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# Pharmacology of Stem Cell Therapy and Regenerative Medicines

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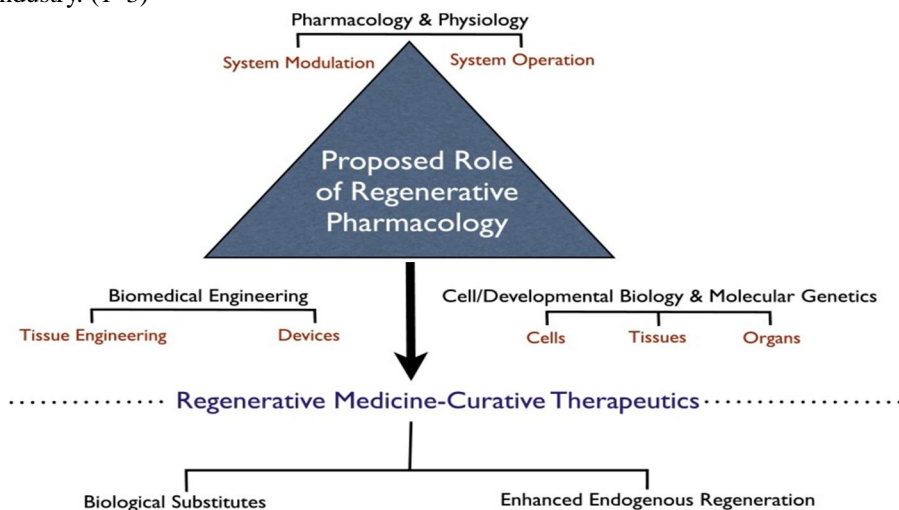
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**Abstract:** Regenerative medicine is a rapidly evolving multidisciplinary, translational research enterprise whose explicit purpose is to advance technologies for the repair and replacement of damaged cells, tissues, and organs. Scientific progress in the field has been steady and expectations for its robust clinical application continue to rise. The major thesis of this review is that the pharmacological sciences will contribute critically to the accelerated translational progress and clinical utility of regenerative medicine technologies. In 2007, we coined the phrase “regenerative pharmacology” to describe the enormous possibilities that could occur at the interface between pharmacology, regenerative medicine, and tissue engineering. The operational definition of regenerative pharmacology is “the application of pharmacological sciences to accelerate, optimize, and characterize (either in vitro or in vivo) the development, maturation, and function of bioengineered and regenerating tissues.” As such, regenerative pharmacology seeks to cure disease through restoration of tissue/organ function. This strategy is distinct from standard pharmacotherapy, which is often limited to the amelioration of symptoms. Our goal here is to get pharmacologists more involved in this field of research by exposing them to the tools, opportunities, challenges, and interdisciplinary expertise that will be required to ensure awareness and galvanize involvement. To this end, we illustrate ways in which the pharmacological sciences can drive future innovations in regenerative medicine and tissue engineering and thus help to revolutionize the discovery of curative therapeutics.

## I. INTRODUCTION

Historically, small molecule (i.e., compounds of <500–800 mol. wt.) pharmaceutical research and development has focused on compounds with increasingly selective mechanisms of action. This makes sense from a symptom-based approach to the treatment of disease, wherein one wishes to focus on the primary mechanism of action required for drug efficacy while simultaneously limiting off-target effects and minimizing adverse events/side effects. The development requirements for regenerative pharmacology will be much more demanding. In fact, the challenges associated with regenerative pharmacology, that is, curative therapeutics, will in many instances require complex mixtures of compounds [i.e., growth factors such as fibroblast growth factor (FGF), epidermal growth factor (EGF), platelet-derived growth factor, nerve growth factor (NGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), bone morphogenic proteins (BMPs), etc.] for restoration of tissue/organ function. These latter compounds have significantly higher molecular weights (generally ≈10,000 to >100,000 mol. wt.) than those traditionally developed by the pharmaceutical industry. (1–3)



## II. PHARMACOLOGICAL PRINCIPLES OF STEM CELL THERAPY

Stem cell therapy follows unique pharmacological principles because stem cells act as living biological agents rather than conventional chemical drugs. Their therapeutic effects are achieved through mechanisms such as differentiation into specialized cells, secretion of growth factors and cytokines (paracrine action), immunomodulation, and stimulation of the body's natural repair processes. Unlike traditional drugs, stem cell dosage is determined by cell number, viability, and functional potency, and their pharmacokinetics involve administration, migration (homing) to injured tissues, survival, and eventual clearance or integration into host tissues. The route of administration, including intravenous, local, or intrathecal delivery, significantly influences efficacy and safety. Understanding these principles is essential for optimizing therapeutic outcomes while minimizing adverse effects in regenerative medicine. (2,4,5)

Stem cell therapy follows different pharmacological principles compared to conventional drugs because stem cells act as living biological agents. These cells produce therapeutic effects by differentiating into specialized cells or by releasing growth factors and cytokines that promote tissue repair and regeneration. In stem cell therapy, the dose is based on the number, viability, and potency of cells rather than milligrams or milliliters. The pharmacokinetics of stem cells include their administration, distribution to injured tissues (homing), survival, and eventual clearance from the body. The route of administration, such as intravenous or local injection, plays an important role in determining the effectiveness and safety of the therapy. (6,6–8)

## III. BACKGROUND—BIOLOGY AND HISTORICAL DEVELOPMENT

Stem cells, present in both embryonic and adult tissues, possess remarkable abilities for self-renewal and differentiation into various functional cell types. These cells are categorized based on their developmental potency, which indicates the diversity of cell types they can produce. Totipotent cells, such as the zygote, have the highest differentiation potential and can form all cell types of an organism, including extraembryonic tissues. Pluripotent cells, such as embryonic stem cells, can self-renew and generate all cell types of the body but cannot form extraembryonic tissues. Multipotent cells, including hematopoietic and mesenchymal stem cells, can differentiate into cells within a specific lineage. 7 Oligopotent cells, such as myeloid stem cells, have a more limited differentiation potential. Unipotent cells, such as spermatogonial stem cells, can differentiate into only one cell type. The use of zygote-derived totipotent cells and embryonic stem cells is strictly restricted due to ethical issues, rendering them impractical for therapeutic use. There is extensive ongoing research focused on harvesting terminally differentiated cells from patients, converting them into induced pluripotent stem cells (iPSCs), and differentiating them into specialized cells that can be administered into the patients as therapies. In 2019, the first clinical trial of this kind using iPSC-derived natural killer cells were tested in patients with cancer. 8 Despite their potential, iPSC clinical studies are at its infancy and currently account for only a small number of clinical trials. In contrast, multipotent cells, such as HSCs and MSCs, make up the majority of current clinical trials. These will be the focus of this review, although other less common stem cell types will also be discussed. (4–6,9)

### A. Hematopoietic Stem Cells

HSCs are multipotent cells capable of differentiating into blood cells. Thus, HSC transplantation is well-established for managing and potentially curing numerous hematologic diseases by reconstituting blood cells as a regenerative therapy or reprogramming the immune system as immunotherapy. Current HSCT procedures involve collecting HSCs from donors, purifying them, and transferring them to patients following preparative immunosuppressive conditioning. In certain cases, the purified HSCs are modified and expanded ex vivo before transplantation to enhance their therapeutic potential. 10 Since the initial demonstrations of HSCT's feasibility and clinical utility, the protocol has been significantly refined to improve therapeutic outcomes and reduce transplant-related complications. (10–12)

The progress in HSCT began in the 1950s. Edward Thomas first introduced the procedure of allogeneic HSCT, transferring bone marrow cells from normal healthy donors to six patients in 1957. All patients in this trial died within 100 days post-transplantation due to human leukocyte antigen (HLA) mismatching, which was discovered in 1969 as a critical factor for the safety of allogeneic HSCT. In the 1970s, the shortage of HLA-matched donors remained a major bottleneck for HSCT, with only around 25% of patients in need having HLA-matched stem cell donors. 13 This challenge of HSCT was addressed with the development of stem cell isolation and cryopreservation protocols for autologous peripheral blood and allogeneic umbilical cord blood. The first autologous HSCT was performed in humans in 1976, and the first umbilical cord blood allogeneic HSCT was conducted a decade later in 1988. Over time, these developments have enhanced HLA-matching flexibility, improved HSC availability, and thus broadened the applicability of HSCT. (1,7,13)

**B. Mesenchymal Stem cells**

MSCs are a distinct class of multipotent cells known for their ability to differentiate into various mesodermal cell types and their capacity to modulate the immune system. Consequently, MSCs have been extensively studied for both regenerative and immunomodulatory applications in clinical settings. Compared to HSCs, MSCs have a relatively shorter history in clinical research, spanning about four decades. The first infusion of MSCs in a patient was reported in 1995, marking the beginning of a broad exploration of their clinical potential. (13–15)

MSCs can be isolated from multiple sources, such as bone marrow and adipose tissue. They can also be obtained from traditionally discarded sources like umbilical cord tissue and placenta, which are advantageous for clinical translation. A typical clinical dose of MSCs, ranging from 100 to 150 million cells, can be isolated from just mL of bone marrow aspirate. These cells can be readily grown and expanded in culture and have demonstrated the potential to differentiate into various mesenchymal tissue lineages including bone, cartilage, fat, and tendon under specific in vitro conditions. (8,14,16)

**C. Major Advances in Stem Cell Research**

Thanks to technological advancements and a better comprehension of cellular biology, stem cell research has advanced significantly over the last ten years. Researchers have improved their medicinal use, addressed safety problems, and increased their capacity to manipulate stem cells. In addition to increasing the possibility of stem cell-based treatments, these developments have brought up new moral and scientific issues. This section lists recent discoveries that have influenced the field, including induced pluripotent stem cells (iPSCs), organoids and disease Modeling, gene editing and CRISPR-Cas9, and clinical applications. (3,17–19)

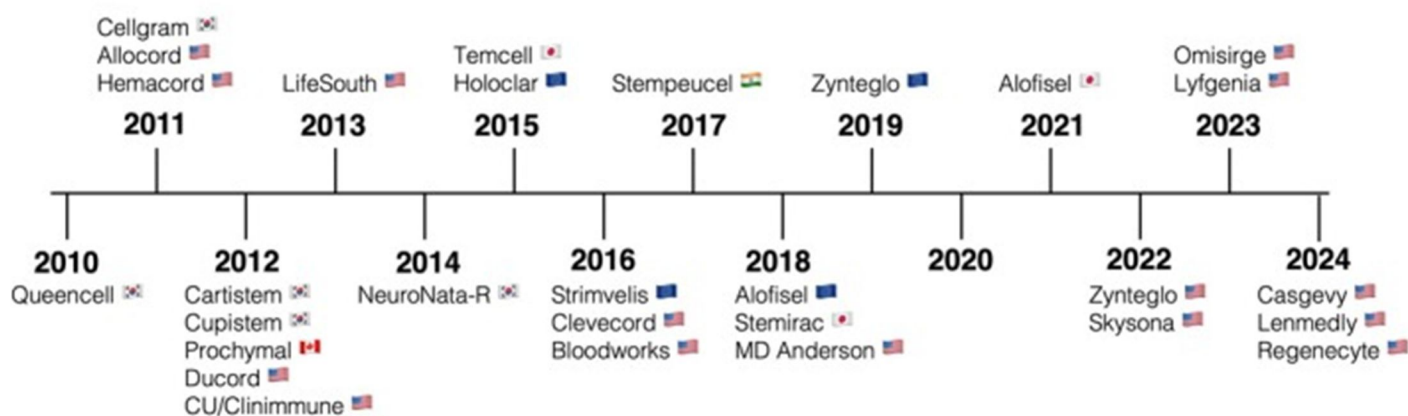
**D. Induced Pluripotent Stem Cells (iPSCs)**

iPSCs have transformed stem cell research and regenerative medicine as a flexible and moral substitute for embryonic stem cells (ESCs). Since their development, iPSCs have demonstrated enormous promise in drug discovery, disease modeling, and possible clinical uses. However, several issues still hampered their complete therapeutic implementation. (20–22)

Adult cells are reprogrammed into an embryonic-like pluripotent state by introducing transcription factors known as iPSCs. Shinya Yamanaka and Kazutoshi Takahashi initially made this revolutionary finding in 2006 when they successfully reprogrammed mouse fibroblasts using four essential transcription factors: Oct3/4, Sox2, Klf4, and c-Myc. A significant turning point in stem cell research was reached in 2007 when the method was modified for use with human cells. (23–25)

**E. Approvals of Stem Cell Therapy**

**Timeline of stem cell approvals 2010-2024**



**IV. APPROVED HSC PRODUCTS**

Notably, 16 HSC-based cell therapy products have been approved in the United States (Food and Drug Administration, FDA) and Europe (European Medicines Agency, EMA)—1 product by both agencies, by only the FDA, and 1 by only the EMA. The FDA and EMA are the only agencies to formally approve HSC products, despite the widespread clinical practice of HSCTs worldwide. Data suggest that 1.5 million HSCT procedures have been performed globally between 1957 and 2019, with an increasing trend toward the use of allogeneic sources.

The clinical prominence of HSCT continues to rise, as recent annual reports show more than 20,000 procedures in the United States and nearly 50,000 across Europe each year. Importantly, transplant rates outside the United States and Europe are on the rise as well. For example, an analysis of HSCTs for acute myeloid leukemia shows that while high-resource regions may have the greatest overall number of procedures, the sharpest increases are occurring in more resource-limited regions, particularly in Africa and the Eastern Mediterranean. Given the global prominence of HSCT, it is important to note that not all approaches or practices utilize approved products or require agency approval. The FDA Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products outlines two primary criteria for regulation: minimal manipulation and homologous use. If donor tissue undergoes minimal manipulation (i.e., no novel methods or protocols involving cellular engineering, manufacturing, or other modification) and is transplanted to perform the same basic function (e.g., bone marrow tissue is used to replace, reconstitute, or supplement the hematopoietic system), the cells or tissue used do not require FDA approval. (18,26–28)

## V. CONCLUSION

Stem cell therapy and regenerative medicine represent a major shift in how diseases are treated, moving beyond symptom management toward true tissue repair and functional restoration. The concept of regenerative pharmacology highlights the importance of applying pharmacological principles to living therapies such as stem cells, which behave very differently from conventional drugs. Understanding factors such as cell dose, delivery route, survival, and interaction with the host environment is essential for translating laboratory discoveries into safe and effective clinical treatments.

Over the years, significant progress has been made, particularly in the clinical use of hematopoietic and mesenchymal stem cells, as well as in the development of induced pluripotent stem cells. These advances have expanded therapeutic possibilities while also revealing new challenges related to safety, regulation, and long-term outcomes. Despite these hurdles, the growing success of approved stem cell therapies demonstrates the real potential of regenerative approaches to transform modern medicine.

Ultimately, the future of regenerative medicine depends on strong interdisciplinary collaboration between pharmacologists, biologists, clinicians, and engineers. By integrating pharmacological science with stem cell biology, regenerative pharmacology can help guide the development of more precise, reliable, and curative therapies, bringing regenerative medicine closer to routine clinical practice and improving patient outcomes worldwide.

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