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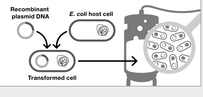
Cell therapy manufacturing workflow

Cell therapies offer an exciting new treatment paradigm for patients, but the development journey is often far more complex than traditional medicines. Beyond the initial cell type or autologous versus allogeneic decision, there is genetic modification, different delivery methods, and other factors to consider that greatly impact the manufacturing strategy.

At Thermo Fisher Scientific, we understand your cell therapy manufacturing process is as unique as you are, and that's why we offer flexibility and choices in manufacturing strategies, equipment, and methods. This infographic presents a high-level example of a genetically modified cell therapy workflow, introduces some of the manufacturing strategy choices you may be presented with, and ends with a brief overview of Thermo Fisher's cell therapy manufacturing services.

Plasmid production → Viral vector production → Cell isolation → Genetic modification → Cell expansion → Fill-finish, cryopreservation → Cold chain logistics

Plasmid & viral vector production

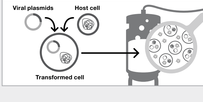


Plasmid production

Transform plasmid into *E. coli*, replicate via cell expansion, then harvest, lyse, and purify resulting plasmids.

Viral vector expansion

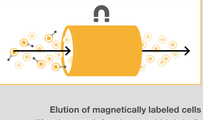
Viral plasmids and host cells are transduced into host cells, which are expanded to replicate the viral vectors. The host cells are then lysed, and viral vectors are harvested and purified.



Cell isolation

Label specific cell type(s)

Specific cells are labeled with antibodies and magnetic particles.

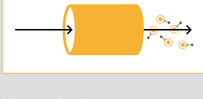


Magnetic separation of cell types

Cells then flow through a magnetically charged column where non-labeled cells are washed through and magnetically labeled cells are captured within the column.

Elution of magnetically labeled cells

When the magnetic force is removed, labeled cells are eluted from the column. It is possible to isolate cells via both positive and negative (untouched) selection. This example shows positive selection.



Isolation efficiency | Recovery | Purity

Characterization of isolated cells

Cell characterization factors to consider for isolation include number and phenotype of isolated cells, efficiency, purity, and recovery of desired cell type.

Genetic modification

	Viral	Electroporation	Nanoparticles
Pros	High efficiency	Delivery of multiple genes	Low cytotoxicity
Cons	No co-delivery of multiple genes	Challenges with cytotoxicity and scale	Low efficiency

Design and decide on delivery method

There are viral and nonviral options for delivery of genetic material. Choosing viral or nonviral delivery strategies is an important step in the therapeutics design process.

Nonviral delivery of genetic material

Two popular options for nonviral delivery of genetic material into cells are electroporation and nanoparticles.

Viral delivery of genetic material

Two popular options for viral vehicles for delivery of genetic material are lentivirus (LV) and adeno-associated virus (AAV).

Editing efficiency | Genomic validation | Functionality

Characterization of genetically modified cells

Cell characterization factors to consider for genetic modification include editing efficiency (% edited versus non-edited cells), validation of genomic material, and functionality.

Cell expansion

Seed cells into culture vessels

Genetically modified cells are seeded into culture vessels for expansion. Vessel choice can impact cell health, viability, and expansion potential and thus represents an important strategic choice. While static cultures are still utilized, the industry is trending toward dynamic methods such as rocking motion and stirred-tank bioreactors.

Optimize cell growth and expansion

As cells expand, nutrients are depleted, and addition of the right nutrients at the right time is critical for cell health and expansion. There are many choices in culture media systems, and choosing the right one with attributes optimized for GMP clinical and commercial manufacturing can be imperative to success.

Characterization of expanded cells

Cell characterization factors to consider for expansion include fold expansion, phenotype, functionality, and viability.

Fold expansion | Phenotype | Functionality | Viability

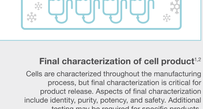
Fill-finish, cryopreservation

Harvest and formulate

The expanded cells go through wash and volume reduction before they are formulated into the final product, which can be a single dose or multiple doses.

Fill into final product containers

The final cell product is filled into primary packaging containers (bags or vials), sealed, and prepared for cryopreservation as needed.



Cryopreserve final cell product

If a cell therapy product calls for cryopreservation, it will be transferred to control-rate freezers and then stored before final transportation.

Final characterization of cell product[1,2]

Cells are characterized throughout the manufacturing process, but final characterization is critical for product release. Aspects of final characterization include identity, purity, potency, and safety. Additional testing may be required for specific products.

Identity | Purity | Potency | Safety

Cold chain logistics

Temperature-controlled storage and distribution

Maintenance of chain of custody and temperature requirements during storage and distribution are critical to ensure that the drug product arrives on time, in full, and at temperature.

Ensure IND readiness for the clinic and beyond

Thermo Fisher provides a foundation of support systems and technical expertise for your unique cell therapy manufacturing process that can help ensure IND readiness for the clinic and beyond. We are setting the pace of evolution in cell therapy manufacturing by offering flexibility and broad expertise in a variety of existing systems, balanced by continual assessment and incorporation of new product innovations. Our approach to manufacturing readiness balances the need for speed with an unwavering focus on quality, and configurable fit-for-purpose suites ensure long-term scalability for autologous and allogeneic products.

Upstream: Plasmid production → Viral vector production → Cell isolation → Genetic modification → Cell expansion
Cell therapy manufacturing services
Downstream: Fill-finish, cryopreservation → Cold chain logistics

Cell therapy process development and cGMP manufacturing services with integrated upstream and downstream offerings include:

1. Modified (viral or nonviral) and non-modified manufacturing processes for immune cells (T, NK) and stem cells (iPSC, MSC, HSC) utilizing various existing and emerging manufacturing systems
2. GMP readiness assessment of raw materials, equipment needs, and process optimization, including transition to closed manufacturing
3. Dedicated program management, regulatory support, and analytical development and testing services

Learn how Thermo Fisher Scientific can deliver your life-saving cell therapies to patients with confidence.

References

1. FDA guidance document: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs). 2020. https://www.fda.gov/media/113760/download.
2. FDA guidance document: Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products. 2022. https://www.fda.gov/media/156896/download.

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