The Right Tools to Optimize Cell Therapies

Challenges and opportunities for efficient process development

The global market for cell therapies just keeps growing. Whether it's CAR-T cells for cancer therapy, gene therapy applications, or another infusion of living cells, developing cell products for commercial therapies poses novel challenges in all aspects of development, testing, and manufacturing.

With a living cell product, safety testing, regulatory requirements, and large-scale manufacturing cover uncharted territory. Autologous products, which are made to order in small batches from patient cells, are labor-intensive to produce. Allogeneic therapies intended for off-the-shelf use require different methods of testing and regulatory standards than conventional small molecule drugs.

"Each cell therapy is unique, they're all case-by-case," says Shawna Jackman, PhD, senior principal research scientist with Charles River Laboratories. We're able to support these programs by leveraging our expertise in different areas to provide guidance and tools to advanced medicine researchers."

Start strong, finish strong

Choosing the appropriate starting material can go a long way toward smoothing the path to a successful final product. Yet the starting material is too often a source of great variability when it comes to cell production. To meet regulatory quality standards, working with a trusted supplier to provide consistent, high quality cells is essential.

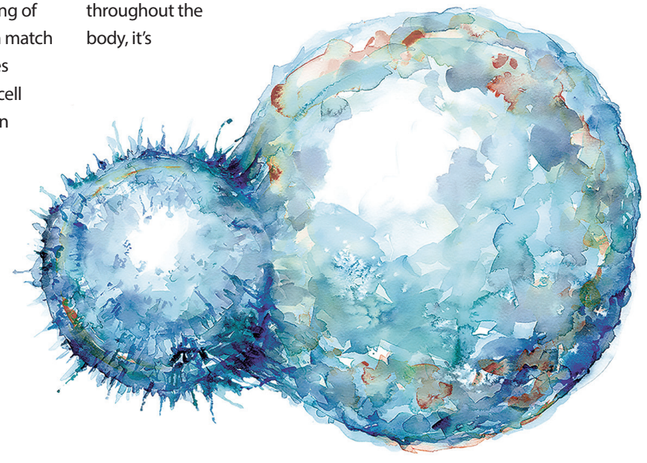
Access to a large and diverse donor pool allows for close matching of characteristics to the criteria needed in the final product. "If you can match early, you save valuable resources when transitioning to later phases of process development," says Dominic Clarke, PhD, global head of cell therapy at HemaCare. For instance, he says, it can be useful to screen donors by HLA type, disease state, or age. Whether for allogeneic or autologous products, matching donor characteristics can be a critical but easily overlooked step in building a consistent and efficient manufacturing process.

The perfect balance: safety and efficacy

Once the candidate therapy is engineered from the starting material, it's time for lead optimization. "Different versions of a cell therapy are compared to each other, in terms of functionality, potency and cross-reactivity in different bioanalytical tests," says Sanne Holt, PhD, group leader at Charles River Discovery. Using CAR-T cells as an example, she points out that while selecting for higher potency seems desirable resulting in higher cancer cell death, cells with the highest potency also pose the highest potential safety risks. "The in vitro efficacy tests that you perform first, will help identify that optimal lead candidate," she says. "Is the best candidate also the safest candidate? Ideally you need to find a perfect balance, where it's safe and still potent enough."

Following efficacy testing, in vitro safety testing aims to identify risks to normal healthy tissues through potential off-target effects of these therapies. "You select human tissues of suspected risk, either tissues exhibiting low level expression of the target antigen or major organs which need to be evaluated," Holt says. Co-culturing the lead candidates with healthy primary human cells, and verifying there's no response, provides a scientific rationale that the therapy will work as intended without causing unintended havoc around the body.

Once several promising candidates have made it through in vitro testing, they are evaluated in animal models to further demonstrate their safety and efficacy. "Cell therapies possess unique attributes and evaluating these products can be different from the traditional approaches to drug discovery," says David Harris, PhD, research director at Charles River Discovery Services. "These therapies can replicate and persist throughout the body, it's important to understand how they will behave in animal models, before they are tested in humans."



As far as possible, the cellular therapy being tested in animals should mimic the attributes of the final clinical grade product, to accurately evaluate the potential functionality in patients. Using the example of CAR-T cells, Harris explains, the cells are engineered to express a receptor that binds to an antigen on a target cell. But if the target antigen is also expressed on healthy tissues, there can be unintended and potentially serious responses. "There can be life-threatening consequences of engaging these highly activated cytotoxic T cells in certain situations," Harris says. The in vivo pharmacokinetic studies help identify potential side effects, allow researchers to determine the optimal dose and provide critical information about the pharmacodynamic properties of the therapy. "Generally, one is trying to find that sweet spot of robust activity with the optimal number of cells."

Utilizing an appropriate animal system is also critical. The preclinical models should express the specific target and represent the tumor type that will be treated, Harris points out. "We utilize a wide variety of different tumor model systems depending on the nature of the cell therapy evaluated."

These studies play a critical role in establishing efficacy and evaluating safety that are required for regulatory approval. Here again, cell therapies push manufacturers into uncharted waters when it comes to drug development

Traditionally, regulatory agencies require that studies are conducted according to GLP guidelines. However the dynamic systems involved in assessing living cell therapies mean it's not always possible to adhere strictly to GLP guidelines. "In these exceptions, all the components needed for reliable robust and reproducible data are still incorporated," Jackman says. "We work with clients to navigate those specifications and present the high quality science necessary to meet regulatory expectations."

Process optimization and scale up

Once efficacy and safety have been established, it's time to start manufacturing. "The goal is not only to develop a safe product, but to develop a consistent and repeatable process," says Clarke. The path will be slightly different for autologous products from disease patients than for allogeneic products made from healthy donor cells.

For development of an autologous product, establishing a well-defined process is difficult given the inherent patient-to-patient variability. Ideally, the disease-state starting material would be used, but sourcing large amounts of cells from sick donors represents a key hurdle. Due to the sourcing limitations, starting material from healthy donors is used. In order to develop a process that can accommodate the variability, it's important to work with heterogeneous donor material, like a leukapheresis collection, because that will resemble more closely what's collected from the patient. "Working with the right starting material during process development is critical as it enables you to gain downstream processing proficiency," Clarke says. "Ultimately, you're building a consistent manufacturing process that's going to allow you to characterize and deliver a final product that consistently meets the target product profile."

With allogeneic, or off-the-shelf products, establishing safety and consistency of the donor-derived starting material becomes more critical. Having access to an extensive, highly characterized donor pool for selection and sourcing is important for initial process development and long-term supply continuity. Cells from certain donors might have characteristics that allow for more efficient transduction or faster cell expansion rates. "There's ultimately both internal and external variability associated with the donors, and that variability impacts how that product is manufactured downstream," Clarke says. "One of the critical components we provide is access to recallable donors, which are donors that have demonstrated long-standing commitment and are reliable." If certain donor cells work best, having access to additional collections from those same donors provides a significant benefit to manufacturers by reducing variability and establishing process and product consistency.

Ultimately, the donor starting material in support of allogeneic therapies will have to be collected and manufactured to cGMP (current Good Manufacturing Practice) compliant standards for clinical application. "This is something we work with our clients on through early and active collaboration," says Clarke. "Not only can we collect the cells but with onsite GMP-compliant cleanrooms, we can support some of the key manufacturing steps including cell isolation and cryopreservation necessary to support clinical and commercial production."

Delivering the final product

The GMP release and characterization testing that is applied to cell therapies follow the basic tenants for all biologic drugs: Sterility, mycoplasma, endotoxin, viability, identity and potency assessments. Many of these tests need to be performed using a rapid testing platform, as the time from harvesting the cell therapy to dosing the patients can be relatively short. Collectively, this testing provides end to end documentation that assures the safety and efficacy of the production of the cell therapy products.

The safety risks for each product and process can vary with each type of cell therapy, but the overarching goal is to provide consistent and effective therapies and specific testing strategies that ensure patient safety. Partnering early is an important aspect to creating the support and continuity necessary for success. It is good to remember that with new therapies come new challenges—these are exciting times. ■

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