Putting CAR-T therapy on the fast track

An ongoing research collaboration between Sartorius and University College London has captured major time and efficiency gains in CAR-T cell therapy production.

Since 2017, seven autologous chimeric antigen receptor (CAR) T-cell therapies—treatments that reengineer a patient's own immune cells to recognize and attack cancer—have gained FDA approval, transforming outcomes for many patients.

Yet as a treatment method, CAR-T therapy is not fully mature. Current applications remain largely restricted to a narrow range of blood cancers, including B-cell malignancies and multiple myeloma, while high costs and manufacturing complexities limit its availability even to eligible patients.

Nevertheless, CAR-T therapies are poised for significant growth as developers seek to extend the technology to solid tumors, autoimmune conditions, and other diseases. They're also looking into additional therapeutic cell types, including allogeneic T cells and natural killer cells.

Realizing these broader applications, however, depends on addressing fundamental bioprocessing bottlenecks. Encouragingly, recent results from a longstanding collaboration between Sartorius—a solutions provider for life science research and the biopharmaceutical industry—and the Cell and Gene Therapy Bioprocessing group at University College London (UCL), led by Qasim Rafiq, show considerable potential to do so.

Tricks of the trade

Many of the efficiency gains seen in other areas of bioproduction have yet to reach CAR-T cell manufacturing, highlighting clear opportunities for improvement. Still, the methods developed for large-scale bioprocessing of biologics or vaccines from cell lines do not directly translate to the autologous production of small batch, engineered T cells from individual patients.

Developers have also needed time to pinpoint which characteristics of CAR-T cell therapies drive lasting clinical benefit. "Obviously, there is an increased understanding around what clinicians are looking for in the final product, in terms of the marker profiles and phenotypes that work," says Nicola Bevan, manager of Application Development at Sartorius.

Clinical data indicate that CAR-T therapies are most effective when the infused cell product contains more long-lived, less-differentiated T cells and fewer exhausted or immunosuppressive ones. With this in mind, Sartorius and UCL collaborated to develop scalable bioprocessing strategies aimed at producing T cell products with phenotypic and functional attributes linked to improved clinical outcomes.

Accelerating growth

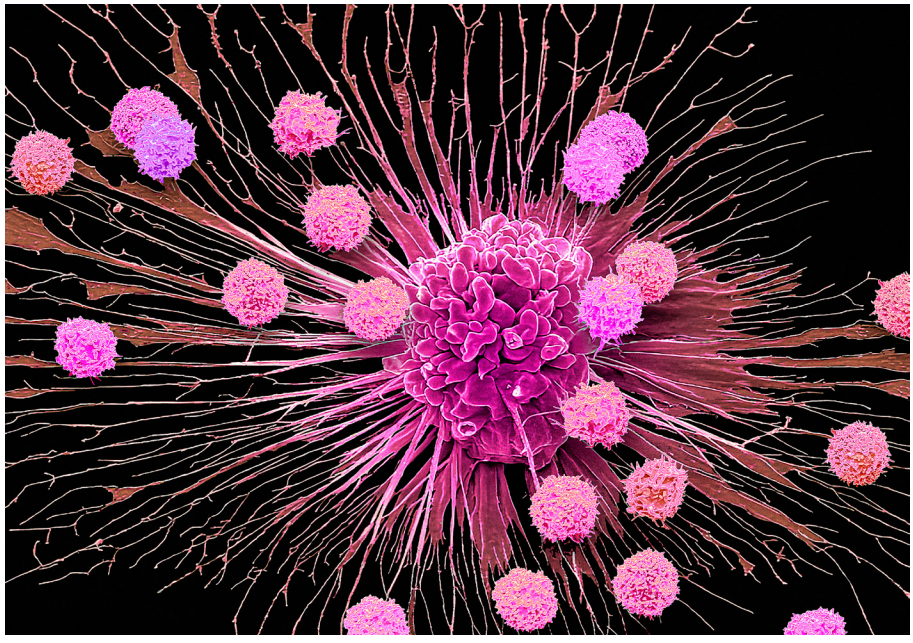
The field of cell therapy has relied on a variety of culture systems with different levels and types of agitation—from static vessels to stirred-tank and rocking-motion bioreactors—that impact T-cell expansion and phenotype. When Sartorius and UCL began their partnership, T cell therapies were just entering clinical use and little was known about their behavior in production environments. "The prevailing understanding was that T cells were fragile," says Bevan, "suggesting they could only be grown in the most gentle culture systems." However, Sartorius and UCL showed that T cells, including CAR-T cells, can be efficiently and reliably expanded in stirred-tank bioreactors without loss of quality or function.

Another major focus has been finding ways to grow patients' modified T cells more quickly, since reaching a sufficiently high cell density can be the slowest

IMAGE: PROVIDED BY SARTORIUS

step in the production process. The partners have shown that perfusion-based approaches—involving the continuous supply of fresh media to and removal of waste from a stirred-tank bioreactor—outperform conventional fed-batch methods, producing more cells in less time. By testing different perfusion rates and start times, they attained a 4.5-fold improvement in cell yield while cutting the time to reach the appropriate cell density by more than 50%. For patients with late-stage disease, speed is critical. "They don't have much time, and the focus is on generating the dose as quickly as possible," says Rafiq.

The team also developed a flexible perfusion strategy that adjusts to the growth dynamics of each individual CAR-T cell culture. This requires real-time visibility into the culture—tracking factors such as glucose consumption, lactate production, oxygen levels, and pH—and the ability to adjust the process in response to the data. "The way I like to frame it is to provide the cells with what they need when they need it," says Rafiq. The researchers learned that it was possible to reduce the perfusion rate as cell densities rise, and the culture's growth rate starts to slow. This resulted in an 11% reduction in the amount of media required without any effects on the quality of the final product. In a clinical production environment, those cost savings could be significant.



Tumor cells with immune cells.

IMAGE: PROVIDED BY SARTORIUS

The allogeneic opportunity

Real-time monitoring of cell cultures is increasingly recognized as an essential component for scaling CAR-T manufacturing processes. While autologous CAR-T therapies typically require smaller-scale systems—such as 250-mL stirred-tank bioreactors—to produce a personalized dose for a single patient, the need for accurate and continuous monitoring becomes more pronounced in the development of allogeneic CAR-T therapies.

Unlike autologous treatments, allogeneic therapies employ donor-derived T cells that are genetically engineered to reduce immune rejection. This enables large-scale production of standardized off-the-shelf products capable of serving multiple patients from a single manufacturing run.

Although no allogeneic CAR-T therapy has yet received regulatory approval, the promise of streamlined manufacturing continues to drive strong interest in the field. To this end, advanced analytical tools have become invaluable, offering real-time insights into key process parameters.

In the allogeneic setting, the emphasis shifts from rapid turnaround to quality and efficiency, aiming to produce multiple consistent, high-quality doses from a single batch. According to Rukmini Ladi, segment technology manager for Cell Therapy at Sartorius, the scale-up process has progressed smoothly. "We have successfully scaled our process from a 250-mL stirred-tank bioreactor to a 2-liter stirred-tank vessel while maintaining cell quality, phenotype, and expansion performance," says Ladi. "At the 2-liter scale, batch yields have reached levels that could correspond to more than 100 potential CAR-T doses, depending on clinical dose requirements and release specifications."

Real-time release?

In the autologous setting, Sartorius and UCL continue to seek new gains as well. Having established the possibility of cutting CAR-T expansion times in half, the partners now aim to reduce the entire CAR-T production cycle—from vein to vein—in half, by focusing on the other big bottleneck in the process, quality assurance.

It can take at least a week to complete the assays required to ensure that a given dose has the appropriate identity, potency, purity, and concentration. The ultimate goal is to improve production monitoring and control so that products can be released in real time, with little or no additional testing, as long as they stay within the proper quality limits. For now, that is a "utopian" ideal, says Rafiq.

In the meantime, Sartorius and UCL are looking at new functional approaches and new assays that will contribute to the development of a 'faster CAR'. By simplifying and streamlining complex production processes, they promise to bring the power and precision of CAR-T therapies to more patients.