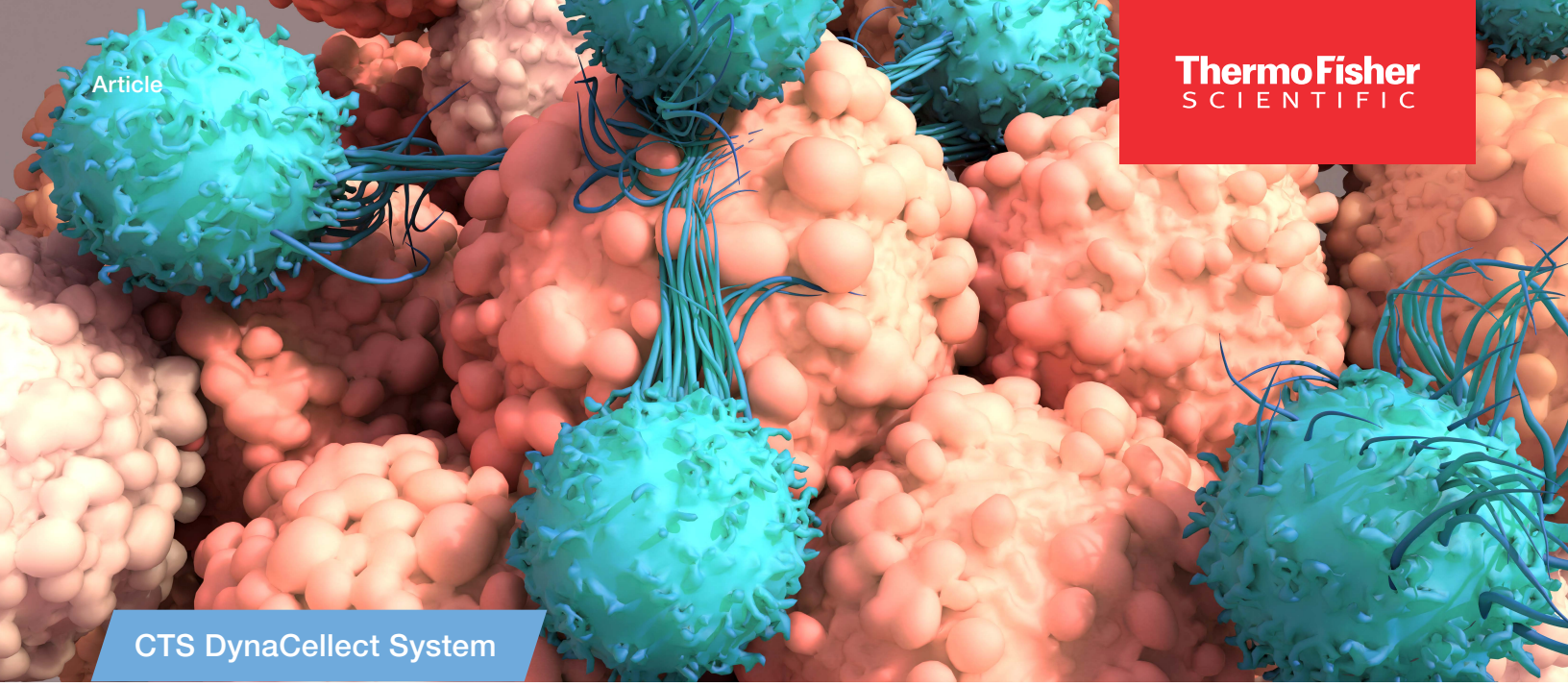

Breaking down barriers in cell therapy manufacturing

Adoptive cell therapy involves the isolation of immune cells from donors—either the patients themselves (autologous) or healthy individuals (allogeneic)—for genetic modification and expansion, to be reinfused back into patients to fight diseases. Therapies that utilize this technology, such as chimeric antigen receptor (CAR) T cell therapy, can be life-changing for those facing diseases like cancer. However, the complexity involved with producing these types of treatments can pose many challenges, such as those associated with collecting and isolating the desired cellular population for the manufacturing process.

Current goals in cell therapy manufacturing

Safety and cost have traditionally been the biggest challenges in cell therapy production. This has recently led the industry to prioritize reducing complexity in order to create safer and more cost-efficient processes. A by-product of several groups attempting to do this in parallel is that there is a lack of standardization across the cell therapy production sector. The lack of standardized processes combined with current capacity constraints is leading to the sector only reaching an estimated 20% of total demand [1]. Recent and ongoing innovation in cell therapy technology and understanding should enable the industry to update existing workflows and allow for more standardized processes.

The most prominent strategies being employed to reduce failure rates aim to shorten, close, and automate all steps in the workflow

A related challenge that developers face is that there is zero failure tolerance with the production of these therapeutics, resulting in manufacturing failure rates as high as 9% for some CAR T cell programs [2]. When the end manufacturing product is deemed unusable, it can be a catastrophic blow. The obvious plan of action is to start the process over; however, this is often an impossibility for autologous therapies, because the patients are unable to donate more cells. The most prominent strategies being employed to reduce failure rates aim to shorten, close, and automate all steps in the workflow, thereby reducing the time that the cells are ex-vivo and eliminating touchpoints.

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In order to work toward these goals, developers must coincidentally address other fundamental challenges, such as scalability and the need to maintain an efficacious T cell population. Understanding these challenges and how to overcome them is essential to streamline the manufacturing process and ultimately expose more patients to these game-changing therapeutics.

Shortening the manufacturing process means that treatment can be given faster, which can be crucial in patients with rapidly progressive diseases

Manufacturing time management

Development time is fundamental when it comes to managing costs, so there is always an economic drive to reduce manufacturing time frames. However, processing time can also directly impact the biology of the drug. A manufacturing system cannot provide identical conditions to the human body, so accelerating the manufacturing process to minimize the cells' time outside the body is vital. For example, it has been shown that freezing and thawing T cells may impact cell viability and anti-tumor reactivity compared with fresh cells, although this may not affect the overall efficacy of the treatment [3]. In addition, shortening the manufacturing process means that treatment can be given faster, which can be crucial in patients with rapidly progressive diseases.

Unfortunately, many currently available cell therapy manufacturing technologies have not been designed with speed in mind. This is largely due to the fact that some of the currently used technology is up to 30 years old, and therefore outdated when compared to the knowledge base and priorities of the industry today. Now that more is known about the biology of the cell therapy production process, new technology must be designed to leverage this deeper understanding and create safer, more efficient, and highly efficacious treatments.

The Gibco™ CTS™ DynaCellect™ Magnetic Separation System is an example of this. This platform technology is a robust, fit-for-purpose instrument that helps streamline and enhance the cell isolation phase of cell therapy production. By automating the process, the CTS DynaCellect system helps drive consistency while increasing throughput and maintaining a high level of precision. The system can process up to 1 L of volume, or ~10 billion target cells, in less than 100 minutes, reducing both the time and labor required to isolate cells. Technologies such as this allow cell therapies to be produced more precisely and consistently, making them more reproducible and cost-accessible around the world. In addition to automation, the digital integration of the system is also important for the industry to oversee process control and free up manual time. The system works with Gibco™ CTS™ Dynabeads™ CD3/CD28 beads, which are then removed following cell isolation and activation without impacting cell recovery or viability. This is an example of technology developed with other devices and consumables in mind to help optimize and accelerate processes.

Scaling up, out, and even down

Another area of particular focus is the scalability of the manufacturing process. When scaling a process, there can be several routes to achieving the same goal. For example, scaling up involves increasing the size of the bioreactor used, while scaling out involves increasing the number of bioreactors.

As capabilities improve and innovative workflows emerge, the industry must be able to scale up and out while also keeping the process closed to minimize touchpoints and risk

Being able to scale up or out is important, especially when moving from R&D toward clinical development. Scaling up is a common strategy for allogeneic therapies, as it results in larger batches that can be used for several doses, thereby lowering the quality control costs and space needed per dose. Benefits of scaling out for autologous therapies are that several relatively small batches can be produced in parallel and centrally controlled, reducing operational costs per batch as well as the physical footprint necessary to produce individual treatments. Therefore, as capabilities improve and innovative workflows

emerge, the industry must be able to scale up and out while also keeping the process closed to minimize touchpoints and risk.

Bigger is not always better, however. In the case of autologous therapies, developers may also be scaling down in order to produce therapeutic doses in smaller volumes at a more rapid pace. As our knowledge around CAR T cell biology increases, the industry realizes the importance lies in the quality of the cells produced, not necessarily the quantity. When the therapy is effective, the patient's body will support clonal expansion of therapeutic cells. This historical mindset was that a large number of cells was required to ensure the presence of the necessary cells. With experience and increased understanding, cell subpopulations that are highly efficacious as cell therapies have been identified, and smaller quantities of these cell are sufficient to achieve the desired outcomes.

With these different approaches in mind, a key goal when it comes to scalability is flexibility. Knowing which route to take when it comes to scaling a process can be a challenge. Therefore, being able to have the freedom to apply the same technology to achieve different scalability targets will fundamentally help to streamline the manufacturing process and improve efficiency. The CTS DynaCellect system can accommodate a range workflows—including both autologous and allogeneic—that have very different scalability goals. This agility means developers do not have to make a fresh start every time they want to develop a different therapy for a different patient or indication. The flexibility of the system enables it to be both physically and digitally integrated into existing workflows, or even work as a stand-alone system, making it well suited to a range of applications.

The importance of T cell phenotype

For cell therapy to be effective, naïve and young central memory T cells (TCM), which display high proliferative capacity, increased survival, and enhanced immunostimulatory cytokine production, are desirable. Over the years, research has demonstrated that infusion of these less differentiated cells correlates with higher-efficacy T cell therapies, due to the superior engraftment, persistence, and antitumor immune response conveyed by these younger cell types [4].

As knowledge around optimizing T cell health continues to grow, media formulation should be adapted accordingly

Promoting strong T cell proliferation and maintaining TCM phenotype requires intelligent media design. The choice of media can significantly influence T cell population growth, differentiation, viability, and the CD8:CD4 ratio during expansion. It is important to select a flexible expansion medium that is compatible with other workflow processes—such as T cell isolation and activation—and various platforms, from static cell culture systems to larger-scale dynamic bioreactors. Innovation in cell culture media is also required when it comes to training T cells to survive across multiple environments. For example, the biology of cells in cancer patients can be different to that of the cells used in therapy development. Similarly, solid tumors have unique microenvironments, so creating media that can prepare the cells to thrive under these conditions is a crucial next step.

As knowledge around optimizing T cell health continues to grow, media formulation should be adapted accordingly. For example, altering certain aspects of the medium to take into account metabolic drivers for cell health and different phases of the T cell life cycle will benefit patients who might not initially respond

to treatment. This will shift the focus to functionality over larger doses, an example of how scaling down is sometimes more effective than scaling up.

Automated platforms, like the CTS DynaCellect system, can circumvent the need for manual handling, helping reduce errors and operator-to-operator inconsistency, as well as accelerating target cell isolation

Evolving to overcome challenges

When building processes and instrumentation with the current cell therapy challenges in mind, it is imperative to provide solutions that maintain high cell purity and viability and support a young cell phenotype. Automated platforms, like the CTS DynaCellect system, can circumvent the need for manual handling, helping reduce errors and operator-to-operator inconsistency, as well as accelerating target cell isolation. Primed with regulatory and traceability documentation, the CTS DynaCellect system can help support developers as they progress toward commercialization. Looking to the future, developing systems that allow a completely closed process can also contribute to the safety of the final product. Combined with advancements in media formulation, advanced technology can pave the way for the industry to help it achieve results quickly and reliably. As understanding continues to grow, these new technologies will help unlock the potential of cell therapy to get effective, lifesaving treatments to those that need them most.

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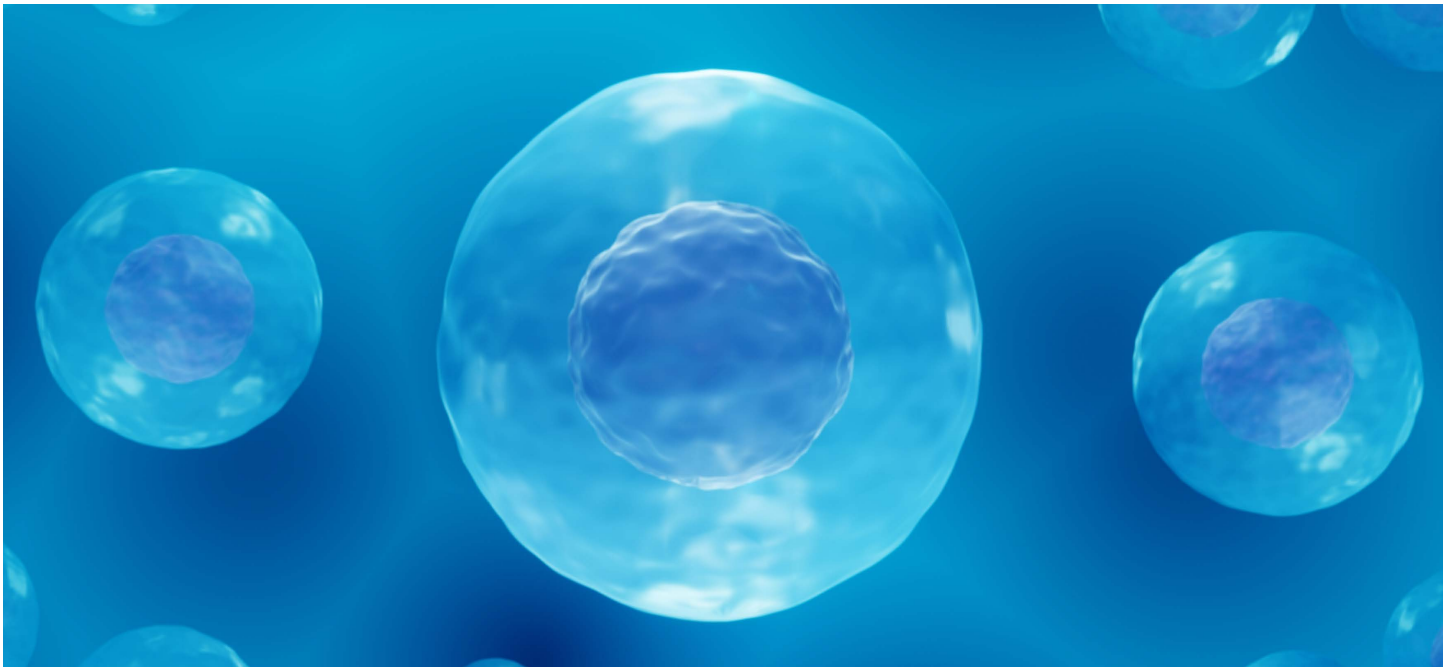

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