Driving the next wave of innovation in CAR T-cell therapies

Unlocking the full potential of CAR T-cell therapies requires investment in four areas.

by Sarah Nam, Jeff Smith, and Guang Yang
Chimeric antigen receptor T-cell (CAR T) therapies have demonstrated the potential to disrupt cancer care—but its application is currently limited to treating patients with select liquid tumors in the relapsed and refractory stage. To unlock the full potential of CAR T, investment is necessary in four areas: optimizing autologous CAR Ts for liquid tumors,¹ expanding the number of healthcare settings that administer CAR T, shortening the innovation cycle time to enable success in solid tumors, and innovating in the manufacturing of next-generation CAR T-cell therapies.

The transformative potential of CAR T

CAR T-cell therapies have transformative potential as a new type of cancer treatment that uses the immune system to fight diseases. CAR T involves genetically engineering T cells (either a patient’s own or a donor’s) to express a chimeric antigen receptor targeting a specific tumor antigen. Groundbreaking scientific advancements have led to three CAR T approvals for ALL and DLBCL since 2017.² Approved CAR T-cell therapies are focused on treating select relapsed or refractory liquid tumors that affect less than 5 percent of cancer patients today.³

The pipeline of investigative CAR T-cell therapies has rapidly expanded to more than 500 trials underway in 2019.⁴ While the earliest studies on CAR T targeted CD19, clinical programs today span a wider range of targets and tumor types. Additional CAR Ts target B-cell maturation antigen (BCMA), a common cell surface antigen in multiple myeloma as well as a number of other cell surface targets. What has carried the tide in the growing industry interest in CAR Ts has been the clinical data. For example, pediatric and young adult patients with relapsed or refractory ALL achieved overall remission rate of 90 percent at 12 months with treatment with an anti-CD19 autologous CAR T therapy.⁵

¹ Autologous CAR T-cell therapies treat the same individual from whom these cells are derived.
² Acute lymphoblastic leukemia and diffuse large B-cell lymphoma.
³ Surveillance, Epidemiology, and End Results program (SEER) research data (1975–2016), National Cancer Institute, November 2018, seer.cancer.gov.
⁴ Total number of Recruiting, Not yet recruiting, Active not recruiting, Enrolling by invitation, Unknown status, and Interventional studies results of “CAR T” studies; for more, see ClinicalTrials.gov, US National Library of Medicine, November 6, 2019, clinicaltrials.gov.

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Challenges to the commercialization of CAR T-cell therapies

Despite the strong efficacy data in clinical trials, there are three key challenges affecting the commercialization of CAR Ts: complex manufacturing and supply chain, high-touch commercial model, and reimbursement challenges (Exhibit 2).

Complex manufacturing and supply chain
All CAR T-cell therapies on the market and a majority of clinical assets (about 75 percent) are autologous,
resulting in complex and costly manufacturing and supply chains driven by the one-batch, one-patient paradigm shift. Manufacturing of autologous CAR Ts today is largely centralized, with limited economies of scale—a model more akin to modular clean rooms and lab-like environments than to manufacturing plants. A shortage of manufacturing slots for either the CAR T cell or requisite viral vector is often cited as a key bottleneck among CAR T centers.

Moreover, transporting apheresed and manufactured cells between manufacturing facilities and hospitals requires a complex cold chain. Since managing the chain of custody and chain of identity of CAR T is critical, CAR T manufacturers have long-term contracts with global logistics majors and specialized “medical only” couriers to optimize their supply chains and ensure handling quality. Some have also partnered with software
companies, such as Vineti and TrakCel, to offer digitized technology solutions that trace and track cell therapies with enhanced transparency.⁶

Most critical to patient outcomes is the “vein to vein” time, often defined as the time that elapses between apheresis and product delivery at the hospital. Given the rapid progression of disease, the current two-to-three-week vein-to-vein time is problematic and can impact CAR T eligibility for end-stage patients. Companies are continuously exploring opportunities to reduce vein-to-vein time—such as shipping unreleased products, optimizing time-limiting quality control processes, or storing cells from early apheresis—as a competitive differentiator.

These manufacturing challenges have led to an extremely high cost of goods sold with a significant fixed portion, hesitation to utilize CAR T beyond end-of-line patients, and patient drop-offs along the treatment journey.

**High-touch commercial model**

As mentioned, the CAR T patient treatment journey is lengthy and logistically challenging. In the United States, only a limited number of certified academic medical centers (AMCs) offer commercial CAR T, often requiring patients to travel long distances to receive care.⁷ One of the main reasons for the limited number of commercial sites is the laborious site setup process—which involves extensive preparation and certification to offer CAR T. The amount of effort necessary to establish standard operating procedures has slowed growth in the introduction of new CAR T protocols. Indeed, the arduous setup process means that most hospitals will need to assess whether adopting multiple products with the same target will be justified. However, there is growing interest to reduce the burden around site setup by adopting existing certification standards (such as the Foundation for the Accreditation of Cellular Therapy) and harmonizing protocols with other manufacturers’ CAR T requirements.

Furthermore, the complexity of CAR T care requires cooperation among multiple stakeholders, including the treating physician, nurse practitioner, pharmacist, apheresis lab technician, transplant administrator, and financial coordinator. The challenge for CAR T manufacturers today is providing these stakeholders with high-touch, end-to-end customer service. Such service often involves a large support staff, including an account manager dedicated to the site of care, a cell processing facilitator to manage logistics (such as cryopreservation or preparation for shipment), dedicated sales forces and medical field teams, and nurse educators. CAR T companies that recognize the highly involved nature of this model can shift from “white glove” to “right glove” service—that is, enabling self-service for some commercial services and scaling down high-touch support.

**Reimbursement challenges for CAR T**

In addition to manufacturing and commercial models, CAR T-cell therapies encounter significant market-access challenges in the United States and in other countries around the world. Centers face uncertain economics regarding CAR T under current policies set by the Centers for Medicare & Medicaid Services. In the inpatient setting, the current diagnosis-related group payment is insufficient to cover the cost of CAR T care. Even with the outlier and new technology add-on payments (NTAP), hospitals have stated that they are expected to take a net loss on Medicare patients treated with CAR T.⁸

In contrast, in the outpatient setting, Medicare Part B would reimburse using the ASP plus model, which would ensure cost recovery for providers. New CAR T therapies including BCMA CAR Ts and select CD19 CAR Ts are being evaluated to determine if their safety profile is suitable to administer in an outpatient setting.⁹

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Moreover, commercial payers currently approve CAR T on a case-by-case basis with payer-specific justification documents, and centers often find these documents cumbersome for use in demonstrating patient eligibility. Yet patients who are considered for CAR T therapies often have aggressive diseases; given the rapid deterioration of health for relapsed or refractory patients, delays in payer approval can affect patient eligibility for CAR T.

To solve these challenges, innovative contracting mechanisms are starting to be considered, including outcomes-based contracting. Given the uncertainty of long-term response durability, it is important for manufacturers to continue generating evidence to support the value of CAR T for patients.

**Overcoming challenges to advance CAR T**

Despite CAR T’s arrival as an approved cancer treatment, several advances are still needed to expand its application into earlier lines of therapy and in solid tumors. Therefore, manufacturers must invest in critical gaps and barriers, including optimizing autologous CAR Ts for liquid tumors, expanding treatment models into new healthcare settings, reducing the innovation cycle time to enable success in solid tumors, and transforming manufacturing processes.

**Optimization of autologous CAR Ts for liquid tumors**

Despite all the challenges and pipeline competition (such as from bispecifics), to date CAR T has shown unprecedented efficacy. Early results also demonstrate its durability of response. As a result, CAR T will likely remain an important treatment option for end-stage-liquid-tumor patients. The following enabling technologies and processes will further improve the process, mitigate some of the aforementioned challenges, and raise the tide for the entire industry:

**Advanced gene transfer tools can improve efficiency.** The industry faces a well-known viral-vector capacity constraint and a limited number of third-party suppliers, so manufacturers must either invest heavily to build in-house production or lock down contracts with these viral-vector manufacturers. In addition, the lenti- or adeno-associated-virus-based approaches are often time-consuming and inefficient. There is massive value for efficient gene-transfer tools that enable rapid modification of T-cells with CARs (such as transposon, CRISPR, among others) and an increasing list of additional modifications (such as removing donor T-cell receptors, adding on-off switches that can turn off the CAR T to prevent toxicity, and secreted factors). Using advanced gene-transfer tools may also allow testing multiple modifications in a modular fashion, reducing innovation cycle time through faster, less expensive testing.

**Innovate the patient journey to collect healthier patient cells earlier in the treatment cycle.** Currently, relapsed or refractory patients—those who have exhausted more conventional therapies—demonstrate inconsistent apheresis cell recovery due to multiple rounds of lymphocyte-depleting therapies, such as chemotherapy, prior to CAR T treatment. Collecting and storing healthy lymphocytes from patients earlier in their treatment cycle may therefore serve as a sort of insurance policy for patients who eventually progress to relapsed or refractory stages and need CAR T treatments. If redundant transportation is cut out, healthier and ready-to-use cells for expansion could also reduce vein-to-vein time by about a week. However, today’s storage infrastructure is not in place to ensure the collection and long-term storage of large numbers of patient samples. Given that most earlier-line therapies for liquid tumors are not curative, many more stored samples will be used than were previously, thus raising the bar for storage quality. In addition, it is unclear which stakeholders should pay for collecting and storing

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11 CAR T-cell therapies show durable responses, new research also explores combination therapies to extend and enhance treatment responses,” American Society of Hematology, December 1, 2018, hematology.org.


13 Clustered regularly interspaced short palindromic repeats.
the cells of patients who are cured and therefore no longer need the stored lymphocytes.

**Implement harmonized procedures to remove apheresis-capacity constraints.** As more candidates enter clinical trials and CAR T achieves commercial success, the apheresis-center capacity bottleneck will remain. This burden is exacerbated by the significant time and resources required to open each apheresis facility—including required training, compliance or legal documentation, and audits, all of which may vary for each company.¹⁴ A centralized organization that standardizes apheresis or manages capacity and distribution among apheresis centers working with manufacturers can streamline procedures, freeing up valuable time and resources to serve patients.

**Enable fast turnaround and quality assays.** Many simple quality-control assays (regarding sterility or mycoplasma, for example) add significant uncertainty and length—on average a few days, but sometimes up to weeks—to the current process. Some manufacturers have no choice but to insource these routine tests that have significant economies of scale to reduce vein-to-vein time. High-quality assays, process innovations (such as cloud-based data transfer), and tracking and validating each step of manufacturing all help reduce turnaround time.

**Adoption of traditional healthcare settings to administer CAR Ts**

Nearly all CAR T treatments are provided in inpatient settings at AMCs. While this highly concentrated expertise allows for close monitoring of adverse events, it also is extremely cumbersome for patients who often need to travel multiple times (for diagnosis, apheresis, or transfusion) while with an advanced-stage cancer. If appropriate training, quality collection and administering of therapy, and patient safety are properly ensured, then adoption of the following traditional healthcare settings could significantly improve patient pain points.

**Outpatient settings.** Compared with inpatient reimbursement, treatment in outpatient facilities can increase number of patients who would benefit from CAR T and improve economics for hospitals. The main challenge will be ensuring closely monitored and addressed patient safety—for example, through tech-enabled monitoring or sufficient training.

**Community transplant centers.** Community transplant centers provide access to a more diverse patient population, which becomes more important as more CAR T therapies are developed. Because of the low referral rates from the community setting to AMCs (such as for multiple myeloma), expanding channels to community transplant centers could significantly increase the volume of patients who could benefit from CAR T.

**Enabling rapid innovation of cell therapy with solid tumors**

CAR T’s turning point will be its expansion into solid tumors, which afflict the majority of cancer patients. So far, this goal has been elusive—indeed, a meta-analysis of all solid-tumor CAR Ts tested in humans revealed a mere 4.1 percent complete responses.¹⁵ Only anecdotal success has been reported for glioblastoma patients treated with IL13Rα2, HER2, CMV, and EGFRvIII CAR T and for advanced gastric and pancreatic cancer patients treated with Claudin-18.2 CAR T.¹⁶ Most scientists attribute this limited success to a lack of a highly solid-tumor-specific antigen that will not lead to on-target toxicity, lack of effective homing to the solid tumor mass by CAR Ts, or tumor microenvironments that lead to T-cell exhaustion.

Given the wave of pipeline products attempting to address each of these barriers with various approaches (often in combination), for CAR T to

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¹⁵ Jessica Hartmann et al., “Clinical development of CAR T cells—challenges and opportunities in translating innovative treatment concepts,” EMBO Molecular Medicine, 2017, Volume 9, Number 9, pp. 1183–97.

succeed in solid tumors there is a need for multiple parallel approaches—and short cycle time is essential. It is critical to evaluate a multitude of CAR T configurations and hypotheses simultaneously in a rapid, high-throughput fashion (in human subjects) with high scientific quality; this means applying learnings from a single iteration to the design and execution of the next round.

**Lead academic–clinical partnerships.** Innovative clinical partnerships with academic research institutions provide an avenue to accelerate advances for solid tumors. Conquering solid tumors requires iterative learnings simply because all CAR T configurations cannot be tested simultaneously; therefore, the clinical partnership with the shortest innovation cycle would provide the ultimate differentiation in a crowded field.

Imagine a preferred AMC, with access to a large number of patients that can generate a solid-tumor CAR T concept, manufacture the cells on site, test the version in a small cohort of patients, and generate human data that inform design of the next iteration of products. There has already been a proliferation of academic-sponsored CAR T trials, and it is worthwhile for the industry to determine the optimal operating model to tap into the innovation engine.

**Take advantage of China’s growing clinical-research infrastructure.** The “China factor,” or the ability to more rapidly innovate in China, could provide another significant boost to the innovation speed of CAR T. With a large concentrated patient base, much lower cost to manufacture and test inpatients iteratively, and a potentially less stringent regulatory environment, China provides a fertile environment to break new ground in solid tumors. In 2018, the number of CAR T clinical trials in China surpassed those in the United States, with a large fraction targeting solid tumors.¹⁷ There are nearly 50 local companies pursuing cell therapy currently in China. To ride the wave of accelerated CAR T innovations in China, companies in the West are starting to establish a clinical presence in China through business-development channels, such as partnerships and joint ventures.

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18 Good manufacturing practice.
Decentralized manufacturing may be achieved either with a network of manufacturing plants (potentially on site at hospitals) or by implementing GMP-in-a-box solutions. The former is investment-intensive for each hospital and, given the limited role of manufacturers in the drug production, could fundamentally disrupt the pharmaceutical business model. Regardless, updated regulatory frameworks are required to ensure the quality of distributed manufacturing sites without making the requirements overly onerous.¹⁹

**Develop allogeneic products.** Allogeneic CAR T cell procedures can provide a number of significant advantages in manufacturing, including reduced cost of goods sold; a simplified supply chain; and avoidance of issues with autologous CAR T cells in harvesting, product variability, long vein-to-vein time, and T-cell dysfunction. Having this alternative source of CAR T cells could expand treatment to additional patients, such as those with low T-cell levels, harvest failures, or those who need treatment before autologous CAR T cells can be manufactured. Clinical testing is already underway, so it is critical to validate lack of graft-versus-host disease and clearance of allogeneic cells.²⁰ Besides the clinical aspect, improvements to the manufacturing part of the equation are expected to fully unleash the allogeneic potential—including, for example, the shift from an adherent to a suspension manufacturing archetype.

CAR T is poised to be a disruptive therapy in cancer care, but unlocking its potential requires placing strategic bets. Scientific advances and manufacturing innovations are rapidly increasing—with potential for CAR T to not only treat niche liquid tumors but a broader range of solid and liquid tumors in the coming years. Manufacturers that make smart investments can drastically increase the number of patients they serve as well as the success rates of their treatments.

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