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Centralized vs Decentralized Manufacturing of Personalized Cell Therapies: Overview and Logistics

Sadik Kassim, PhD

Boro Dropulić, PhD MBA

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Since the 2017 landmark FDA and EMA approvals of the first ever chimeric antigen receptor T (CAR-T) therapies, Kymriah and Yescarta, the cancer cell therapy field has exploded in growth. In fact, hundreds of new investigational cell therapies have been added each year, nearly quadrupling since 2017. The 1,597 cell therapies in active development now represent the largest therapeutic platform category in the immune-oncology space.[i]

All of the cancer cell therapies on the market, and a majority of clinical assets (about 75 percent) are autologous[ii], meaning the cell therapy treats the same individual from whom these cells are derived. This leads to a one-batch, one-patient manufacturing paradigm. Unlike other more traditional therapeutic modalities, the majority of cell and gene therapy products are developed and initially tested at academic medical centers. For example, of the five FDA approved cancer cell and gene therapies, Provenge, Kymriah, Yescarta, Tecartus, and Breyanzi, four started in the academic setting. In fact, a recent analysis found that of trials listed in ClinicalTrials.gov and active as of January 2019, the biopharmaceutical industry sponsored or funded less than half (46%) and was the sole funder for 36%.[iii] This leads to an additional set of unique challenges with respect to scaling out cell therapies in the commercial setting. This brief white paper will review logistical factors associated with various manufacturing models that can drive the successful scale out of these therapies to patients.

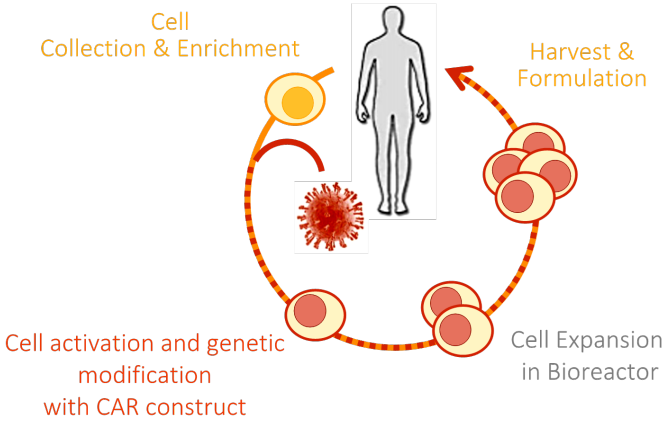

Figure 1. Major steps in the CAR-T manufacturing process.

The manufacturing process starts when blood from a vein in the patient's arm flows through a tube to an apheresis machine, which removes the white blood cells, including the T cells, and sends the rest of the blood back to the patient. The T cells are isolated and activated using special reagents. The gene for a special receptor called a chimeric antigen receptor (CAR) is inserted into the T cells using a viral vector or non-viral vector delivery platform that reprograms the T cells into CAR-T cells that target and kill cancer cells. Millions of the CAR T cells are grown in the laboratory and then given to the patient by intravenous infusion. Figure 1 depicts the core steps that are used in the manufacturing process of autologous CAR-T cells.

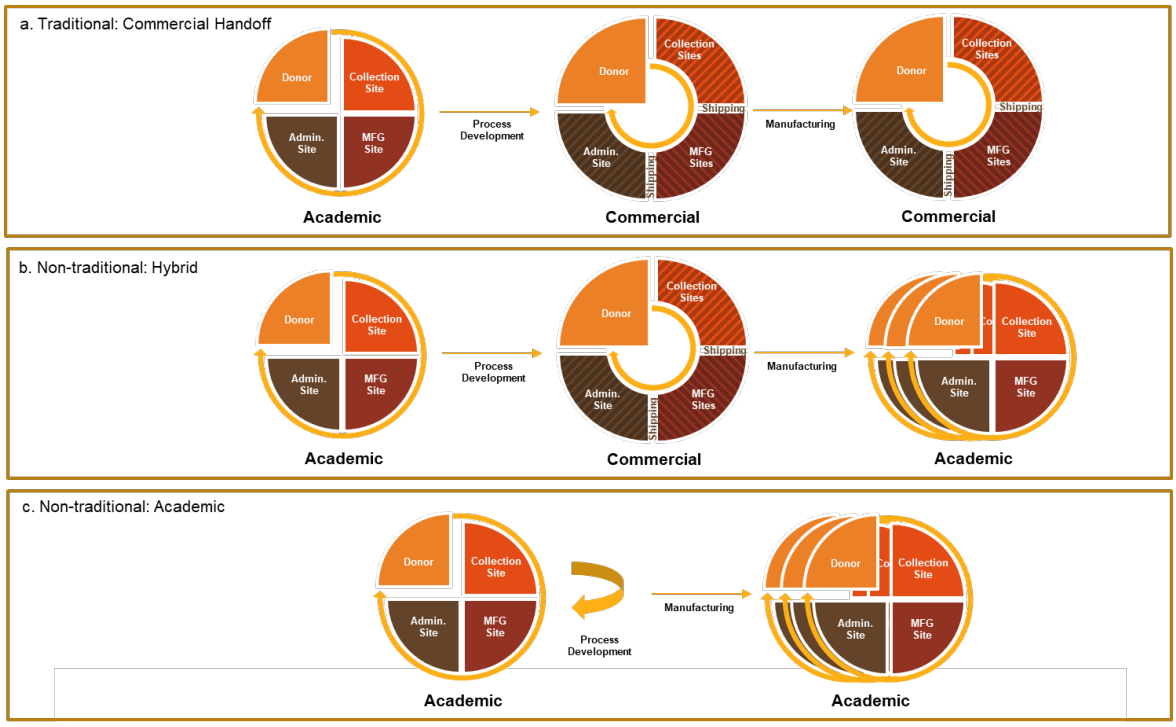

Figure 2. Three manufacturing paradigms for cell and gene therapies originating from academic environments. (A) Traditional handoff from academic to commercial entities results in limited centralized commercial manufacturing sites; (B) hybrid model with handoff to commercial for process develop and industrialization purposes but further transfer back to academic sites for decentralization and increased patient access; and (C) academic to academic model where entities are enabled to develop and market without commercial partner intervention.[iv]

The manufacturing logistics for autologous cell and gene therapy products can be broken down into three major segments: donor collection site, manufacturing site, and administration site (Figure 2). In a purely academic paradigm, all these components exist at the same physical campus, which enables streamlined operational logistics. To date, the transition to a commercial entity has involved the fragmentation of this workflow to provide greater control over the critical process development and eventual manufacturing of the drug product (Figure 2A). Other non-traditional models attempt to shift the clinical manufacturing back into distributed academic centers to leverage the simplified logistics and increased access to patients while still relying on commercial partners for late stage development expertise (Figure 2B). Towards a full academic ecosystem, increased capabilities of academic and clinical centers are now beginning to perform rudimentary in-house process development and minimize reliance on industry (Figure 2C).

To date, the scale-out of the FDA-approved commercially available autologous cell therapies has followed the model depicted in Figure 2A. This has led to well-documented problems with the manufacturing process, as well as with shipping and handling.[v] Many of these issues can potentially be reduced and avoided through a return to the place-of-care academic model of manufacturing.

In the European Union (EU), for example, the quickly evolving nature of these advanced therapies paired with the ability to provide rapid patient access is widely viewed as a challenge. To counteract this, the creation of a hospital exemption for ATMPs attempts to alleviate these issues and has the potential to pave the way for this pure academic model and enable clinical centers at large to develop and eventually market their own therapies. Recently, for example, The Spanish Agency of Medicines and Medical Devices (AEMPS) has approved a CD19 CAR-T therapy called ARI-0001, which was developed by El Hospital Clinic de Barcelona, as an advanced therapy drug for its use in patients over 25 years of age with lymphoblastic leukemia that is resistant to conventional treatments. It is the first CAR-T developed and approved for commercialization entirely within an academic setting. This recent groundbreaking approval highlights that innovative and non-traditional manufacturing models for personalized cell therapies are possible.

More recently, the Medicines and Healthcare products Regulatory Agency (MHRA), which regulates drug approvals in the United Kingdom announced that it wants to build a regulatory framework that would enable point of care (POC) decentralized manufacturing[vi]. This POC regulatory framework would balance regulatory requirements for the control of these products to ensure levels of safety equivalent to current products, which are manufactured using the centralized paradigm, while avoiding unnecessary regulatory barriers and enabling broader access to patients. Also, the FDA has taken notice. In a recent address to manufacturers of biologic and gene therapy products, Dr Janet Woodcock, the acting commissioner of the FDA, and Dr Peter Marks, the Director of CBER, both commented on the need to develop regulatory pathways for distributive manufacturing biological products [vii].

Centralized manufacturing has been the dominant model for large-scale production of goods, including pharmaceutical drug products since the Industrial Revolution. Centralization provides benefits from economies of scale. Yet, personalized cancer cell therapies provide an opportunity to reconsider this model and work toward a more decentralized manufacturing approach that remains proximal to the patient at the treatment center and eliminates the logistical and manufacturing challenges that have been faced, to date, with the commercially available autologous cell therapies.

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[i] Nature reviews. Drug Discovery, 31 Oct 2020, 19(11):751-752

[ii] Driving the next wave of innovation in CAR T-cell therapies https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/driving-the-next-wave-of-innovation-in-car-t-cell-therapies?cid=eml-web

[iii] Kassir Z, Sarpatwari A, Kocak B, Kuza CC, Gellad WF. Sponsorship and Funding for Gene Therapy Trials in the United States. *JAMA*. 2020;323(9):890–891.

[iv] Cell & Gene Therapy Insights 2020; 6(6), 697–714

[v] Scott C. Challenges and Opportunities in CAR T-Cell Development and Manufacturing. BioProcess International. January 31, 2020.

[vi] **Consultation on Point of Care manufacturing.** **https://www.gov.uk/government/consultations/point-of-care-consultation/consultation-on-point-of-care-manufacturing**

[vii] NIIMBL Annual Meeting, July 2021, Washington D.C.