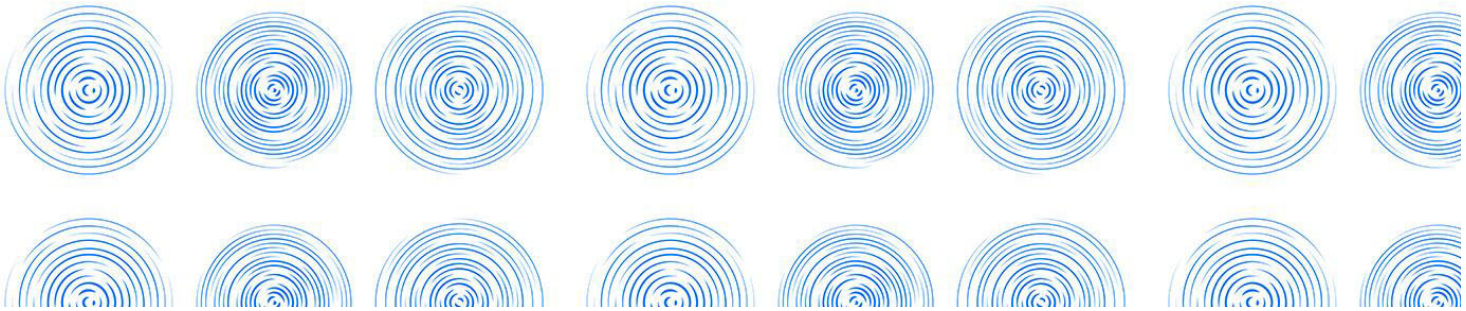

Cell Expansion for Cell Therapies

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Cell-based therapies—using cells from patients (autologous) or donors (allogeneic) that are engineered to treat diseases and then reintroduced into—offer exciting opportunities for treating and possibly curing diseases. The sheer number of cells required to treat one patient boggles the mind (e.g., 100s of millions to billions in one course of autologous therapy). Thus, it is essential to expand engineered cells into many copies, building the population into an army sizeable enough for the therapeutic course. Scientists are developing methods to scale up expansion while keeping patient safety and efficacy in mind; indeed, recent work shows that the expansion process of CAR-T cells can affect their therapeutic outcome. Here's a look at some challenges researchers are facing and potential solutions.

Starting with high-quality DNA

The engineering of therapeutic cells starts with transfecting or transducing them with specific DNA sequences, so they will express proteins that equip them to target cancer cells, for example. A challenge in all genetic-based medicine, cell therapies included, is the production of DNA sequences by cell-based DNA manufacturing, says Matthew Hill, Founder and CEO of Elegen. "We believe the critical bottleneck in cell therapy development is the production of custom synthetic DNA required to ensure that the optimal candidate is selected for cell expansion," he says. Elegen specializes in manufacturing long, synthetic, sequence-verified DNA, which is invaluable in determining the optimal DNA sequence to choose during expansion.

Cell therapy development involves optimizing the cells for expansion and efficacy through iterative cycles of DNA design and testing. "The hierarchical assembly and cell-based cloning process used to produce the highly accurate DNA needed for cell-therapies can slow each development iteration by weeks, often adding months to development," says Hill. Elegen's proprietary cell-free DNA synthesis technology yields DNA that is 99.999% accurate and reliably delivered in about 7 days.

Elegen verifies every DNA sequence using next-generation sequencing. Their fast delivery combined with low error rates help to avoid delays that can otherwise occur during design iterations. "Cell and gene therapy programs can save 2–3 weeks with every order, and over 3 months with every project, by skipping early rounds of cloning to evaluate and optimize custom payloads—and thus move to the cell expansion stage faster," says Hill. "This rapid access to full-length, high-quality DNA from Elegen's cell-free manufacturing process can accelerate the discovery of new therapeutics and clinical production to bring new therapies to markets 6–10 months faster."

Reducing costs, increasing safety, and consistency

One of the biggest challenges is reducing manufacturing costs of cell-based therapies while maintaining their safety. Scientists are tackling this from several angles. One method is to hasten the manufacturing process of cell-based therapies, "establishing rapid manufacturing processes that are characterized by *ex vivo* times at or below 48 hours, which would inherently reduce the manufacturing spend by eliminating much of the costly culture time," says Evan Zynda, Senior Staff Scientist at Thermo Fisher Scientific.

Innovations that allow cultures to grow in a closed and automated environment enhance safety in cell therapies by reducing the chance of contamination or human error. "The ideal state, especially for autologous therapies, is to develop a completely refined process in the pre- and early-clinical stages that is fully automated, and requires no human intervention," says Zynda. Closed cell culture vessels such as bioreactors are especially suited for this. "We see stirred tank reactors as the future here, since they offer the most flexible and intimate environmental control, a broader range of scalability, and a smaller footprint per volume, all of which increase consistency, reduce labor demands and cost, and improve the quality of cellular output," adds Zynda.

Closed and automated systems are important elements in establishing a robust manufacturing process that consistently delivers high-quality autologous cells. Another is integrated sensors. "One of the biggest challenges is that we don't have enough process analytical technologies integrated into culture platforms," says Matt Hewitt, VP and Technical Officer of Cell and Gene Therapy and Biologics at Charles River Laboratories. These are tools, such as sensors for temperature, pH, and O_2, that help to ensure the cells are in an optimum growth environment. "We're moving more toward including sensors that allow us to assess cell counts, metabolites such as glucose, lactate, and amino acids that are helpful in determining how the cells are expanding."

Allogeneic therapies

One of the hopes for allogeneic therapies is lower costs. Researchers are still working out how to grow large batches of allogeneic cells that can be frozen and stored for later use, as needed, for off-the-shelf cell therapies. "We're gaining a better understanding of how these cells are working in the body, and their temporal nature," says Hewitt. "For many allogeneic programs, the cells are eventually eliminated by the patient's body, and the question is how long do they need to persist in a patient to get the desired effect of eliminating cancer?" Studies are underway to learn whether allogeneic therapies measure up to autologous therapies for some blood cancers, and their performance against solid tumors will likely be more complex. "We'll also have to have a discussion about the long-term feasibility of finding donors for the starting materials for allogeneic cells," explains Hewitt.

Allogeneic therapies involve a riskier transfer of donor-derived cells to the patient, so require particular attention to quality control (QC) checks at additional costs. "However, the increased QC needs can be tolerated since one manufacturing batch can equate to a large number of doses over which to spread the additional investment," says Zynda. Not everyone is convinced of the allogeneic cost savings, however. "I think the jury's still out on whether we're going to see cheaper pricing for allogeneic therapies," says Hewitt. "Currently, the cost of manufacturing doses of allogeneic cells is very expensive, and we're still gathering the clinical results."

Bringing down manufacturing costs will also make treatments more accessible to patients who cannot currently afford them, but are strong candidates clinically. "Production costs need to be significantly lower so that these therapies can continue to transition toward an earlier line of treatment and be available to a wider population of patients," says Zynda.

Stay tuned for upcoming developments in cell therapies—in December, the FDA will issue decisions on applications for two new cell therapies for sickle cell disease, from Bluebird Bio (lovo-cel), and VERTEX Pharmaceuticals and CRISPR Therapeutics (exa-cel).