

Cell therapy

Causing a stir in cell therapy scale-up

Cell therapy research is thriving, with important advances in bioprocessing techniques driving progress in this rapidly expanding field and opening additional treatment areas. This includes solid tumors, repairing cartilage and spinal cord injuries, and boosting a weakened immune system [1]. The use of cell therapy has previously been limited because of initial cell therapy techniques being autologous—using cells isolated from each patient—and the associated financial and logistical challenges. However, allogenic cell products—using cells isolated from different individuals of the same species—are universal and can therefore be produced at a larger, more commercially viable scale, opening up new possibilities. To keep up with demand and facilitate the success of this next-generation treatment option, manufacturers must implement effective cell therapy scale-up strategies.

Automation and scalability, as well as facilitating improved control over processes, is critical to the large-scale manufacturing and successful adoption of these therapies. With this in mind, many manufacturers are leveraging bioreactors when scaling up their processes. The closed and automated nature of bioreactors reduces the likelihood of human error and can shorten the manufacturing times and lower costs. However, there are disparities in process performance and cell expansion between different types of bioreactors. Therefore, considering the type of bioreactor used, and optimizing the conditions during the cell expansion phase are important.

Beyond this, manufacturers must also consider the culture medium used when scaling up their process. Successful workflows at larger scales require a culture medium that is designed to support high-density T cell culture. The Gibco™ CTS™ OpTmizer™ T Cell Expansion Serum-Free Medium (SFM), no phenol red, and Gibco™ CTS™ OpTmizer™ Pro SFM are examples of such media. For allogeneic cell therapies, CTS OpTmizer Pro SFM has the advantage of driving cells towards a central memory phenotype and helping improve cell growth by shifting the cell's metabolism.

To further build on the benefits provided by a robust medium, this article will delve into how dynamic bioreactors may offer performance enhancements over traditional static types and the methods manufacturers can apply to further optimize their bioreactor performance.

Dynamic reactors

Closed, scalable, and automated operation for allogenic therapy production is difficult, especially in static bioreactors. Therefore, the cell therapy industry has explored more dynamic and scalable modalities such as stirred-tank and rocking motion bioreactors. Despite stirred-tank bioreactors being a cornerstone of bioprocessing, the adoption of this technology by the cell therapy sector has been slow. Stirred-tank vessels offer several advantages over rocking motion bioreactors, including better scalability, a relatively smaller footprint, and more finely tuned control of gases and liquids. The increased precision of mixing and gassing is important at large volumes and high cell densities, when nutritional demand is peaking and the headspace gassing is insufficient to maintain dissolved oxygen levels.

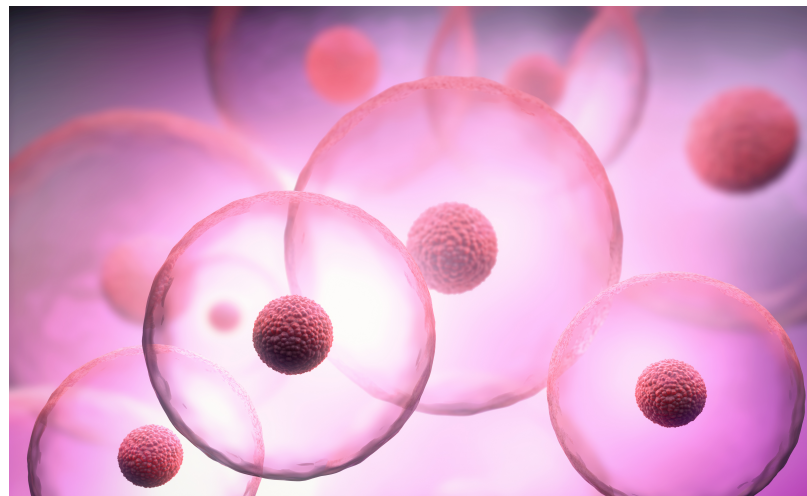
The fundamental difference between stirred-tank and rocking motion bioreactors is in their names—they either use a rotating impeller, as in stirred-tank bioreactors, or a motorized base, as in rocking motion bioreactors. Dynamic reactors are designed to consistently mix cells, gases, and nutrients throughout the vessel, distributing resources to cells equally and propagating healthy, uniform growth of cells. In a study investigating viable T cell growth in three bioreactor types—static, rocking motion, and stirred-tank—both dynamic reactors produced greater fold expansions than static, with the stirred-tank producing the highest growth overall [2]. The cell culture in the stirred-tank bioreactor had a fold expansion of approximately 300 at day 10, while the rocking motion bioreactor and static control reached around 225- and 150-fold expansion, respectively. Furthermore, rocking motion and stirred-tank bioreactors enabled 95% viability of cells, whereas the static bioreactor reached only 90%. This demonstrates that dynamic reactors can help achieve higher productivity compared to static vessels, and stirred-tank reactors can offer even greater cell expansion results compared to rocking motion bioreactors. The study found a correlation between the level of control afforded by the bioreactor and cell culture performance. Therefore, vessels allowing high levels of control, such as stirred-tanks, should be considered by manufacturers looking to scale up [2]. By combining this approach with a robust medium like CTS OpTmizer Pro SFM, the production of allogenic cell therapies could be accelerated.

Ramping up agitation

When using bioreactors, varying levels of agitation are possible depending on the type of bioreactor. It is here that stirred-tank vessels truly stand out from rocking motion bioreactors. In addition to eliminating any dead zones of stagnation in the tank, manufacturers also have the option to control levels of agitation, and even ramp levels up progressively within the stirred-tank to

further optimize and enhance cell expansion. This can be achieved by increasing the impeller speed, as well as considering the impeller orientation and type. Mixing will occur in either a radial flow, axial flow, or a combination of both. To increase agitation and potentially improve yields, manufacturers can reverse flow direction by combining radial and axial flows [3].

Impeller speed is also a key consideration in the optimization of the stirred-tank's performance. It has been found that ramping up agitation from 120 to 600 revolutions per minute (rpm) improved fold expansion by about 20% compared to consistent agitation at 120 rpm [2]. In addition, this ramped agitation slightly increased viable cell density—again demonstrating that more control of the bioreactor can help improve performance. This performance remained high even at higher agitation rates, and cells did not show signs of stress until around 1,000 rpm. Compared to consistent agitation (120 rpm) in a stirred-tank and alternative static vessels, ramping up agitation enabled a significantly higher peak viable cell density [2]. This higher level of agitation may affect media requirements, so developers must choose a robust medium well suited to allogeneic workflows. In summary, coupled with the use of an optimized T cell expansion medium, ramped up agitation in a stirred-tank bioreactor could help improve productivity and optimize performance when scaling up.



Increased control, particularly over liquid and gas inputs, correlates with higher performance and enhanced productivity of a bioreactor.

The benefits of perfusion

Perfusion has also been proven to further improve performance when cultivating T cells. Perfusion is designed to continuously replenish culture medium, increasing a bioreactor's capacity to support a higher density of cells. In a study comparing perfusion and fed-batch cultures in stirred-tank bioreactors, it was found that fed-batch processes plateaued at around 150-fold expansion while perfusion enabled over 300-fold expansion (over 20×10^6 cells/mL). Perfusion also helped maintain a higher viability of cells, remaining well above 95%, whereas fed-batch processes were not able to maintain high viability [2]. To support successful, large-scale perfusion workflows and to create a controlled environment, a robust culture medium like CTS OpTmizer T Cell Expansion SFM or CTS OpTmizer Pro SFM is necessary. With the right medium in place, perfusion may be a key approach to consider in a manufacturer's scale-up strategy.

Optimizing bioreactor performance

Tests have shown that increased control, particularly over liquid and gas inputs, correlates with higher performance and enhanced productivity of a bioreactor. Therefore, using dynamic bioreactors, such as stirred-tank vessels—which enable high levels of environmental control—can help deliver maximum performance, particularly when compared with static vessels. Ramping up agitation can also have a positive impact on cell expansion and should be considered as part of a scale-up strategy. The additional contribution of perfusion methods results in a more desirable environment that helps improve cell expansion, supports high cell density, and maximizes viable cell density with minimal impact on the cell phenotype. To realize the full benefits of these methods, it is crucial to choose the right medium that can support high levels of productivity. CTS OpTmizer Pro SFM is a good example of a medium that has been designed for optimized cell therapy production and has demonstrated many benefits. Overall, there are many measures that can be taken to implement efficient scale-up to help accelerate both allogeneic and autologous cell therapy research, and ultimately improve treatment accessibility.

References

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