Syner•G

WHITE PAPER

Cell Therapy Manufacturing: Ensuring Manufacturing Success

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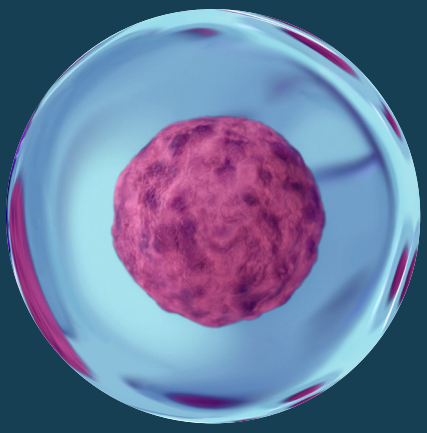
Cell therapies are an emerging and exciting space in the biotech world, with the potential to positively impact patient lives all over the world. Many cell therapy companies are currently working on novel therapeutics for previously untreatable diseases and cancers. Cell therapy also has the potential to restore the function of a gene over time and may allow patients to manage diseases without the need for ongoing treatment. We are at a development tipping point, with some of the first cell therapies becoming commercially available on the market and many more in the research and clinical pipeline.

Cell Therapy

In cell therapy, viable cells are injected, grafted or implanted into a patient in order to effectuate a medicinal effect to boost immunity in the case of immunotherapy, or to regenerate diseased tissues in the case of stem cell therapy. Novel cellular therapy products include cellular immunotherapies (autologous, allogeneic or CAR-T cells), hematopoietic stem cells and adult and embryonic stem cells.

Cell therapy involves creating a genetically modified cell line with a gene or target DNA sequence of interest inserted and delivering these modified cells to a patient. In some platforms, these modified cells can be retrievable from a patient and do not alter the patient's own genome, providing some potential advantages over traditional gene therapy. Other common cell therapies include modifying B cells or T cells, which work with a patient's own immune system to fight certain tumors, cancers, and other diseases.



Ex vivo vs. In vivo Therapies

Cell therapies are often described to be either ex vivo or in vivo. In vivo therapies mean that the therapy is administered directly to the patient, with gene modification happening within the patient. In ex vivo therapies, cells are removed from the patient and the cells are modified outside the patient's body before being reintroduced to the patient.

The terms allogenic and autologous are used to describe the method in which cells used in cell therapy are sourced. Allogenic therapies are sourced from multiple donors and pooled, while autologous cell therapies are sourced from a single donor or patient per batch. There are pros and cons to each cell therapy method and special considerations to make when developing each process.

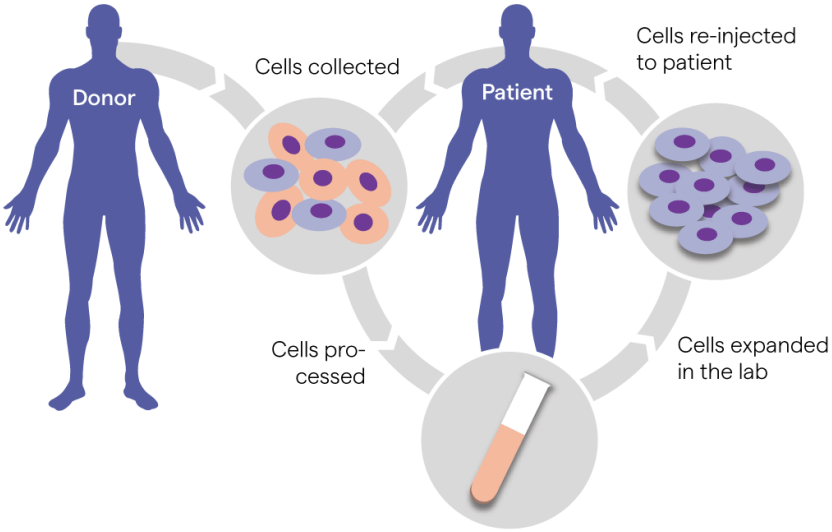


Figure credit Lonza: https://bioscience.lonza.com/lonza_bs/US/en/cell-and-gene-therapy

Allogenic cell therapies are pooled from multiple donors, which is beneficial from a lot to lot variability perspective and decreases the amount of testing needed when compared to single donor manufacturing processes. Allogenic processes are also more manageable from a timing and logistics perspective, and allow for more flexibility regarding QC testing and release of material. However, one downside of allogenic cell therapy is the possibility of graft vs. host reactions.

Autologous cell therapies most often use the patient's own cells. This means that the cells are often collected via apheresis from a patient. This is a way of isolating a patient's T cells, B-cells, or dendritic cells, modifying them in some way, and then returning them to the patient at a later time for therapeutic effect.

This can create unique logistical or time constraints. Having a manufacturing facility in the same location as a clinical site/hospital or at least the same geographic area can help to alleviate any time or import related issues. The nature of autologous cell therapies can vastly increase costs, since each batch is unique to an individual patient.

Release assays and stability testing are generally truncated based on timing and the narrow window allowed for manufacturing. Patients are usually heavily monitored over the course of these therapies. Retrospective QC testing becomes a more common way to mitigate timing constraints in patient specify therapies.

Patient Specific Therapies

Patient specific therapies are also becoming increasingly common. There are many different types of personalized medicines or patient specific therapies such as Chimeric Antigen Receptor (CAR) therapies, dendritic and macrophage cell therapies. There are special considerations when developing patient specific therapies, due to the complexity of both the manufacturing process and individualized testing needed. Timing is often critical, depending on the disease indication, as patients may be growing increasingly at risk for adverse disease effects as time to treatment lengthens (as is the case in cancer immunotherapies).

01

CAR-T, CAR-B, TCR and Bispecific T-Cell Engager (BiTE) Therapies

Chimeric Antigen Receptor T-Cell or “CAR-T” and T cell receptor engineering “TCR” technologies both involve modifying a patient’s T cell receptors as a way to combat tumor cells. TCR and CAR-T therapies are ways to specially design and modify T-cells with the ability to find and destroy cancer cells in a patient’s body. Different cancer and tumor cells have specific antigens, and CAR-T cells are engineered to bind to these specific antigens. The difference between CAR-T and TCR is CAR-T can bind to cancer cell antigen sites, while TCR receptors bind with major histocompatibility complex (MHC) proteins. T cell modification can be very effective against previously hard to treat types of cancers.

CAR-B therapies are similar to CAR-T, but modify B-cells rather than T-cells. Clustered regularly interspaced short palindromic repeats (CRISPR) systems are often used to modify B-cells, and then re-administered to patients for therapeutic effect. CAR-B therapies are less common than CAR-T therapies, but promising research continues in this area.

Bispecific T-Cell Engager Therapy (BiTE) is also an emerging immunotherapy used to treat certain types of cancers. BiTE is a bispecific antibody construct, that allows for binding of an antigen on tumor cells and a surface molecule on T-cells to induce tumor lysis.

02

Dendritic Cells and Macrophage Therapies (Regulator Cells)

Dendritic cell therapy is a process of modifying a patient’s own white blood cells which are later readministered to destroy tumor cells. These can be used to elicit immune responses in a patient and can be used not only in cancer treatment but also various autoimmune diseases. Dendritic cells modified in this way are often administered via vaccine.

Macrophages are used in some cell therapies. There are new developments in individualized medicine and CAR-M (CAR macrophage) therapies. In this type of therapy, monocytes are removed and isolated by apheresis, and then modified with a specific antigen chimeric receptor. Macrophages can also be manufactured using allogenic donor methods and used to deliver therapeutic molecules to patient cells.and regenerative medicine.

03

Stem Cells

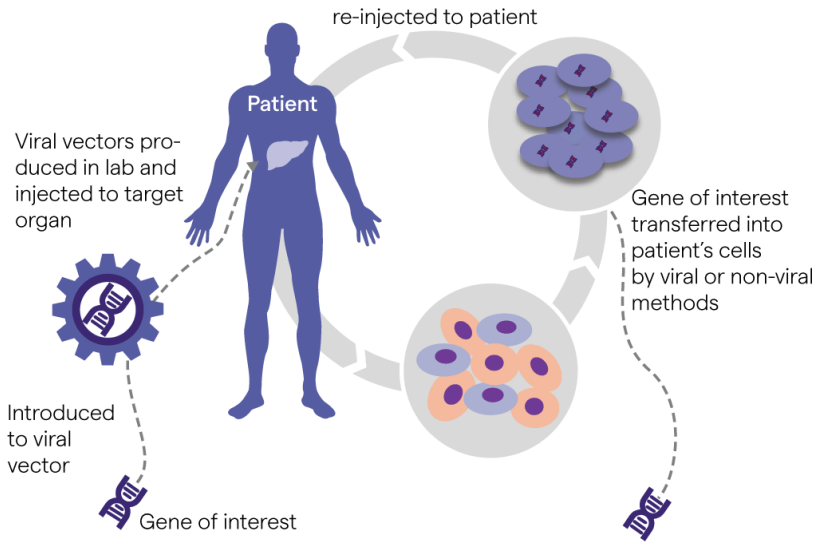
There are several types of stem cells are commonly used in cell therapies. Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) can divide into embryonic cells and therefore all types of adult cells. Pluripotent stems cells are used in several clinical trials for cell therapies for diseases such as Type I diabetes and Parkinson's disease among many others.

Overview of Manufacturing for Cell Therapies

Due to the variety of cell therapy types, manufacturing processes for cell therapies can vastly differ. However, there are general guidelines across all types of cell therapy to keep in mind.

In Vivo and Ex Vivo Manufacturing Processes

The basic process for in vivo vs. ex vivo cell manufacturing is outlined below. Keep in mind that the types of cells used in therapies broadly differs and therefore there are specific process nuances for each.



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Cell Culture Manufacturing Considerations

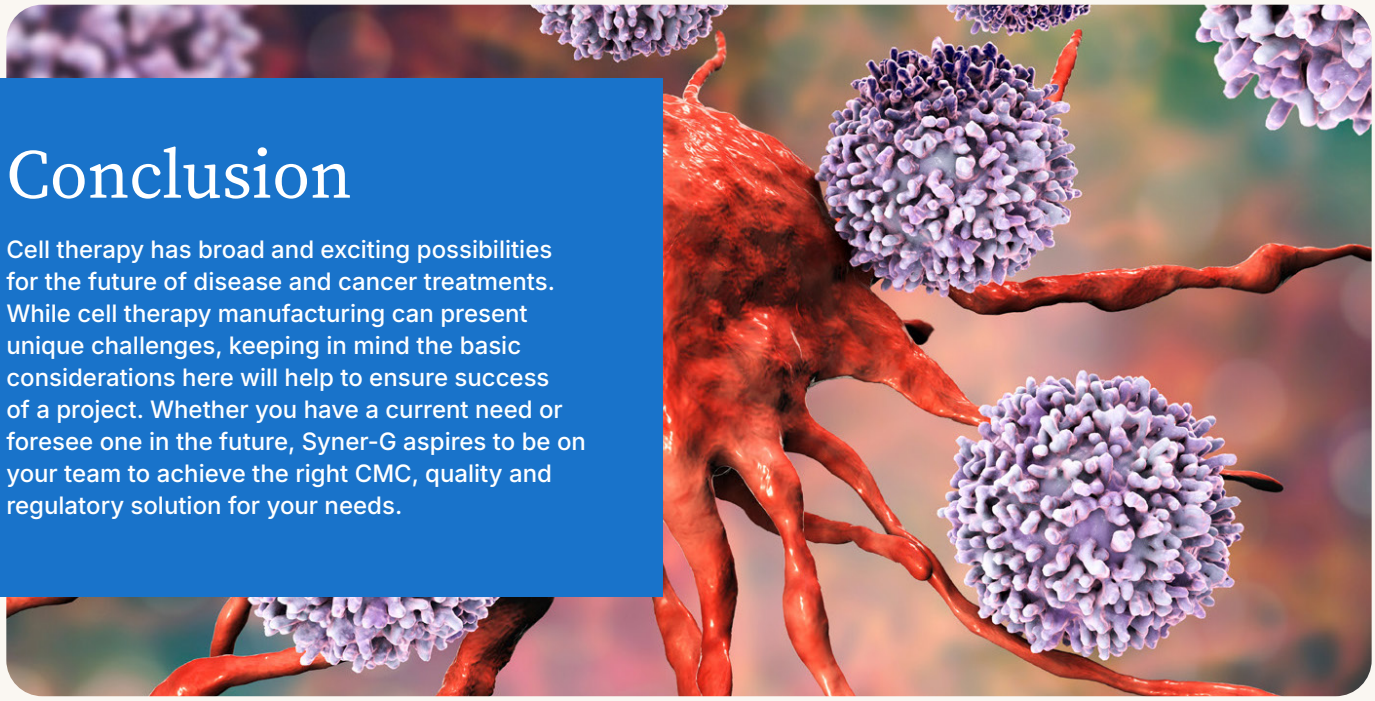
Cell culture remains a core component of cell therapy manufacturing. Serum free media or other animal-free media sources should be evaluated or at least considered when designing a new cell culture process. This will help to eliminate any issues surrounding animal origin, specifically bovine sources, to make for smoother regulatory submissions and global supply planning. It also helps to limit the introduction of adventitious agents to a therapeutic.

Supply Chain and Logistical Considerations for Cell Therapy

Cells are subject to much more regulation when shipping and sourcing from other countries. Additional import documentation is generally required to move cells across borders and can slow expected manufacturing timelines and create inventory challenges. Genetically modified cells are again subject to additional screening requirements. Transporting live cells can be challenging, and special requirements such a shipping studies must be completed in order to de-risk shipments. Sourcing courier companies with broad networks and easy access to dewars and other LN2 shippers can make shipping faster and less time consuming for internal staff. When developing cell manufacturing processes and selecting a CMO or internal manufacturing site, keep in mind where clinical or commercial manufacturing sites will be located. This will help guide and narrow geographic locations for manufacturing sites and storage facilities that will shorten the time to treat each patient.

Regulatory

In the US, cell therapy products are regulated by the FDA's Center for Biologics Evaluation and Research. In the EU, cell therapy products are categorized under advanced therapies and these products are designated as Advanced Therapy Medicinal Products. Given the novelty of these treatment modalities, the lack of significant pharmaceutical development precedence and the potential for increased risk to patients, the regulatory framework for the clinical development and commercialization has been minimal and conservative. Recent emergence of increased interest has resulted in issuance of several guidance documents from the FDA and EMA to facilitate the expedited development of safe and efficacious life saving cell therapies. Regulations are less stringent for testing up front due to complexity of manufacturing processes and necessary timing to implant therapies back into a patient.



Conclusion

Cell therapy has broad and exciting possibilities for the future of disease and cancer treatments. While cell therapy manufacturing can present unique challenges, keeping in mind the basic considerations here will help to ensure success of a project. Whether you have a current need or foresee one in the future, Syner-G aspires to be on your team to achieve the right CMC, quality and regulatory solution for your needs.

ABOUT

Syner-G

Syner-G is the premier solution provider of Chemistry, Manufacturing, and Controls (CMC) services for the life sciences industry. The company's approach is based on CMC 360™, a fully integrated suite of CMC solutions that encompasses pharmaceutical development, regulatory affairs, and quality/cGxP compliance. The entire Syner-G organization is built around the premise of guiding small molecule, biologics, cell and gene therapy, and medical device innovators through the CMC process.

Since its founding in 2007, Syner-G has enabled clients in their quest to bring life-saving and life-enhancing products to patients. Today, the company has grown to more than 100 employees globally, been recognized as one of the "Top 10 Drug Development and Consulting Services Companies" by Pharma Tech Outlook, and served as an integral part of more than 500 various types of successful regulatory filings. For customers looking for offshore resources, Syner-G also offers CMC services based in India. Syner-G's operations in India follow the same CMC 360™ model used in the U.S., further differentiating the company from typical CMC consultants.

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