ADVANCES IN STEM CELL THERAPY AND REGENERATIVE MEDICINE

Mary Sheela David[1], **Mini Rani Mary Beth**[1], **Safia Ali Belal**[1], **Maria Blesilda Bonto-Llaguno**[2], **Sadguna Mupparpu**[3], **Vidhya Thirunavukkarasu**[1]

[1]Lecturer, Department of Nursing, College of Applied Medical Sciences King Faisal University,Kingdom of Saudi Arabia. msheela25@yahoo.com

[2]Lecturer, Department of Nursing, College of Applied Medical Sciences King Faisal University,Kingdom of Saudi Arabia. miniranimarybeth@gmail.com

[3]Assistant Professor, Department of Nursing, College of Applied Medical Sciences King Faisal University,Kingdom of Saudi Arabia. sofy3131@gmail.com

[4]Assistant Professor, Fakeeh College for Medical Sciences and Fakeeh Care Group, Jeddah, Kingdom of Saudi Arabia

[5]Assistant Professor, Adventist College of Nursing. Bengaluru,INDIA sadgunasantosh@gmail.com

[6]Assistant Professor Department of Nursing,College of Applied Medical Sciences,King Faisal University,Kingdom of Saudi Arabia. drvidhyatr@gmail.com

ORCID IDs: 0000-0003-1187-1031; 0000-0001-6839-8076; 0000-0001-9822-9214; 0000-0002-7436-6318; 0009-0008-4736-5396; 0000-0002-7006-3694

ABSTRACT

Advances in stem cell therapy and regenerative medicine have expanded the possibilities for repairing, replacing, and regenerating damaged tissues and organs. Stem cells, because of their self-renewal and multilineage differentiation capacity, have emerged as central tools in both experimental and clinical regenerative strategies. Major progress in embryonic stem cells, induced pluripotent stem cells, adult stem cells, gene editing, organoid technology, biomaterials, and bioprinting has improved disease modeling, therapeutic development, and targeted tissue repair. Regenerative applications are being explored across multiple systems, including cardiovascular, neurological, musculoskeletal, ophthalmic, hepatic, pancreatic, and dental tissues. In parallel, cell-free approaches such as extracellular vesicles, exosomes, and secretome-based therapies are gaining attention as safer and more scalable alternatives to whole-cell transplantation. Despite these promising developments, several barriers continue to limit widespread clinical translation, including heterogeneity of cell products, manufacturing challenges, ethical concerns, immune rejection, tumorigenicity, and high treatment costs. Future progress will depend on standardized protocols, robust clinical trials, improved delivery systems, and personalized approaches that align therapeutic products with specific patient needs. Overall, stem cell therapy and regenerative medicine represent a rapidly evolving field with significant potential to transform modern healthcare.

Keywords: Stem Cell Therapy, Regenerative Medicine, Induced Pluripotent Stem Cells, Exosomes, Tissue Engineering.

How to cite this article: David MS, Beth MRM, Belal SA, Bonto-Llaguno MB, Mupparpu S, Thirunavukkarasu V. Advances in stem cell therapy and regenerative medicine. Int J Drug Deliv Technol. 2026;16(73s): 712-716. DOI: 10.25258/ijddt.16.73s.78

INTRODUCTION

Regenerative medicine is an interdisciplinary field that aims to restore, replace, or regenerate damaged tissues and organs by leveraging the unique proliferative and differentiation capacities of stem cells, bioactive molecules, and biomaterials. [1] Stem cells, defined by their ability to self-renew and differentiate into one or more specialized lineages, form the biological foundation of many contemporary regenerative strategies across cardiovascular, musculoskeletal, neurological, and dermatologic systems. [2] Over the past two decades, major advances such as the derivation of embryonic stem cells (ESCs), the discovery of tissue-specific adult stem cells, and the generation of induced pluripotent stem cells (iPSCs) have transformed conceptual and practical approaches to tissue repair. [3] Parallel developments in gene editing, organoid technology, 3D bioprinting, and cell-free approaches have expanded the therapeutic toolbox and enabled more precise modeling of human disease. [4]

Clinically, stem cell-based therapies are now being explored or implemented for a wide spectrum of indications, including ischemic heart disease, neurodegenerative disorders, bone and cartilage defects, chronic wounds, and immune-mediated conditions, with several products progressing into advanced-phase trials or limited clinical use. [4] Despite this progress, challenges related to cell sourcing, manufacturing, safety, immunogenicity, and long-term functional integration continue to limit broad translation and routine clinical adoption. [1] In this narrative review, we summarize the major types and sources of stem cells relevant to regenerative medicine, highlight recent technological advances, discuss organ- and system-specific applications, and emerging cell-free and alternative strategies. In addition with, current challenges, outline future directions, and provide practical considerations for clinicians who are increasingly encountering patients interested in, or eligible for, stem cell-based regenerative interventions.

STEM CELL TYPES AND SOURCES

Stem cells are broadly categorized by their developmental potential into totipotent, pluripotent, multipotent, and unipotent populations, each of which offers distinct advantages and limitations for regenerative applications. [3] Embryonic stem cells (ESCs), derived from the inner cell mass of blastocysts, are pluripotent cells capable of differentiating into virtually all somatic lineages, making them attractive for generating diverse cell types but also raising significant ethical, regulatory, and tumorigenicity concerns. Induced pluripotent stem cells (iPSCs), generated by reprogramming somatic cells through defined transcription factors, provide an autologous, patient-specific source of pluripotent cells that can be used for disease modeling, drug screening, and potentially personalized cell therapies, although issues of genomic instability, reprogramming efficiency, and differentiation fidelity remain. [5]

Adult or somatic stem cells, typically multipotent, reside in various tissues and maintain homeostasis and repair throughout life. Hematopoietic stem cells (HSCs) from bone marrow, peripheral blood, or umbilical cord blood represent the most established clinical example, routinely used for hematologic malignancies and inherited blood disorders, and increasingly combined with gene therapy approaches for conditions such as hemoglobinopathies. [4] Mesenchymal stem/stromal cells (MSCs) are non-hematopoietic, multipotent cells that can be isolated from bone marrow, adipose tissue, umbilical cord, placenta, and other perinatal tissues, and are characterized by their capacity for trilineage differentiation (osteogenic, chondrogenic, adipogenic), immunomodulatory effects, and paracrine secretion of trophic factors, making them one of the most widely investigated cell types in regenerative medicine. [6] Tissue-specific progenitor cells, including neural, cardiac, hepatic, and epithelial progenitors, offer a more lineage-committed source for organ-targeted regeneration, although their limited abundance, expansion capacity, and sometimes invasive harvesting procedures constrain their widespread use. [2]

Perinatal tissues such as umbilical cord blood, Wharton's jelly, amniotic fluid, and placenta constitute an increasingly important reservoir of stem and progenitor cells, combining relative ease of collection with favorable immunological properties and robust proliferative potential. [3] These sources are being explored not only for their cellular components (for example, cord blood HSCs, cord-derived MSCs) but also for their extracellular vesicles and exosomes, which contribute to the paracrine mechanisms underlying many regenerative effects. [7] In selecting a stem cell source for a given indication, key considerations include differentiation capacity, immunogenicity, scalability, genomic stability, risk of tumorigenesis, ethical acceptability, and regulatory status, all of which must be balanced against the clinical context and intended route of administration. A nuanced understanding of these diverse stem cell types and sources provides the foundation for rational design and implementation of next-generation regenerative therapies. [6,4,7]

ADVANCES IN STEM CELL TECHNOLOGIES

Recent progress in stem cell biology has shifted the field from simple cell replacement toward sophisticated engineered systems that improve control over cell fate, function, and delivery. [8] One major advance is the development of good manufacturing practice-compatible and xeno-free culture systems, which improve clinical safety, reduce contamination risk, and support large-scale expansion of stem cells for translational use. Single-cell omics, especially single-cell RNA sequencing, has also improved the characterization of stem cell heterogeneity and lineage commitment, helping researchers identify more stable and therapeutically relevant cell populations. [9]

Genome editing has further expanded the therapeutic value of stem cells by enabling correction of pathogenic mutations and creation of disease-specific cellular models. [10] CRISPR-based strategies are especially important for patient-specific iPSC platforms, where edited cells can be used for disease modeling, drug screening, and potentially autologous repair. [9] In parallel, organoid technology and 3D tissue engineering have made it possible to reproduce organ-like microenvironments that are far closer to native human tissues than conventional two-dimensional culture systems. These models are increasingly used to study development, test therapies, and explore regenerative strategies for complex organs such as the brain, retina, liver, and intestine. [10]

Another important advance is the use of biomaterials, scaffolds, hydrogels, and bioprinting to improve stem cell survival, engraftment, and spatial organization after transplantation. [8] These approaches help cells remain viable in hostile injury sites and can also direct differentiation through mechanical and biochemical cues. Finally, progress in cell tracking and monitoring, including nano-biosensing and imaging-based methods, is improving the ability to follow stem cell fate after administration and to assess treatment success more accurately. Together, these innovations are moving stem cell therapy from experimental transplantation toward precision regenerative medicine.

REGENERATIVE THERAPIES BY ORGAN/SYSTEM

Stem cell–based regenerative therapy has shown the broadest progress in the hematologic, neurologic, cardiovascular, ophthalmic, musculoskeletal, and endocrine systems. [10] Hematopoietic stem cell transplantation remains the most established clinical application and is widely used for malignant and nonmalignant blood disorders. [11] In neurology, stem cell approaches are being explored for Parkinson's disease, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, and Alzheimer's disease, with most strategies aiming to replace lost cells, support endogenous repair, or modulate inflammation. Although many neurologic interventions remain in early clinical stages, the field has already shown that carefully designed cell products can be delivered safely in selected settings. [7]

In cardiovascular medicine, stem cell therapy has been studied for myocardial infarction, heart failure, and ischemic injury, with outcomes focused on improving perfusion, reducing fibrosis, and enhancing ventricular function. [7] The 2024 review on stem-cell therapy notes that cardiac, diabetes, spinal cord, and tissue-repair applications remain among the most actively investigated areas. [6] In ophthalmology, regenerative therapy has advanced particularly well because the eye is relatively accessible for local delivery and immune protection; retinal pigment epithelium replacement and iPSC-derived retinal cell approaches are among the most visible examples. [8] Diabetes research has also remained a major target, especially beta-cell replacement using pluripotent stem cells and encapsulation systems designed to protect transplanted cells from immune attack. [10]

Dentistry and musculoskeletal repair have shown strong translational potential because tissue defects in bone, periodontal structures, pulp, and cartilage are highly suitable for cell-assisted regeneration. [11] Dental pulp stem cells, periodontal ligament stem cells, and bone marrow-derived mesenchymal stem cells are being explored for pulp-dentin regeneration, periodontal repair, and mandibular bone reconstruction. [12] In autoimmune and inflammatory disease, mesenchymal stem cells are often used not primarily as replacement cells but for their immunomodulatory and anti-inflammatory effects. [13] This organ-based expansion of stem cell therapy reflects a shift from one-cell-one-disease thinking toward a broader regenerative framework that combines replacement, repair, and immune regulation.

CELL-FREE THERAPIES AND ALTERNATIVES

Cell-free regenerative approaches have gained strong attention because they may preserve many therapeutic benefits of stem cells while avoiding problems such as low engraftment, immune rejection, uncontrolled differentiation, and tumorigenicity. [14] Among these alternatives,

extracellular vesicles, exosomes, secretome products, and conditioned media are the most widely studied. [15] These products carry proteins, lipids, mRNA, and microRNA that can influence inflammation, angiogenesis, tissue repair, and apoptosis without transferring live cells into the patient. This makes them attractive for situations where living-cell transplantation is impractical or unsafe. [6]

MSC-derived exosomes and secretome-based products are especially prominent because mesenchymal stem cells exert many of their beneficial effects through paracrine signaling rather than direct tissue replacement. [16] Cell-free approaches may be easier to store, standardize, and administer than whole-cell products, and they are likely to have a lower risk of ectopic tissue formation or neoplasia. [17] These limitations mean that cell-free therapy is promising, but still requires stronger manufacturing and regulatory frameworks before broad clinical implementation.

Other alternatives include biomaterial scaffolds, decellularized matrices, growth-factor-based therapies, and endogenous regeneration strategies that stimulate resident stem cells rather than transplanting new ones. [18] In some settings, these strategies may be combined with cells or exosomes to create hybrid regenerative systems with better durability and tissue integration. Overall, the move toward cell-free and hybrid regenerative therapies reflects an effort to improve safety, consistency, and scalability while maintaining biological efficacy. [19]

CHALLENGES

Stem cell therapy has advanced rapidly, but several barriers still limit routine clinical use. A major challenge is producing cell products that are sufficiently pure, stable, and functional, because differentiation protocols may still generate off-target cells or heterogeneous populations with variable potency. [20] In addition, poor engraftment, limited survival after transplantation, and inadequate functional integration into host tissue remain central reasons for inconsistent clinical benefit. [21] These problems are especially important in ischemic, inflamed, or fibrotic tissues, where the local microenvironment can impair cell retention and survival. [22]

Manufacturing and standardization are another major hurdle. Clinical-grade products require xeno-free culture, reproducible expansion methods, validated potency assays, and strict quality control, yet these are still not harmonized across centers. [22] Regulatory complexity, high cost, and difficulties in scaling up production further limit accessibility and slow translation from bench to bedside. Ethical issues also remain relevant, especially for embryonic stem cell-derived products and gene-edited cell therapies, where long-term safety, informed consent, and oversight are essential. [23]

Another important challenge is the weakness of preclinical-to-clinical translation. Many animal models do not fully reproduce human disease, so promising laboratory findings may fail in humans because of differences in immune response, delivery route, disease stage, or outcome measures. Finally, unproven commercial stem cell interventions and “stem cell tourism” continue to create patient-safety concerns, making evidence-based practice and regulatory vigilance especially important. [21]

FUTURE DIRECTIONS

The future of regenerative medicine is likely to move toward more precise, personalized, and safer therapies. Human pluripotent stem cells, especially iPSCs, will remain central because they can generate specialized cell types for disease modeling, drug testing, and autologous cell replacement. [24] Gene editing is expected to play a larger role by correcting inherited defects before transplantation and by improving cell performance through targeted engineering. [25] At the same time, improvements in differentiation protocols and organoid systems should make it easier to generate more authentic and clinically useful cell products. [26]

A second future direction is hybrid regenerative therapy, where cells are combined with biomaterials, hydrogels, scaffolds, or encapsulation systems to improve delivery and survival. [27] These approaches can protect transplanted cells from immune attack, increase local retention, and create a more favorable repair environment. [23] In parallel, cell-free strategies such as extracellular vesicles, exosomes, and secretome-based products are likely to expand because they may provide many of the paracrine benefits of stem cells with lower risk and simpler storage. These alternatives are especially attractive for chronic diseases where repeated or long-term therapy may be needed. [24]

Future progress will also depend on better manufacturing and trial design. Automated bioreactors, standardized potency assays, and harmonized regulatory frameworks will be needed to make cell products more reproducible and affordable. [23] Clinical trials will increasingly need objective biomarkers, longer follow-up, and more meaningful functional outcomes rather than relying only on subjective improvement. [20] As the field matures, the most successful therapies will likely be those that combine biological precision with scalable production and clear clinical endpoints. [23]

PRACTICAL CONSIDERATIONS FOR CLINICIANS

Clinicians should first confirm whether a stem cell intervention is evidence-based, investigational, or unproven before recommending it to patients. Patient selection is critical, because benefit depends on disease type, severity, tissue environment, and the specific cell product being used. [28] Informed consent should clearly explain expected benefit, limitations, alternative treatments, the experimental nature of many interventions, and possible risks such as infection, immune reaction, ectopic tissue formation, or lack of efficacy. This is especially important when patients request treatment after seeing commercial advertising or nonregulated clinic claims.

Clinicians should also pay attention to product quality and regulatory status. Ideally, the therapy should come from a licensed facility with documented manufacturing standards, traceability, potency testing, and institutional or national regulatory approval. Route of delivery matters as well, because intravenous, local, intrathecal, or scaffold-based administration all have different safety and efficacy profiles. Follow-up should include structured monitoring for adverse events, treatment response, and long-term complications, especially when the therapy involves pluripotent or gene-edited cells. [29]

Clinicians should also counsel patients realistically and discourage participation in unverified commercial programs. A useful practice is to ask whether the therapy has published clinical trial data, whether the product is manufactured under GMP conditions, and whether the protocol includes safety monitoring and ethics oversight. Multidisciplinary collaboration with surgeons, rehabilitation specialists, immunologists, and tissue-engineering teams can improve case selection and follow-up planning. In routine practice, the most important role of the clinician is to protect patients

from unsupported claims while guiding them toward evidence-based regenerative options.

CONCLUSION

In conclusion, advances in stem cell therapy and regenerative medicine have transformed the understanding of tissue repair by offering promising strategies for replacing damaged cells, restoring organ function, and improving outcomes across a wide range of diseases; however, despite major progress in stem cell technologies, organ-specific regenerative approaches, and cell-free alternatives such as exosomes and secretome-based therapies, routine clinical translation is still limited by challenges related to safety, standardization, manufacturing, cost, and long-term efficacy. The future of the field will depend on stronger clinical evidence, better regulatory oversight, improved biomaterial and gene-editing platforms, and a more personalized approach that matches the right therapy to the right patient, making regenerative medicine an increasingly important component of modern clinical practice.

REFERENCE

Maldonado VV, Patel NH, Smith EE, Barnes CL, Gustafson MP, Rao RR, Samsonraj RM. Clinical utility of mesenchymal stem/stromal cells in regenerative medicine and cellular therapy. Journal of biological engineering. 2023 Jul 11;17(1):44.

Jin Y, Li S, Yu Q, Chen T, Liu D. Application of stem cells in regeneration medicine. MedComm. 2023 Aug;4(4):e291.

Sadiq IZ, Abubakar FS, Katsayal BS, Ibrahim B, Adamu A, Usman MA, Aliyu M, Suleiman MA, Muhammad A. Stem cells in regenerative medicine: Unlocking therapeutic potential through stem cell therapy, 3D bioprinting, gene editing, and drug discovery. Biomedical Engineering Advances. 2025 Jun 1;9:100172.

Ebrahimi F, Pirouzmand F, Cosme Pecho RD, Alwan M, Yassen Mohamed M, Ali MS, Hormozi A, Hasanzadeh S, Daei N, Hajimortezayi Z, Zamani M. Application of mesenchymal stem cells in regenerative medicine: A new approach in modern medical science. Biotechnology Progress. 2023 Nov;39(6):e3374.

Stoltz JF, de Isla N, Li YP, Bensoussan D, Zhang L, Huselstein C, Chen Y, Decot V, Magdalou J, Li N, Reppel L. Stem cells and regenerative medicine: myth or reality of the 21th century. Stem cells international. 2015;2015(1):734731.

Hussen BM, Taheri M, Yashooa RK, Abdullah GH, Abdullah SR, Kheder RK, Mustafa SA. Revolutionizing medicine: recent developments and future prospects in stem-cell therapy. International Journal of Surgery. 2024 Dec 1;110(12):8002-24.

Kim W, Park E, Yoo HS, Park J, Jung YM, Park JH. Recent advances in monitoring stem cell status and differentiation using nano-biosensing technologies. Nanomaterials. 2022 Aug 25;12(17):2934.

Han H, Chen BT, Liu Y, Wang Y, Xing L, Wang H, Zhou TJ, Jiang HL. Engineered stem cell-based strategy: a new paradigm of next-generation stem cell product in regenerative medicine. Journal of Controlled Release. 2024 Jan 1;365:981-1003.

Kumar D, Gupta S, Gupta V, Tanwar R, Rani P, Bansal V. Stem Cells to Organoids: Pioneering the Future of Regenerative Therapies. Stem Cell Reviews and Reports. 2026 Jan;22(1):118-43.

Aly RM. Current state of stem cell-based therapies: an overview. Stem cell investigation. 2020 May 15;7:8.

Mirzapour SM, Jalali F. Stem cell therapy for regenerating periodontal bony defects: A narrative review. Journal of Advanced Periodontology & Implant Dentistry. 2025 Mar 3;17(1):1.

Ashri NY, Ajlan SA, Aldahmash AM. Dental pulp stem cells. Biology and use for periodontal tissue engineering. Saudi Med J. 2015 Dec;36(12):1391-9.

Huang Y, Wu Q, Tam PK. Immunomodulatory mechanisms of mesenchymal stem cells and their potential clinical applications. International Journal of Molecular Sciences. 2022 Sep 2;23(17):10023.

Wong RS, Tan EW, Ng NC, Goh BH. Mesenchymal Stem/Stromal Cell-Free Therapies: Challenges and Opportunities. Molecular Biotechnology. 2026 Jan 25:1-6.

Gill JK, Rehsia SK, Verma E, Sareen N, Dhingra S. Stem cell therapy for cardiac regeneration: past, present, and future. Canadian Journal of Physiology and Pharmacology. 2024 Jan 16;102(3):161-79.

Son Y. Recent advances in stem cell researches and their future perspectives in regenerative medicine. Tissue Engineering and Regenerative Medicine. 2017 Dec;14(6):641-2.

Li F, Fu C. Stem cell revolution: bridging the gap between research and clinical application. Stem Cell Research & Therapy. 2025 Nov 26;16(1):661.

Wang AY, Aviña AE, Liu YY, Kao HK. Pluripotent stem cells: Recent advances and emerging trends. Biomedicines. 2025 Mar 21;13(4):765.

Xu XL, Yi F, Pan HZ, Duan SL, Ding ZC, Yuan GH, Qu J, Zhang HC, Liu GH. Progress and prospects in stem cell therapy. Acta Pharmacologica Sinica. 2013 Jun;34(6):741-6.

Christiansen JR, Kirkeby A. Clinical translation of pluripotent stem cell-based therapies: successes and challenges. Development. 2024 Apr 1;151(7):dev202067.

Nguyen PK, Neofytou E, Rhee JW, Wu JC. Potential strategies to address the major clinical barriers facing stem cell regenerative therapy for cardiovascular disease: a review. JAMA cardiology. 2016 Nov;1(8):953-62.

Grogan S, Kopcow J, D'Lima D. Challenges facing the translation of embryonic stem cell therapy for the treatment of cartilage lesions. Stem Cells Translational Medicine. 2022 Dec 1;11(12):1186-95.

Mayeen NF, Salma U, Kasim NH, Mahmoud O, Haque N. Hurdles to overcome for mesenchymal stem cell translation from bench to bedside. World Journal of Stem Cells. 2025 Dec 26;17(12):114349.

Desgres M, Menasche P. Clinical translation of pluripotent stem cell therapies: challenges and considerations. Cell Stem Cell. 2019 Nov 7;25(5):594-606.

Mousaei Ghasroldasht M, Seok J, Park HS, Liakath Ali FB, Al-Hendy A. Stem cell therapy: from idea to clinical practice. International journal of molecular sciences. 2022 Mar 5;23(5):2850.

Christiansen JR, Kirkeby A. Clinical translation of pluripotent stem cell-based therapies: successes and challenges. Development. 2024 Apr 1;151(7):dev202067.

Gupta R, Losordo DW. Challenges in the translation of cardiovascular cell therapy. Journal of nuclear medicine. 2010 May 1;51(Supplement 1):122S-7S.

Nguyen PK, Neofytou E, Rhee JW, Wu JC. Potential strategies to address the major clinical barriers facing stem cell regenerative therapy for cardiovascular disease: a review. JAMA cardiology. 2016 Nov;1(8):953-62.

Grogan S, Kopcow J, D'Lima D. Challenges facing the translation of embryonic stem cell therapy for the treatment of cartilage lesions. Stem Cells Translational Medicine. 2022 Dec 1;11(12):1186-95.