical companies with cloud-based supply chain management solutions, such as coordination across multiple professionals or patient sample tracking, have been launched by the UK company TrakCel (through a partnership formed in June 2019 with the US non-profit organization BE THE MATCH) and the US company Vineti (which is backed by the US venture capital companies GE Ventures and Mayo Clinic Ventures). According to TrakCel, cell transport requires detailed scheduling to the minute and must be tailored to conform to a hospital’s reception and treatment times. These SCM services enable schedules to be calculated systematically and managed by using the alert function in coordination with the hospital situation, and also product quality to be assured because the proper management of the patient sample can be verified from the chronological recording of the transport process.

2. High-end cold chain logistics

Companies offering services for the international transport of patient samples include World Courier (a company belonging to the AmerisourceBergen drug wholesaler group, US) and Marken (UPS group, US). In Japan, major drug wholesalers have set up subsidiaries specialized in cell and gene therapy products and other specialty pharmaceuticals to step up their efforts. Those companies include S.D. COLLABO (Suzuken Group, Japan), SPLine (Medipal Holdings, Japan), and Specialty Medical Distribution (SMD) (Alfresa Holdings, Japan). According to World Courier, which focuses on the international transport of cell and gene therapy products, personnel who handle the transport of patients’ cells, which has life-or-death implications for patients, must undergo more than 100 tests, including the knowledge of professional transport practices, pharmaceuticals, and the products entrusted for transport. The company thus points to the necessity of high level human resource education. Meanwhile, Cryoport (US), which develops its own containers (dry shippers and cell shippers) that can be filled with liquid nitrogen (Figure 6) and provides them along with container management services to pharmaceutical companies, has partnered with transportation companies to establish rules and regulations for ultra-low temperature logistics (-150°C).

Figure 6: US company Cryoport’s dry shipper containers

Source: Cryoport Inc.
3. Specialty pharmacies

Growth is also anticipated for the specialty pharmacy business, which provides comprehensive services to accommodate the needs of the patient along their “patient journey,” beginning from the application of advanced medical treatment through to the payment of medical expenses. Major pharmaceutical wholesaler McKESSON (US) and medical services giant Cardinal Health (US) (which formed a partnership in April 2019 with the US specialty pharmacy operator PANTHERx Rare) have started offering end-to-end services for cell and gene therapies geared toward not only insurers, but also for hospitals, patients, and pharmaceutical companies (Figure 7). The functions required of specialty pharmacies depend on the country and region. For example, in Japan, drug pricing is not negotiated for each treatment of CAR-T cell therapy, suggesting there may be limited demand for supporting functions to receive medical benefits. On the other hand, Japan appears to have the need for such as call center functions, treatment process management, staff training, logistics management, support for the collection of side effect data, and kitting services for collectively delivering necessary medical materials for each treatment. Moreover, in the future, the accumulation and utilization of medical treatment data and medical benefits data are expected to become the foundation for a new medical expense payments system (including personalized reimbursement models) that is based on the cost-effectiveness of individual treatments.

4. Cell Processing Center (CPC)

Currently, Novartis manufactures Kymriah in the US at its own CPC in Morris Plains, New Jersey. With the aim of expanding the market for Kymriah, in Europe, Novartis partnered with the Fraunhofer Institute for Cell Therapy and Immunology IZI in Germany (2015), acquired the French company CELLforCURE (April 2019), which owns a network of cell and gene therapy manufacturing facilities, and then established its own CPC in Switzerland (November 2019). In Asia, Novartis is also expanding its manufacturing bases such as through the transfer of the technology for manufacturing investigational drugs to Japan’s Foundation for Biomedical Research and Innovation at Kobe, and an alliance with China’s Cellular Biomedicine Group.

In Japan, production facilities are also being expanded for cell and gene therapy products other than Kymriah. Hitachi Chemical, for example, has established a CPC in Yokohama that leverages the contract cell manufacturing expertise of US-based Caladrius Company, in which it invested in 2017. Also, in January 2020, Takara Bio began operating a facility, with floor space of approximately 14,500 m², for cell and gene therapy product manufacturing and R&D.

FUTURE PROSPECTS: FORMATION OF A “CELL & GENE THERAPY ECOSYSTEM”

In this report, CAR-T cell therapy has been presented as a specific case of a new treatment process and supply chain along with the new services that have emerged in the West, where the markets are more advanced than
in other regions. It is hoped that these new services will organically connect various stakeholders, which include patients, governments, scientific societies, academia, medical institutions, insurers, and pharmaceutical companies, to create a “cell and gene therapy ecosystem” (Figure 8). The efficient circulation of products, services, and data in this new ecosystem is expected to promote the creation of an environment that will enable doctors, who closely engage with patients, to provide their patients with advanced cell and gene therapies, such as CAR-T cell therapy, in a sustainable and stable manner. In addition, visualization of the supply chain and utilization of real world patient data are expected to lead to optimization of treatment processes and more effective use of medical resources.

Lastly, when introducing personalized services and establishing a “cell and gene therapy ecosystem,” tailored development in conformity with the each country’s medical system is necessary. To that end, the key to achieving smooth provision of cell and gene therapies to patients will lie in incorporating the viewpoints of the healthcare providers, namely hospitals and physicians.

Figure 8: Schematic diagram of the cell & gene therapy ecosystem

![Cell & Gene Therapy Ecosystem](image)

Source: Compiled by MGSSI based on various interviews