WHITEPAPER

Beyond Urban Centers: Expanding CAR-T Therapy with Decentralized Manufacturing

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Abstract

Chimeric Antigen Receptor T-cell (CAR-T) therapies are having remarkable success in treating certain cancers, but global accessibility to treatments like these is limited. This whitepaper examines the potential of a Decentralized Manufacturing Model (DMM) to address the distribution challenges that currently limit the widespread availability of CAR-T therapies, and furthermore Advanced Therapeutic Medicinal Products (ATMPs), under the prevailing Centralized Manufacturing Model (CMM). In the CMM, logistical bottlenecks such as transportation, scaling, and infrastructure continue to constrain the distribution of ATMPs. As a discussion to address these problems, this paper outlines the current CAR-T manufacturing process and presents a case study on how the process can be scaled out into a DMM. We also discuss the DMM and how its implementation could alleviate the disparities in patient accessibility, particularly in the U.S., and the considerations necessary for making ATMPs available in economically diverse and global populations. This whitepaper argues that the integration of DMM in for autologous ATMP distribution is a crucial step towards healthcare equity, proposing that DMM is not just an option, but a necessity in bridging the gap between medical innovation and universal accessibility.

Introduction

CAR-T therapies have demonstrated a 90% success rate in treating specific indications, marking a groundbreaking advancement in oncology, and revolutionizing the approach to fighting cancers such as leukemia and lymphoma [1]. Nevertheless, the distribution of these therapies is limited by logistical bottlenecks, including transportation challenges, scaling complexities, and the need for supportive clinical infrastructure. The CMM that exists today in the biotech and pharmaceutical industries does not fully support the widespread distribution of personalized medicine like CAR-T and others. However, the DMM proposes a shift in the manufacturing model, from a ‘scale-up’ to a ‘scale-out’ strategy, to manufacture therapies at the point-of-care. Although a DMM is not currently standard practice for manufacturing CAR-T therapies, there are significant benefits to this model that should be considered, especially as the addressable patient population is anticipated to double within the next 5-10 years [1]. This whitepaper will first

outline the autologous cell therapy manufacturing process as it is performed today, with CAR-Ts serving as the archetype for autologous ATMPs. We will then discuss how decentralized manufacturing for CAR-T is carried out, using a case study. Lastly, we will discuss the current disparities in accessibility, focusing on the U.S., and consider what it means to open access to CAR-Ts, and additionally ATMPs, in global and economically diverse populations.

Overview of the CAR-T Manufacturing Process

CAR-T manufacturing is a logistically challenging, finely-tuned process focused on engineering Peripheral Blood Mononuclear Cells (PBMCs). It is especially important to consider that manufacturing a personalized, living product is unforgiving and extremely susceptible to errors and delays that lead to cell death. The manufacturing process begins with leukapheresis, where the patients' blood is drawn and immune cells are isolated [3]. These cells are then cryopreserved, transported, and thawed prior to manufacturing at a specialized production facility. Within this facility, manufacturing equipment like the CliniMACS Prodigy® (Miltenyi Biotec, Bergisch Gladback, Germany) is loaded with the patient's cells to sort and isolate CD4+ and CD8+ T cells through magnetic separation [3]. The isolated T cells are then activated via CD3 and CD28 stimulation and subsequently genetically modified to express the synthetic chimeric antigen receptor (CAR), using a lentivirus [3]. Following activation and transduction, T cells enter a period of rapid expansion, which involves several hundred to even thousand-fold expansion over a period of 6-12 days. [3]. In a CMM, these cells are then cryopreserved to allow for analytical testing, transport, and subsequent transfusion

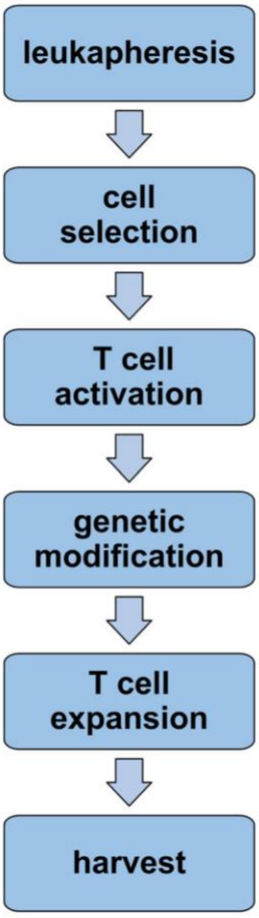

Figure 1. Flowchart of the CAR-T manufacturing process from patient cell collection to harvesting for transfusion.

Adapted from: Cost of decentralized CAR-T Cell Production in an Academic Nonprofit Setting. Ran, T et. al.

back to the patient, but often at the expense of reduced efficacy of the cells. Additionally, some ATMPs using stem cells or NK cell therapies cannot tolerate cryopreservation.

Prior to being infused into the patient, each CAR-T cell product undergoes rigorous viability, identity, and sterility testing, with additional assessments for cryopreserved cells to ensure viability and potency [3]. After the final CAR-T cell product is reinfused, the patient is closely monitored for potential side effects, marking the culmination of a process where technology and medical innovation intersect to use the body's own immune cells to target cancer [3].

A Decentralized Manufacturing Model Case Study

ATMPs can be produced through both the CMM and the DMM, but the DMM could offer significantly more flexibility and accessibility in global suburban and rural regions. The CMM, though already established and especially practical in urban areas, grapples with logistical complexities for widespread distribution such as sensitive material handling and often can involve patient travel and housing costs [1]. DMM, focusing on 'scaling out' rather than 'scaling up,' reduces logistical and financial burdens by enabling on-site manufacturing [Figure 2]. A 2022 case study illustrates this advantage in DMM's value, showcasing a successful collaboration between a bone marrow transplant facility in India and Caring Cross, effectively producing CD19 CAR-T cells at a cost reduction of 80-90% [4]. As DMM gains traction, the limitations of CMM in reaching beyond urban areas are becoming increasingly apparent [1]. However, it's essential to

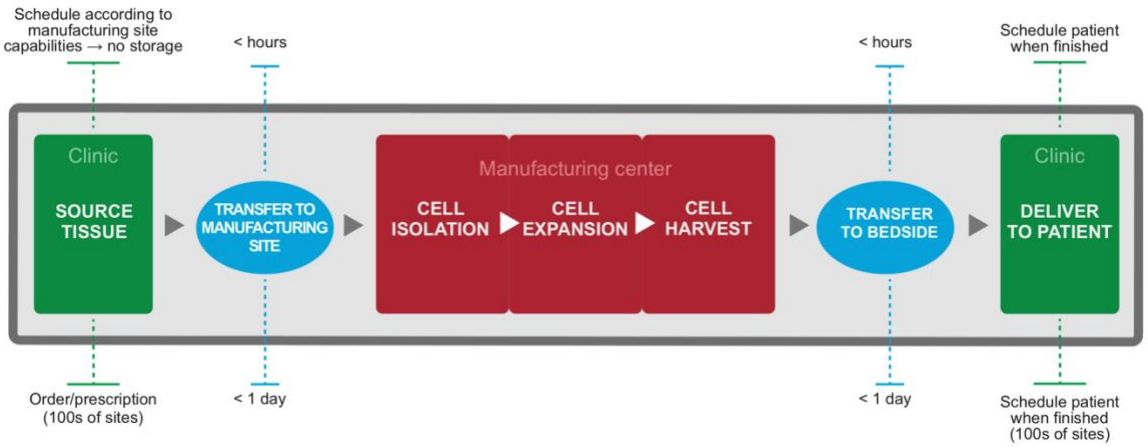

Figure 2. In a Decentralized Manufacturing Model, the process for fresh infusion of autologous cell therapies is streamlined, eliminating additional logistical and transportation steps.

Source: Global Manufacturing of CAR-T Cell Therapy (Levine, B. & Wonnacott, K.)

acknowledge that DMM, while promising, is not without its own set of challenges. Some identified challenges include ensuring consistent standards across all sites, and monitoring product quality in a decentralized network. However, the restrictive nature of CMM in a global landscape demonstrates that even in DMM's early stages, its promise in delivering expansive, equitable access to ATMPs is possible.

Expanding Healthcare Equity, a U.S. Perspective: Currently Available vs. Potentially Available Regions

When looking at the U.S., a DMM is a promising avenue to increase the geographical scope of CAR-T therapies and address disparities by state. Patients living in service deserts must travel significant distances to receive treatment, as seen in Figure 4 with how few centers there are for the U.S. population.

Figure 3. There are 110 Approved Treatment Centers (ATC) in the U.S., however, patients must travel to these centers for extended periods of time in order to receive treatment. Image Source: Kite Pharmaceuticals

However, in order to expand the reach of CAR-T therapies into these underserviced areas, it must be economically accessible as well. The high costs of CAR-T therapy and hospitalization, compounded by potential delays in hospital reimbursement, raise community concerns about affordability and accessibility [5]. Increasing available treatment facilities for patients by integrating the DMM lowers the overhead cost of treatment to patients who otherwise

experience extensive delays for shipping and manufacturing and opens opportunities for patients to gain access to new therapies that otherwise do not tolerate cryopreservation.

Conclusion

The integration of the DMM in the distribution of CAR-Ts and autologous ATMPs is not just a viable solution but a necessary step towards achieving healthcare equity on a global scale. While the CMM has been the traditional approach, its inherent limitations in logistics, scalability, and infrastructure have restricted the widespread availability of personalized therapies. A DMM presents an innovative approach, transforming the manufacturing process from 'scaling up' to 'scaling out', allowing therapies to be produced closer to the point-of-care. This shift not only promises to alleviate the logistical and financial burdens associated with CMM but also significantly expands access to life-saving treatments, particularly in underserved regions.

The case studies and discussions presented in this whitepaper demonstrate the potential of DMM in overcoming the barriers posed by CMM, offering a more flexible and accessible solution. By reducing the need for extensive transportation and enabling on-site manufacturing, DMM could drastically cut down costs and time, making therapies like CAR-T more accessible to patients, regardless of their geographic location. However, the transition to DMM also comes with its challenges, including maintaining consistent standards and monitoring product quality across decentralized networks.

Despite these challenges, the benefits of a DMM, especially in terms of expanding healthcare equity, outweigh its limitations. As the cell therapy field continues to advance, it is important to ensure these innovations are not just limited to urban centers or economically affluent populations. A DMM represents a step towards a more inclusive healthcare system, where advanced treatments are not a privilege, but a right accessible to all. Therefore, it is imperative for stakeholders in the healthcare industry to embrace the DMM and work towards its integration into the larger ATMP distribution framework. By doing so, we can bridge the gap between medical innovation and universal accessibility, ensuring that life-saving treatments reach those who need them the most.

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