An Introduction to Cell Therapy

The use of cells as a therapeutic agent has gained vast popularity.

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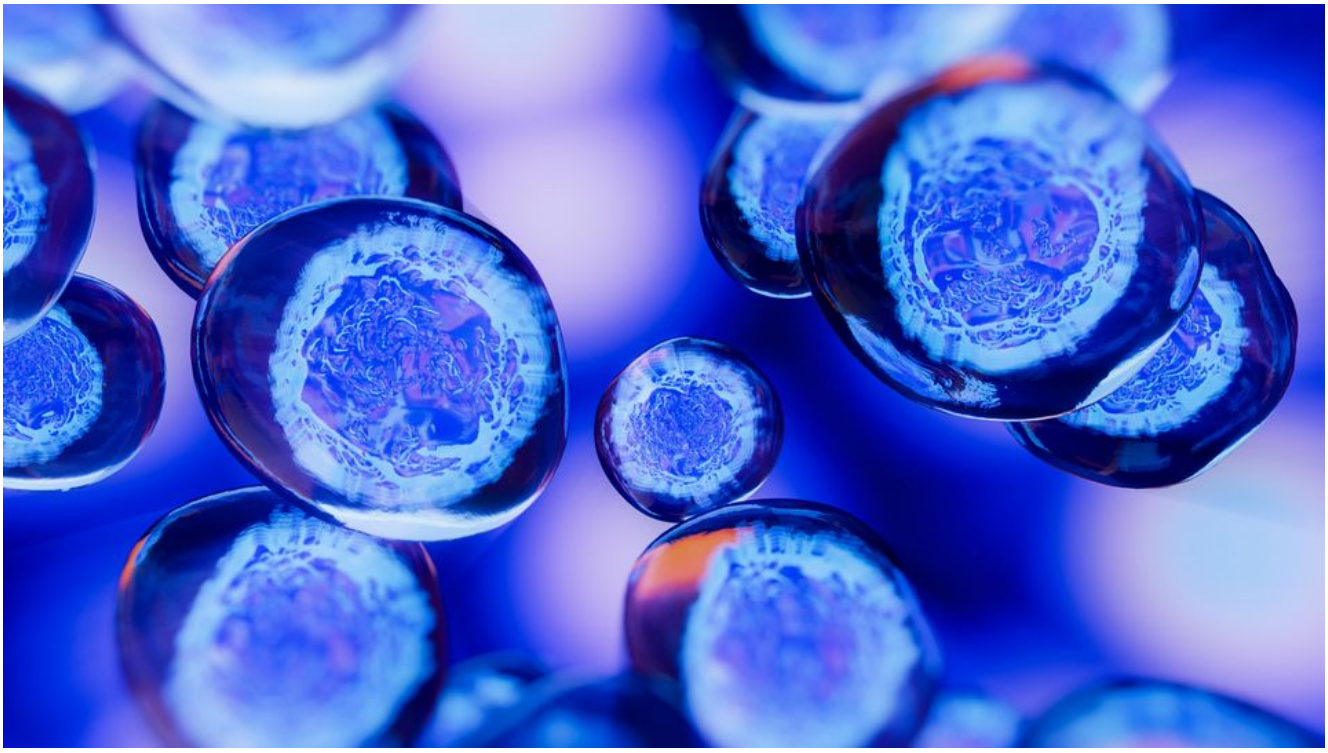

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What is cell therapy?

Using cellular products as a therapy is not a contemporary concept; literature dates back to the late 19th century, when Charles Édouard Brown-Séquard pioneered organotherapy (using organ extracts as a medical treatment) to suppress human aging.[1] While this failed as an anti-aging therapeutic, it did bring into discussion the use of cells as a therapeutic agent, which has gained vast popularity in the modern day.

The term cell therapy refers to the transfer of cellular materials into a patient for therapeutic purposes. The source of these cells can be either autologous (derived from the same person) or allogenic (derived from another person).[2] Cell therapy spans multiple therapeutic domains, including immunotherapy, cancer therapy and regenerative therapy. Here, we look to introduce the different types of cell therapies, including stem-cell and non-stem cell-based unicellular therapies as well as multicellular therapies. We also delve into how regulatory bodies approach cell therapy-based product regulation.

Types of cell therapy

Stem cell-based cell therapies

Stem cells are unspecialized and self-renewing cells that

can differentiate into any cell type. Their potential to differentiate toward a certain cell type is influenced by either internal or external signals that direct these cells to reprogram from proliferation to specialization. Stem cells are either used (therapeutically, e.g., by transplantation) or targeted (i.e., cancer stem cells that are produced by an oncogenic event, such as gene mutation causing tumor formation) by cell therapy and grouped into the categories below:

- **Pluripotent stem cells (PSC)** are a type of stem cell capable of differentiation into almost any type of specialized cell. These capabilities make them an attractive cell source for therapeutics. However, ethical issues arise over cells sourced from human embryos (embryonic stem cells) making their use a controversial therapy. Additional issues may arise from immune rejection by a host.[3] Clinical trials are ongoing to investigate their clinical efficacy as a regenerative medicine for cell differentiation and tissue repair.

- **Adult stem cells (ASC)** are developed but undifferentiated cells, essential for health and the replacement of dead cells. They replenish lost cells and can contribute towards growth or healing of cells by giving rise to progenitor cells – undifferentiated stem cells that are capable of specializing into

multiple different cell types within a certain organ or tissue family).[4] These cells include skin, neural, mesenchymal and hematopoietic stem cells. These cell types have been used in regenerative medicine to repopulate and reset tissue homeostasis after damage, as well as being investigated for the treatment of certain solid tumors since reports show that mesenchymal stem cells play a role in suppression as well as the progression of tumor growth.[5]

- **Cancer stem cells (CSC)** are found in many solid and nonsolid tumors. Like other stem cells, they possess the capacity for self-renewal and differentiation and form the bulk of a tumor. They have been considered a promising therapeutic target since their first identification in leukemia. These cells are thought to contribute to multiple tumor malignancies, such as recurrence, metastasis and heterogeneity, as well as multidrug and radiation resistance.[6,7]

The different types of cell therapy. *Credit: Technology Networks*

Non-stem-cell-based cell therapies

Non-stem cell therapies typically use somatic cells isolated from the human body, propagated, expanded and administered to patients as a curative/preventative therapeutic or as a diagnostic.[8] They are utilized as an *in vivo* source of enzymes, cytokines and growth factors. They are also employed for adoptive cell therapy (ACT) for cancers; for the transplantation of cells for metabolic disorders or as scaffolding cells to treat open wound injuries such as burns or lesions. Techniques for isolation and propagation are dependent on the cell type,

localization and specific use. Non-stem cell therapeutics can be grouped into either immune or non-immune cell types.

- **Non-immune cells** include fibroblasts, chondrocytes, keratinocytes, hepatocytes and pancreatic islet cells. Non-immune cell therapies – such as hepatocyte transplantation – have had a slow progression because of technological hurdles and limited supporting efficacy data. However, islet cell transplantation has shown promise for treatments of insulin deficiency, diabetes and pancreatitis, and has become a standard of care within some European countries, as well as Australia and Canada.[9] Fibroblast cell therapy is also being utilized as an alternative for mesenchymal stem cell (MSC) therapy. This is because fibroblasts are easier to harvest and more robust than MSCs, making them attractive for regenerative medicine.[10]

- **Immune cells** include dendritic cells, natural killer (NK) cells, and macrophages. These cells can be bioengineered to target specific antigens. This modification allows them to used in therapies for indications like cancer, infection and autoimmune diseases as well as for allogenic transplantation.[11] Engineered immune cells feature synthetic receptors. These are receptors produced

by introducing a new gene into the cell to allow surveillance of a target antigen, such as tumor surface protein. Examples of these engineered immune cells include chimeric antigen receptor T cells (CAR-T) and chimeric antigen receptor NK (CAR-NK) cells, which have become a popular platform for cell therapeutics by the biopharmaceutical industry.[12] Non-engineered cells, such as regulatory T cells, tumor-infiltrating lymphocytes (TILs) and virus-specific cytotoxic T lymphocytes (CTLs), have been used successfully as therapeutics.

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Multicellular therapies

Multicellular therapies are defined as therapies that contain at least two stem cell and or non-stem cell types that are cultured from either isolated cells or tissue extracts.[13,14] There is an emerging concept that a mixture of cell types (multicellular) is important in promoting long-term tissue repair versus that of a single cell therapy (unicellular), based on cell-cell communication that persists past embryogenesis and into regenerative processes.[15] Examples of multicellular therapies are explained below:

- **ACT products** are a multicellular therapy that include

different lymphocyte lineages, including T and B cells. ACT-based strategies involve the administration of either modified peripheral or tumor-resident immune cells to mount an immune response. Lymphokine-activated killer (LAK) cells are IL-2-activated peripheral blood mononuclear cells. NK cells, NK T cells, and T cells can all become LAK cells. LAK cells release cytolytic mediators that induce tumor cell killing. Cytokine-induced killer (CIK) cells are a heterogenous mixture of lymphocytes and NK T-Cells produced by PBMC or bone marrow cell stimulation with anti-CD3, IL-2, IL-1 and IFN-γ. Both LAK and CIK cells have been used to treat various hematologic malignancies and solid tumors.[16]

- **Scaffold-based cellular products** are an engineered technology that can deliver different cell types from a seeded tissue biocompatible 3D matrix built from natural or synthetic polymers. Scaffold-free products on the other hand are engineered from densely populated cells used as tissue analogs. These cells are protected by a cell-secreted, tissue-specific extracellular matrix that forms and adheres to a biological surface, such as an open wound.[17]

- **Stromal vascular fraction** (SVF) is a heterogeneous mixture of cells obtained from the processing of adipose tissue that consists of ASCs, granulocytes, monocytes, lymphocytes, pericytes and endothelial

progenitor cells. They are primarily used for the isolation of ASCs but are also being investigated for use in different clinical settings to promote neovascularization, cell repair and for immunomodulation.[18]

- **Stem cell transplant therapies** involve transplants from three stem cell sources: bone marrow, peripheral blood and umbilical cord blood.[19] They are typically used in cases where the body's stem cells are compromised, often due to hematologic malignancies or cancer therapies, to facilitate recovery post-treatment and promote immune system tolerance.

- **Bone marrow aspirate (BMA)-derived therapies** involve the harvest of bone marrow, and include various cell types including hematopoietic stem cells (HSCs), progenitor cells, MSCs, lymphocytes, neutrophils, platelets, red blood cells, eosinophils, basophils and monocytes. BMA-based therapeutics involve various mechanisms of action that drive tissue repair and immunomodulation.[20]

Regulation of cell therapy

Human cell therapies and cell therapy products are defined by the Food and Drug Administration (FDA) under Title 21 of the Code of Federal Regulations (CFR), Part

127.3(d) as, “Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient" .[21] Cell therapies are classified under vaccine, blood and biological materials, subcategorized under cellular-gene products and tissue products. As of late 2023, 65 non-genetically modified cell therapies have been approved globally, according to a report by The American Society of Gene & Cell Therapy (ASGCT).[22] As of June 2023, the FDA has approved 22 cell therapies, from which 8 products are umbilical cord blood derivatives, and 6 are CAR-T cell therapies.[23] This being said, cell therapies are becoming an established form of therapeutic for the treatment of many indications, including cancers and for regenerative medicine and many new products are within the pipeline for clinical trials.

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