TERUMO BLOOD AND CELL TECHNOLOGIES

Unlocking Potential

White Paper

Cellular Acquisitions: Challenges, Methods, and Solutions for Obtaining Optimal Starting Material

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Summary

This white paper provides valuable insights into the critical role of cell collections in the success of CAR-T therapy and hematopoeitic stem cell transplantion (HSCT). It considers the challenges, methods, and solutions involved in optimizing cell collection processes to obtain optimal starting materials for these lifesaving therapies. By understanding the factors affecting collection efficiency, implementing best practices, and leveraging advanced technologies, healthcare professionals can better ensure the highest quality starting material for CAR-T manufacturing and support improved patient outcomes.

Introduction

Cell therapy, particularly chimeric antigen receptor T cell (CAR-T) therapy, has witnessed remarkable advancements in recent years — including the treatment of certain hematological malignancies. Central to the success of these therapies is the availability of high-quality starting materials derived from cell collections. As the complexity of patients and the demands of CAR-T manufacturing continue to evolve, optimizing cell collection processes has become increasingly imperative.

Historically, cells were primarily obtained from healthy donors for transplantation purposes. However, the advent of CAR-T therapy shifted the focus to collecting cells from patients themselves. This offers a personalized approach to treatment while also necessitating the development of specialized techniques and protocols to acquire sufficient and suitable cell populations. Early studies on cell collections laid the groundwork for understanding optimal conditions for cell isolation and preservation.[1-2] Yet the growing diversity of patient populations, including those with complex medical histories and underlying diseases, introduces new challenges.

The emergence of new target antigens and manufacturing techniques requires flexible and adaptable cell collection strategies. To address these challenges and ensure optimal cell collection outcomes, it is essential to understand the various methods and requirements involved in this critical step of CAR-T therapy.

Cell collection methods and common cell collection requirements

As manufacturer guidelines primarily deal with handling the collected product, institutions must establish their own specialized standard operating procedures (SOPs) for apheresis.

Cell therapy manufacturers often specify their product requirements to cell collection centers, but these procedures vary widely by manufacturer. Variation means the collection center must establish its own SOPs to meet each therapy manufacturer's requirements while also ensuring strict adherence to methods that maintain the integrity of the material and mitigate the risks associated with cellular contaminants.

Cellular contaminants — including all non-target cells — pose a challenge throughout the collection process and can impact downstream manufacturing processes and compromise clinical efficacy. In the case of CAR-T manufacturing, the target cell population is lymphocytes, and examples of cellular contaminants are listed in Table 1 with a description of their impact on the manufacturing process. The contamination of the collected starting material with non-target cells may lead to manufacturing failures, which may in turn create a setback in delivering lifesaving therapies. In general, a higher purity of T cells in the starting material corresponds to greater T cell manufacturing success and ultimately better clinical outcomes.[1]

Table 1: Cellular contaminants overview for CAR-T downstream manufacturing processes

Contaminating Cell Type	Risk	Impact	Additional Considerations
Platelets	Can cause clumping, which interferes with accurate cell counts and flow cytometry analysis, and may cause problems expanding cells, depending on the platform.[32]	Cell counts may be inaccurate. Platelet clumps may entrap T cells, reducing their purity.	Platelet aggregation can be influenced by factors such as temperature, pH, and the presence of certain proteins or antibodies.
Monocytes	Interfere with T cell activation and transduction efficiency, and are associated with reduced remission after therapy.[1-6]	Monocyte contamination may lead to poor T cell quality.	Monocyte levels may vary significantly among patients and may be influenced by disease states or other factors.
Granulocytes	Degranulation and neutrophil extracellular trap (NET) formation may cause clumping, which can significantly impact	Granulocytes may release enzymes that damage T cells or interfere with their function.	Granulocyte levels may vary among patients and may be influenced by

	downstream cell processing and expansion.[1,5-6]	NET formation may lead to inaccurate cell counts and low T cell purity.	disease states or other factors.
Red blood cells	Can interfere with cell counts and flow cytometry.[1-2]	Downstream processing may provide inaccurate data.	The presence of red blood cells may be influenced by factors such as patient anemia or the efficiency of the apheresis process.

Moreover, in retrospective studies of mononuclear cell (MNC) collections from patients undergoing CAR-T therapy in Phase I/II trials,[7-8] factors that affected cell collection efficiency were noted to be:

- Patient age[7]
- Pre-collection cell counts[7-8]
- Disease type
- Disease state[1,7]

Understanding which factors affect cell collection efficiency may help identify patients who will be unable to meet cell collection goals.[7-8]

Common cell collection requirements

Collecting T cells for CAR-T manufacturing presents a unique set of challenges, primarily since it relies on obtaining cells from non-mobilized patients.[3,28] Apheresis professionals, skilled in managing collections from mobilized donors, face complexities arising from apheresis platform choice, concomitant medication that affects the number and functionality of circulating T cells, and the infectious status of the patient.[3,26] Although obtaining T cells from patients is the first step in a complex manufacturing process, it is often overlooked, and no guidelines or recommendations have been made until recently (Table 2).[23,25,27-29]

Table 2: Key considerations for leukapheresis collection to ensure optimal T cell fitness and promote CAR-T manufacturing success[27]

Timing	Considerations
Before leukapheresis	Consider leukapheresis and cryopreservation early in the disease process for patients with aggressive/high-risk disease.
	Appropriately timed washout of chemotherapy, medications, and other agents before leukapheresis collection is essential to optimize T cell fitness.
	Provide therapy to reduce the number of circulating blasts before leukapheresis for patients with high disease burden (when possible).
	Recommended to verify adequate absolute lymph count (ALC) and CD3+ cell count a day before and/or on the day of leukapheresis.
After leukapheresis	Recommended to evaluate the need for a second day of collection using a prediction algorithm.
	Account for patient-specific considerations (e.g., infants).
	Cryopreservation of leukapheresis material the same day as collection can improve post-thaw cell viability and manufacturing outcomes.*
	Verify that post-collection leukapheresis specifications for CAR-T manufacturing have been met.

*Manufacturer's instructions might indicate the necessity of a fresh product; shipment at 4 °C to 8 °C is required as soon as possible.

Some manufacturers provide specific collection requirements, while others lack a detailed leukapheresis collection manual (Table 3).[24]

Table 3: Cell collection requirements in different leukocyte apheresis collection manuals for CAR-T cells (adapted from Castillo-Aleman et al, 2023)

Product	Registered Name	Manufacturer	Targeted Antigen	Approval Year	Cell Dose Target to Collect	Blood Volume to Process
Axicabtagene ciloleucel	Yescarta	Gilead	CD19	2017	5 to 10 × 10^9 MNCs	12 to 15 L
Brexucabtagene autoleucel	Tecartus	Gilead	CD19	2017	5 to 10 × 10^9 MNCs	12 to 15 L
Tisagenlecleucel	Kymriah	Novartis	CD19	2020	1 to 4 × 10^9 CD3+ cells ≥ 2 × 10^9 TNCs ≥ 3% CD3+ of TNCs	6 to 10 L
Lisocabtagene maraleucel	Breyanzi	Juno-Celgene-BMS	CD19	2021	Not stated. A collection bag with 450 mL is required.	7 L if lymphocytes in PB are ≥ 1,000/µL. 12 L if lymphocytes in PB are < 1,000/µL.
Idecabtagene vicleucel	Abecma	bluebird bio-Celgene-BMS	BCMA	2021	Not stated.	Not stated.
Ciltacabtagene autoleucel	Carvykti	Legend Therapeutics-Janssen	BCMA	2022	Not stated.	Not stated.

BCMA: B-cell maturation antigen; MNCs: mononuclear cells; PB: peripheral blood; TNCs: total nucleated cells.

CAR-T cells primarily rely on CD3+ T lymphocytes acquired through unstimulated leukapheresis from patients.[23] This procedure encompasses blood withdrawal, centrifugal separation, peripheral blood MNC isolation, and component return.[23] Leukapheresis collections can be completed in a single day in some cases. Still, others require multiple consecutive collection days to achieve collected product targets, which can be costly in terms of resources and time for the collection site and patient.

The cell collection process requires the expertise of apheresis device operators, adequate access to the bloodstream, and specialized cell separator platforms, such as the Spectra Optia™ Apheresis System. In addition, data analytics and algorithms can help optimize cell collections and obtain quality cells. Collecting data and analyzing it helps provide visibility into apheresis processes and understanding of performance across multiple sites, achieving efficient, optimized targets while increasing the quality and yield of starting material. Furthermore, data-driven insights enable safe, predictable, and optimized throughput while reducing collection time and errors.

Challenges in cell collections

Effective apheresis cell collections are vital to achieving the target cell quantities necessary for peripheral blood stem cell (PBSC) transplantation and for the starting materials used to manufacture cell and gene therapies, which are used to treat a growing number of hematological disorders and genetic diseases. Common challenges include:

- **Ensuring adequate patient condition and preparation**: Achieving collected product goals can be especially difficult when patients do not have adequate target cell counts before an apheresis collection occurs.

- **Optimizing the apheresis cell collection procedure**: Efficient collection involves maintaining a steady interface to facilitate effective collection of target cells from the separated layers of blood. An unstable interface — which can occur because of inappropriate device settings and system alarms —

significantly reduces collection efficiency, making it difficult to collect target cells. Maintaining adequate venous flow into the apheresis device is also essential for sustaining a stable interface. Procedure data from the Spectra Optia system can be analyzed for performance tracking and optimization of procedures to improve collection outcomes.

- **Managing procedural events**: Managing alarms that occur during apheresis cell collections is paramount to collecting target cells efficiently. Unanswered alarms can cause unsteady interface conditions, so it is important to train apheresis device operators on how to appropriately respond. Another procedural challenge, platelet clumping, can be caused by improper management of anticoagulant and requires close monitoring by the device operator during the procedure. Data recorded by the Spectra Optia system can also be used to troubleshoot and optimize cell collection procedures to ensure target cell goals are met.
- **Processing the appropriate amount of whole blood**: This procedural factor directly affects whether target cell goals are met. Processing an inadequate amount of blood — based on a patient's pre-procedure target cell counts and the goal for the collected product — can mean additional collection days and the risk of not reaching targets that are required for a patient's transplant or not achieving the required starting materials for manufacturing of cell and gene therapies. Additional collections are costly to the collection center and may impact the patient or their ability to receive treatment. On the other hand, processing more blood than is necessary to meet a target cell product goal can result in a patient spending more time connected to the device than is necessary and less availability of apheresis devices to serve other patients. Collecting a higher volume product can also pose issues of measurement, processing, and storage.

Using data related to the patient, cell collection procedure, and collected product can help address the challenges that are commonly experienced during apheresis cell collections. Using data to manage these challenges and optimize each procedure in a way that is tailored to each patient and target may help achieve more efficient and effective cell products.

Solutions and best practices

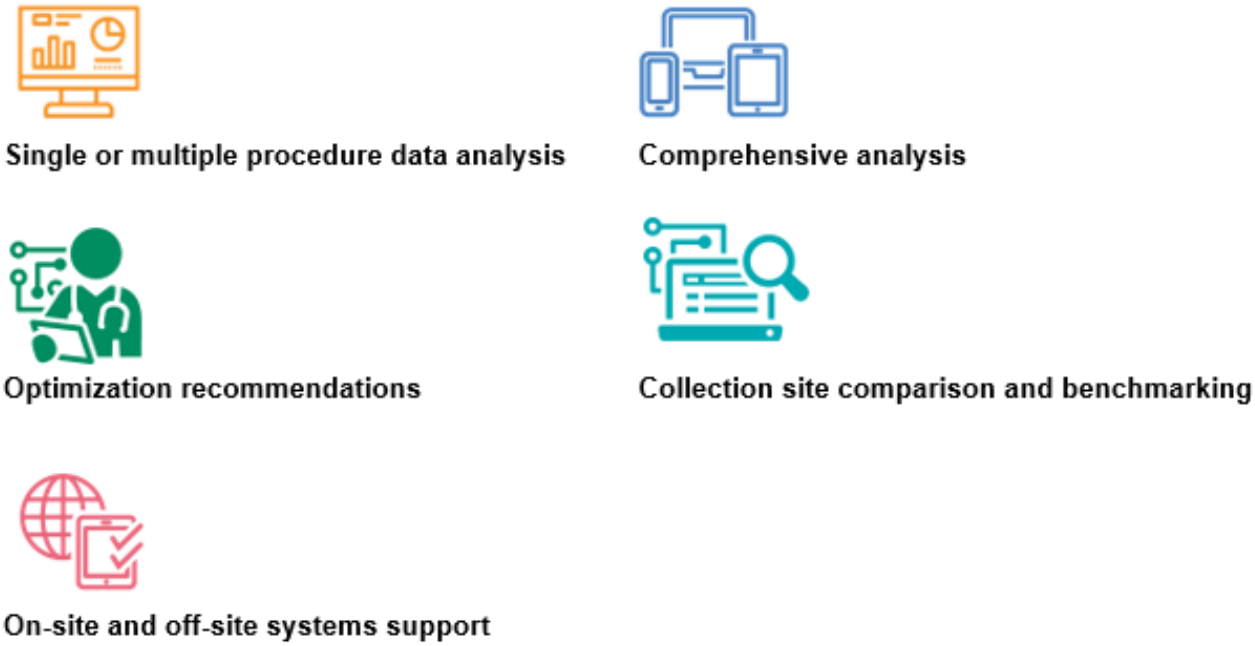
The quality of starting material significantly influences the overall success of the manufacturing process.[5-6] While patient variability and the complexity of cell collection procedures can pose challenges, data analytics offers a strategic approach to optimization.

One best practice is to analyze the procedural data collected from apheresis systems such as the Spectra Optia system. Analysis can provide valuable insights into individual patient characteristics, collection processes, and outcomes, enabling:

- **Identification of trends and patterns:** Historical data can be analyzed to identify common challenges, areas for improvement, and potential predictors of successful collections.
- **Development of predictive models:** Predictive models are created using algorithms to estimate collection outcomes based on various factors (such as patient characteristics and procedural parameters).
- **Optimized collection strategies:** Collection strategies can be tailored to individual patients or patient populations, considering their unique characteristics and the specific requirements of the manufacturing process.
- **Benchmarked performance:** Collection outcomes across different sites help identify best practices and areas for improvement.

One-size-fits-all approaches are no longer sufficient in the context of rapid progress in cell therapy. Considering the individual variability of patients and the specific challenges associated with collecting their cells, visibility and insight gained through leveraging data analytics will support optimal cellular acquisitions and collected product.

Terumo Blood and Cell Technologies offers a comprehensive suite of data analytics services via its Veda™ Solutions portfolio to support the cell collection process with offerings such as:



By combining apheresis industry expertise and experience with procedural data, a customized evaluation will help enable cell collection optimization and quality starting material.

Cell collection technologies and trends

Current market

The emerging evidence that starting material contributes to the success of every stage of cell therapy manufacturing from collections and processing to modification and expansion, and even including clinical efficacy, lends importance to understanding the ecosystem. The needle-to-needle concept of therapy manufacturing considers each step of the process starting from the first moment a needle enters a donor vein to the final delivery of the therapy, as shown in Figure 1.

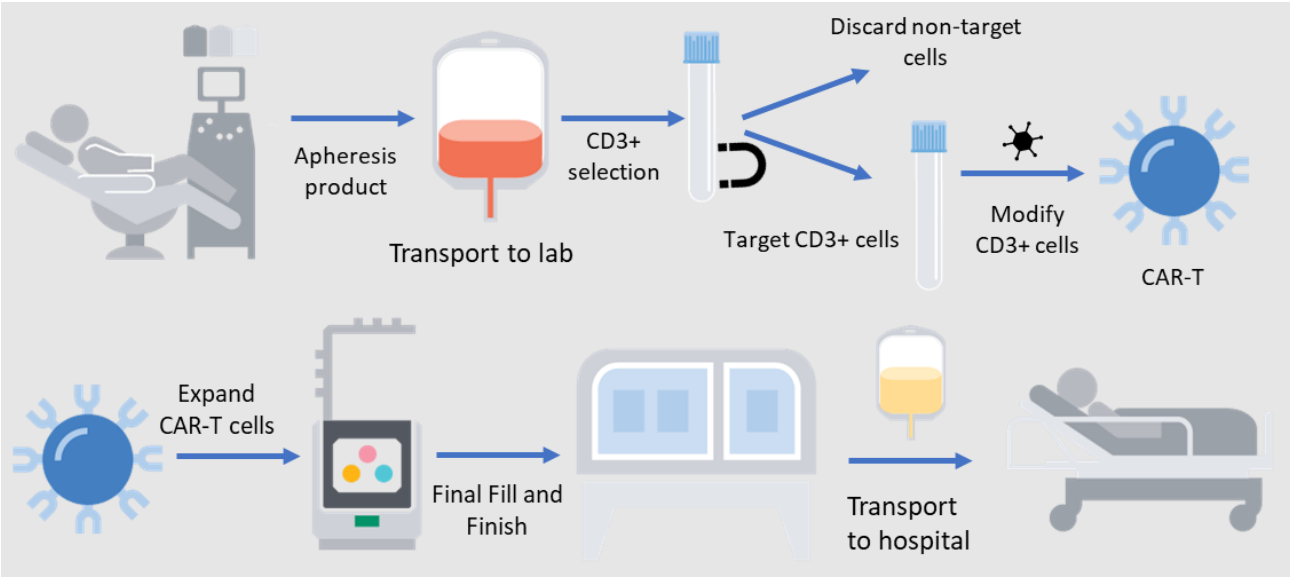


Figure 1. Needle-to-needle CAR-T manufacturing representative workflow

Collections

Cell collection is the primary stage of CAR-T manufacturing. The Spectra Optia system is a therapeutic apheresis, cell processing, and cell collection platform that, in the context of cell therapy, can be used for mononuclear cell collections. This device utilizes an automated interface management (AIM) system to optimize and ensure consistency of target cell collection. The goal is to isolate as many T cells as possible and as few

non-target cells as possible. Some, but not all, cell therapies may include a secondary isolation step to reach an even more pure population of CD3+ T cells. These methods largely include immunomagnetic bead separation but may include newer technology such as microbubble-based cell isolation.[10]

Activation and modification

As we follow the cells on their journey through manufacturing, the next step is activation and modification. Because a T cell is activated through its T cell receptor (TCR) complex, the most common and consistent method is to use a molecular activator containing antibodies that bind to the CD3 molecule of the TCR and the costimulatory molecule CD28. This activation step primes the T cell to be genetically modified to express the CAR. Methods for this genetic modification step typically involve traditional viral transduction techniques where lentiviruses or gammaretroviruses deliver the genetic payload, but alternative methods include lipofection, electroporation, mechanical squeezing, or even non-viral stable genetic integration through transposon/transposase or CRISPR/Cas9 systems. Regardless of gene delivery method, the health of the cell critically determines the success of gene modification and the ability of those cells to expand.

Expansion

T cell expansion is one of the most time-consuming steps in the CAR-T therapy manufacturing process. Even though T cells are among the fastest proliferating cell types, they have a characteristic lag phase in which the log phase expansion does not occur until several days after activation. Moreover, the number of T cells required for various CAR-T therapies can be easily doubled or tripled when considering the need for multiple doses and quality control. For optimal T cell expansion, the environment must be tightly controlled. The Quantum Flex™ Cell Expansion System features a hollow-fiber bioreactor to maintain T cells in a setting that closely matches physiological conditions. The automated, closed system utilizes perfusion to wash away waste molecules while delivering fresh nutrients and oxygen within 100 mm of the cells. This overcomes the diffusion-limited expansion of alternative platforms and closely resembles the microenvironment of human tissues.[11]

Moreover, T cells that are grown in this setting have been shown to display a central memory (Tcm) and stem-cell memory-like (Tscm) phenotype.[12] T cells with these phenotypes, especially Tscm, have been shown to contribute to better clinical outcomes in CAR-T patients by providing a long-lived reservoir of therapeutic cells in the patients.[13] Methods to produce T cells with these optimal phenotypes are active areas of research with significant clinical promise.

Cryopreservation

After the CAR-T cells have been expanded, they are often cryopreserved to bank future doses and to be transported back to the patient's hospital. Manual cryopreservation of cells is somewhat of an art form where precise technique, material temperature, and time of processing are all critical parameters for success. Automated fill and finish devices, like the Finia™ Fill and Finish System, enhance standardization and consistency of mixing cells with a cryopreservant and aliquoting to multiple product bags.

In each step and as a whole, the CAR-T manufacturing process must focus on ensuring the highest quality of cells possible. A common component in each step is the increasing necessity to carry out the process in a closed system and to automate whenever possible. Together, these two actions can significantly de-risk the process from potential microbial contamination, enhance the consistency and health of the cells, and decrease required manual labor in a GMP environment, which drives down cost and opens access to a greater number of patients.

Emerging technologies

As cell and gene therapy technology progresses at an unprecedented rate, therapy manufacturers and providers are armed with a suite of assistant technology. Process analytical technologies (PAT) allow real-time monitoring and/or analysis of various critical process parameters (CPPs) during a cell manufacturing process. While these devices may be available at-line, on-line, or in-line with the core manufacturing platforms, their goal is ultimately the same: decrease failure rates, improve quality, and expedite manufacturing as efficiency improves, which together will drive down manufacturing costs and expand the availability of these treatments to more patients. Some examples of PAT in cell therapy include devices that analyze viable cell counts, metabolic activity as indicated by glucose and lactate measurements, culture pH and dissolved oxygen, amino acid levels,

and even phenotypic and functional assessment of cells. Devices that can be integrated with the base manufacturing platforms in a functionally closed or aseptic manner and are fully automated further enhance the safety and cost-effectiveness of manufacturing.

Conclusion

CAR-T treatments and HSCT rely heavily on the quality of starting materials derived from cell collections. Understanding and addressing the intricacies of T cell collection, such as optimizing the collection process and integrating patient variability into our strategies, can directly impact manufacturing outcomes and, ultimately, patient outcomes.

Next white paper:

Maximizing Collection Efficiency in CAR T-Cell Therapy: Insgihts From a Reference Center

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