Overcoming the Challenges of Cell Therapy Manufacturing

A new era for off-the-shelf cancer immunotherapy

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In recent decades, adoptive cell therapy—also known as immunotherapy—has gained traction as a potential fifth pillar of oncology, treating patients where surgery and conventional methods of chemo-, radiation, and targeted therapy have failed. First approved by the US Food and Drug Administration (FDA) in 2017, chimeric antigen receptor (CAR) T-cell therapy is an example of immunotherapy that works by enlisting and empowering the immune system's innate ability to recognize and eliminate damaged and defective cells. Early-phase clinical trials have shown that CAR T-cell therapies have the potential to make significant strides but, to date, only a few thousand patients have been treated in the US, and the treatment is still largely reserved for second-line therapy against certain relapsed or refractory leukemias and lymphomas.

Conventionally, personalized cell therapies based on individual patients' own cells have been used, but the tortuous and extensive ex vivo workflow required to prepare these autologous therapies is a significant barrier to wider use. Allogeneic approaches—based on the large-scale preparation of batches of cells from a healthy donor—have the power to revolutionize the use of CAR T-cell therapies, overcoming the inherent manufacturing hurdles associated with autologous therapies. Although still in its infancy, this approach is being driven forward by innovative solutions such as fit-for-purpose media designed to optimize cell culture growth and the use of gene editing to "de-identify" cells and prevent unwanted immune response. By powering a new wave of scalable CAR T-cell therapies, these innovations are helping to democratize access to potentially life-saving treatments for cancer patients.

Barriers to change

Scientific interest in CAR T-cell therapies has flourished in recent years, but the only approved treatments in current practice rely on autologous workflows; harvesting the patient's own blood cells for genetic modification to engineer T cell-mediated cytotoxicity. The multi-stage process of a one-to-one autologous therapy—from patient leukapheresis to manufacturing—can take several weeks, requiring highly-skilled personnel and complex logistics for successful execution. The necessary infrastructure and labor result in an overwhelming cost of the therapy; approximately $475,000 per patient when using Kymriah (tisagenlecleucel) for the treatment of B-cell acute lymphoblastic leukemia. In addition to these manufacturing complexities, at the patient level, collecting blood cells from cancer patients contributes to variability in the quality of the harvested cells, and patients can experience lymphodepletion due to their illness and/or intensive rounds of chemotherapy, diminishing the quality and quantity of T-cells and increasing the failure rate of autologous manufacturing. The combination of these issues results in limitations for autologous CAR T-cell therapies in their scope and scalability.

Off-the-shelf cancer therapies

Allogeneic therapies are an attractive alternative to autologous approaches, offering the potential for over-the-counter cell therapies to revolutionize patient access to treatment. Blood cells from healthy donors are collected, modified to target the disease of interest, expanded, and then stored in a centralized cell bank so that a single batch of modified cells can be used for the treatment of multiple patients, potentially transforming the scalability of therapy.

There are several benefits to large-scale batch production of cells. First, cells can be prepared and cryopreserved in advance, allowing clinicians to administer scheduled treatment regimens as required by the patient's disease progression. For the most critically ill patients, time is truly of the essence, and even minor delays to treatment can have catastrophic consequences. With allogeneic therapies, the length of the workflow is no longer a concern for the patient because the cell banks are already in existence, and the use of healthy donor cells eliminates concern of a diminished immune response of the patient's cells. Healthy cells are far more tolerant to collection and ex vivo manipulation, drastically improving the potency of treatment and offering a lifeline to patients that were unsuccessful in donating cells. Lastly, replacing individual cell collection with large-scale batch production runs helps decrease the cost of labor, offering a less expensive, time-saving, off-the-shelf solution to cell therapy. Taken together, the allogeneic approach to cell therapy is expected to lead to a surge in manufacturing success rates and ultimately drive improved patient outcomes.

While the benefits to streamlining manufacturing are abundantly obvious, allogeneic therapies are a contradicting paradigm; introducing foreign cells to elicit an immune response while evading the immune system. The body's defenses are designed to attack and eradicate any unknown, infected, or damaged cells, which can result in severe and life-threatening side effects of allogeneic therapies, including graft-versus-host disease. Cell batches are coming from an alien source, so they need to be stripped of any self-identifying antigens to avoid unwarranted immunological responses. The development and optimization of innovative technologies to evade an immune response—such as the editing tools CRISPR and TALEN—is an active area of research focused on helping to alleviate safety concerns and decreasing use of immunosuppressants.

Innovation can overcome manufacturing hurdles

The future of allogeneic therapies is not without its challenges, but innovative solutions to standardize cell culture workflows are making promising progress. To support large scale manufacturing, adoption, and commercialization of cell-based therapies, manufacturers will be expected to generate large batches of product, requiring reliable and consistent methods of cell culture and storage to retain high yields of viable cells. Inadequate cell culture media can have a detrimental effect on the condition of cells, resulting in devastating consequences for yield.

"Cell culture media can play a direct role in maintaining the quality of the cells, but they are often overlooked. The quality of the cells is paramount, as it translates into enhanced potency or efficacy," explained Roderick O'Connor, research assistant professor at the Center for Cellular Immunotherapies, University of Pennsylvania. "Unfortunately, most media formulations were created years ago, and contain supraphysiological levels of nutrients meant to support robust cell proliferation. However, this is not the best approach for cell-based therapies, as it can negatively affect the quality of the cells, because advanced proliferation by this method can chew up telomeres, promote senescence, and create oxidative stress."

Currently, cell culture media options are available on the market for autologous therapeutic development applications from several key manufacturers. However, for allogeneic treatments in particular, serum-free cell culture media specifically geared toward increasing proliferation of the most potent early memory cells to retain cellular youth, boost immunostimulatory cytokine production, and delay the differentiation of inadequate effector cells is important. Taking these considerations into designing media formulation can contribute to a rapid yield of large numbers of early memory cells and is ideal for the type of large-scale automated workflows that will be vital to future allogeneic CAR T-cell therapies.

The future of cell therapy

Allogeneic treatments have the potential to revolutionize cancer treatment, providing an off-the-shelf alternative where conventional autologous cancer treatments have failed. Advancements in manufacturing and genetic engineering have already come a long way in making allogeneic treatments a reality, and innovations designed specifically for this application may help allogeneic cell therapies become a viable option for cancer treatment in the near future.