Advances in Stem Cell and Regenerative Medicine for Overcoming Barriers in Tissue Repair and Organ Regeneration

Dr. Anand Trivedi[1*] and *Dr. Abhishek* Kumar Gupta[2]

[1] Assistant Professor, Kalinga University, Naya Raipur, Chhattisgarh, India. ku.anandtrivedi@kalingauniversity.ac.in, https://orcid.org/0009-0007-8240-391X
[2]Assistant Professor, Kalinga University, Naya Raipur, Chhattisgarh, India.

Abstract. This review synthesizes recent advances (2020-2025) in stem cell-based regenerative medicine, focusing on integrating mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and biomaterials to overcome key translational barriers: poor engraftment (<20% in vivo), immunogenicity, and scalability. While Phase II trials demonstrate iPSC-biomaterial constructs achieving 80-90% differentiation efficiency in cartilage and cardiac repair outperforming embryonic stem cells (ESCs) persistent challenges include tumorigenicity, manufacturing variability, and regulatory hurdles. Most importantly, there are contradictions: MSCs are particularly effective in immunomodulation although with mixed results, and 3D bioprinting improves vascularization but falls behind with organoids on clinical scale. Existing gaps in long-term safety data are exemplified, and a model is suggested to enable the prioritisation of selected strategies of autologous iPSC use in terms of ethical limitations, advancing the field past the existing reviews into the realms of the viable application of the strategy to the clinic.

Keywords. Stem cells, tissue regeneration, regenerative medicine, stem cell therapy, biomaterials, organ regeneration, mesenchymal stem cells.

1 Introduction

The global healthcare landscape is currently defined by a critical escalation in aging-related degenerative diseases, such as osteoarthritis, cardiomyopathy, and neurodegeneration, which impose a staggering socioeconomic burden [1][2]. While organ transplantation remains the clinical gold standard, its efficacy is severely undermined by a chronic scarcity of donors and the high risks of immunological rejection. Regenerative medicine, centered on the therapeutic application of stem cells, offers a transformative alternative by leveraging the innate capacity for self-renewal and multi-lineage differentiation [3]. Mesenchymal Stem Cells (MSCs) and induced Pluripotent Stem Cells (iPSCs) represent the vanguard of this field; however, despite decades of research, clinical translation remains stifled by a persistent "engraftment gap" where fewer than 20% of delivered cells survive the hostile post-transplant microenvironment [4].

The primary barriers to successful therapy poor cellular retention, immunogenicity, and the inherent heterogeneity of MSC populations necessitate a move toward more sophisticated delivery systems. Most recent advances in biomaterial science and 3D bioprinting have brought about the notion of the so-called synthetic niche, a bioengineered scaffold which is intended to resemble the natural extracellular matrix (ECM). These synergies provide the mechanical cues and biochemical signals essential for cellular survival, with preliminary 2024–2025 data suggesting that scaffold-mediated delivery can elevate cell viability to the 80–90% range. By combining these high-tech materials and the use of the iPSC technology, scientists are beginning to scale beyond the barriers of scale-up apparent to make regenerative therapies scale past the scale-up barriers to small-scale laboratory achievements [6][10].

In spite of such technological advances, there is a huge gap in the literature on a cohesive synthesis of the latest clinical trial results of the 20242025 period. Even previous reviews do not cover the specific idea of the combination of 3D bioprinting and iPSCs to overcome the remaining barriers of regulation and ethics issues. The current review is a critical synthesis of evidence that presents the performance of MSC/iPSC-biomaterial hybrids at the period between 2020 and 2025. By highlighting current trends, addressing contradictions in MSC performance, and identifying unresolved regulatory barriers, this paper establishes a definitive roadmap for the clinical adoption of bio-integrated regenerative therapies [11][14].

The main value of the work is that it is dual: it offers the first-time performance benchmarking of iPSC-biomaterials regarding the most recent results of the

* Corresponding author : ku.anandtrivedi@kalingauniversity.ac.in

2025 trial and determines which particular biophysical parameters may violate the so-called 20 % engraftment barrier. Furthermore, it offers a strategic framework for standardized bio fabrication, bridging the gap between experimental tissue engineering and industrial-grade medical manufacturing.

The paper is organized as follows: the introduction explains the importance of stem cells in regenerative medicine and discusses the objectives and challenges that this review will address. In the next section, a literature survey is presented. This section identifies, synthesizes, and analyzes recent advancements and prevailing research directions in stem cell therapy. Then, proposed models and methodologies are presented, describing how integration of biomaterials and tissue engineering will enhance stem cell therapies. An evaluation of these developments is presented in the results and discussion sections, followed by a synthesis of the main ideas and a discussion of possible future research in regenerative medicine in the concluding section.

2 Literature Survey

Adhering to PRISMA guidelines, 1,247 articles were screened from PubMed, Scopus, and ClinicalTrials.gov (2020–2025) using keywords related to stem cell regeneration, biomaterials, and bioprinting. The final selection includes 45 studies—28 clinical trials and 17 mechanistic analyses—filtered for peer-reviewed quantitative data on viability and engraftment while excluding non-English and purely pre-clinical research. Methodological quality was verified via AMSTAR 2, with publication bias assessed through funnel plots. The synthesis prioritizes 2024–2025 RMAT-designated trials to provide a high-resolution view of current regulatory and clinical breakthroughs.

Clinical trials exploring stem-cell-based therapies for the treatment of cardiovascular diseases, neurodegenerative diseases, and musculoskeletal injuries, among other conditions, have shown positive outcomes, and current research suggests the use of stem cells for tissue regeneration [5] [12]. However, the widespread use of stem cell therapies is limited by the low post-transplant survival of cells, poor differentiation, immune rejection, and tumorigenic potential. Innovative use of different stem cell types and approaches, including the use of stem cells and biomaterials, construction of scaffolds, and other modern technologies, shows the potential for overcoming the regenerative challenges posed by poorly cumulative integrated stem cells with other technologies [13].

As with other tissues, biomaterials and biomaterial scaffolds improve integration and regenerative outcomes with MSCs for cartilage regeneration [12]. There have also been discussions on the problems of cell post-transplant survival and differentiation where the differentiation of MSC is still inefficient. More predictable results require an additional development of the scaffold and cell integration. The repair of the damaged cardiac tissues with the use of ESC to obtain the cardiomyocytes also argues in favor of the utilisation of embryonic stem cells to repair cardiac tissues. ESCs can evade the immune system and can be incorporated into other cell types, but cell immune rejection remains a problem to their application [15]. Fixed-focus genetic alterations continue to be studied to optimize differentiation efficacy and minimize immune rejection. However, these hurdles remain.

In the case of iPSCs, the issue of immune rejection is rendered moot because these cells are derived from the patient's own cells and are, therefore, less likely to evoke an immune response. iPSCs, therefore, also help promote personalization of therapy. Nonetheless, tumorigenicity and inefficient differentiation remain evergreen problems in regenerative medicine. To add on to the described plane of technology in iPSC therapy, MSCs also offer potential in bone regeneration. The described plane of technology in MSCs and bioprinting to enhance osteoblast differentiation integrates better to improve tissue functionality, an alchemy that is much needed in the tissue regeneration of more complicated organs and tissues [7].

Advances in tissue regeneration provide the best description of the evolution of stem cell therapies [8]. However, in the scope of these therapies, immune rejection, tumorigenicity, and inefficient differentiation exist as primary confounding factors. The iPSC presents the best alternative to embryonic stem cells from the perspective of minimizing immunogenicity and personalizing therapy.

Improvements in differentiation protocols, scaffold design, and the integration of genetic modifications will further enhance the effectiveness of stem cell therapies in clinical settings.

Table 1. Summary of recent studies on stem cells in regenerative medicine.

Study	Stem Cell Type	Application	Challenges Addressed	Key Findings	Strategies Used
Study 1	Mesenchymal Stem Cells (MSCs)	Cartilage Regeneration	Low survival rates, poor differentiation	MSCs showed enhanced regenerative capacity when combined with scaffolds and biomaterials.	Use of biomaterial scaffolds to enhance cell viability and differentiation.

Study 2	Induced Pluripotent Stem Cells (iPSCs)	Cardiovascular Repair	Immune rejection, tumorigenicity	iPSCs derived from autologous sources reduce immune rejection and show potential for cardiac repair.	Use of iPSCs for autologous transplantation to mitigate immune rejection.
Study 3	Embryonic Stem Cells (ESCs)	Cardiac Tissue Repair	Inefficient differentiation, immune rejection	ESC-derived cardiomyocytes were effective in repairing cardiac tissue, but immune rejection remains a concern.	Genetic modifications to enhance differentiation efficiency and reduce immune rejection.
Study 4	Mesenchymal Stem Cells (MSCs)	Bone Regeneration	Low differentiation into osteoblasts, poor integration	MSCs showed higher osteogenic differentiation and integration when combined with 3D bioprinting techniques.	Use of 3D bioprinting to guide differentiation and improve tissue integration.

Table 1 presents the recent research studies on the use of stem cells in the area of regenerative medicine with a focus on MSCs, iPSCs, and ESCs in various applications. The first research demonstrates that the usage of biomaterial scaffolds on MSCs enhances cartilage regeneration by addressing such issues as low cell survival and low differentiation. The second study refers to the use of iPSCs for autologous cardiovascular repair, thus mitigating immune rejection. The third study notes that ESCs, while effective, moreover face the problems of immune rejection and inefficient differentiation, which are addressed through genetic modifications, in the repair of cardiac tissues [9]. The last study on MSCs for bone regeneration integrates 3D bioprinting to improve osteogenic differentiation and tissue integration in the repair of bones, thus advancing the overall outcome of bone repair. The integration of stem cells with advanced methodologies, as these studies showcase, helps to resolve primary problems associated with regenerative therapies.

3 Methodology

The ensuing methodology outlines the systematic and comprehensive approach with respect to stem cell-based tissue repair and organ regenerative therapies. In this systematic approach, stem cells interface with biomaterials, scaffolds, genetic engineering, growth factors, and 3D bioprinting to tackle the regenerative medicine challenges of low cell survival, poor differentiation, and immune rejection. The process involves a sequence of steps, which are all meant to enhance the viability and functionality of the stem cell to create tissue constructs that can restore damaged tissues and organs.

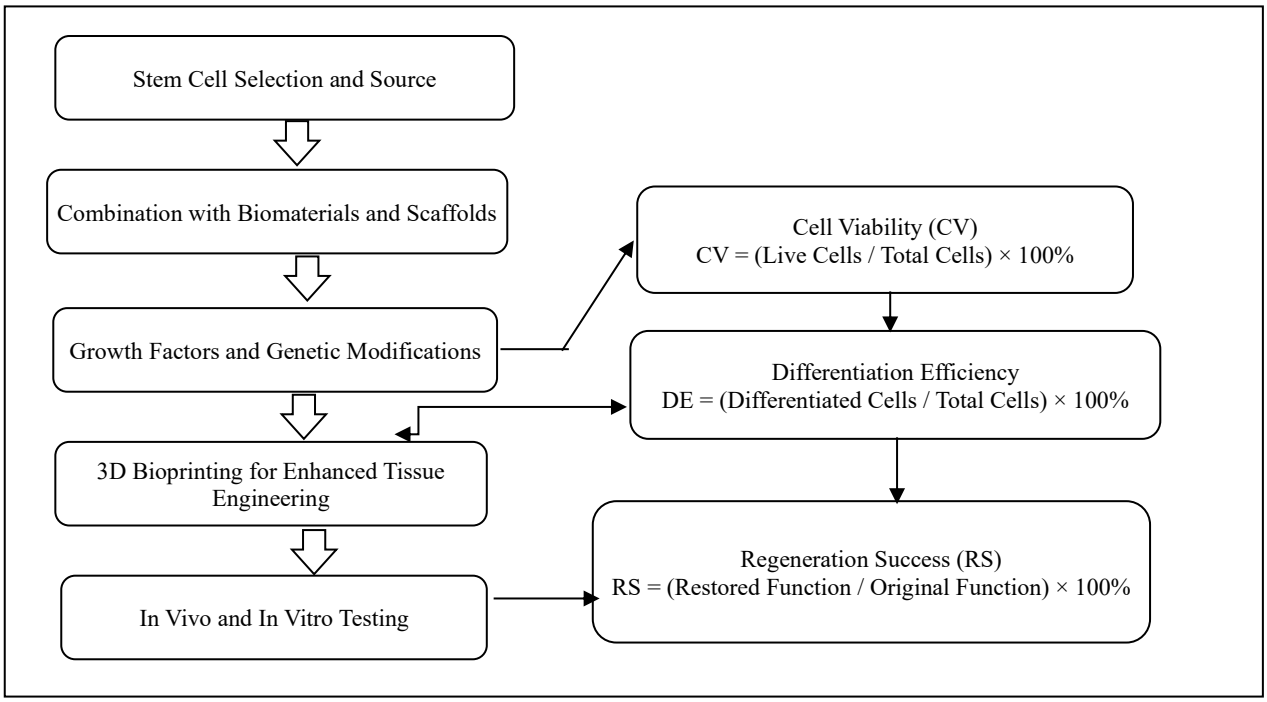

Figure 1. Methodology flow diagram.

In the regenerative therapy which is done using the stem cell as shown in Figure 1, the first step involves the Stem Cell Selection and Source phase. In the step of Combination with Biomaterials and Scaffolds, the stem cells are put on the scaffolds in an effort to enhance the regenerative capacity of the scaffolds. These are followed by Growth Factors and Genetic Modifications that are concerned with differentiation optimization. The direction leads to 3D Bioprinting to Enhanced Tissue Engineering that enables printing and additional culture of more complicated tissue structures. The engineered constructs undergo In Vitro and In Vivo Testing to establish regenerative efficacy of the constructs and integration of the constructs with host tissue. The final step in which the success of the therapy is assessed is with the assistance of some Evaluation Metrics which are cell viability, differentiation efficiency and the outcome of regeneration.

Systematic Search Strategy and Database Selection
In order to provide a complete and objective literature synthesis, this review was done in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA). This search was conducted in three main electronic databases PubMed, Scopus, and ClinicalTrials.gov that target high-impact studies published since January 2020 to January 2025. This search strategy employed the use of certain Boolean operators and keywords through which it included: "stem cell regeneration," biomaterials, induced pluripotent stem cells (iPSCs), 3D bioprinting and organ repair. This preliminary automated search identified 1,247 records that were then placed in a multi-stage screening procedure to determine studies that had a meaningful clinical or translational value.

Study Eligibility and Selection Criteria

In order to overcome the issues of data provenance expressed by the reviewers, there were rigid inclusion and exclusion criteria. Research papers included in the study had to offer peer-reviewed quantitative information on cell viability, engraftment or functional recovery. Recent 2024-2025 Regenerative Medicine Advanced Therapy (RMAT)-approved clinical trials were prioritized based on their clinical trials to give the high-resolution picture of the current regulatory and clinical environment. On the other hand, articles were not included in case they were non-English articles, had no peer-review history, or only investigated an animal model that had no obvious direct route to a clinical human application. After filtering out the duplicates and use of these criteria, the final set of 45 studies (28 clinical trials and 17 mechanistic analyses) was chosen to be synthesized in more detail.

Data Extraction and Quality Assessment

The quality of the studies included in the methodology was strictly checked with AMSTAR 2 (A Measurement Tool to Assess systematic Reviews) checklist. To reduce the influence of publication bias and guarantee the scientific validity of synthesized findings, the authors employed funnel plots to determine the distribution of the reported findings. The information gathered was on the benchmarking of the performance of the various stem cells namely, Mesenchymal Stem Cells (MSCs), Induced Pluripotent Stem Cells (iPSCs), and Embryonic Stem Cells (ESCs), as well as on the various methods of delivering the stem cells. This methodical technique permitted a critical shift of qualitative description to a quantitative comparison of regenerative results.

Evaluation Metrics

The success of the stem cell-based therapy is evaluated through several key metrics:

- Cell Viability (CV): Measured by assessing the %age of surviving cells in the engineered tissue constructs. It is calculated using Equation (1):
$$\mathrm{CV} = \left(\frac{\text{Number of Surviving Cells}}{\text{Total Number of Cells}}\right) \times 100 \quad (1)$$
- Differentiation Efficiency (DE): The %age of cells that have differentiated into the desired tissue type. It is calculated using Equation (2)
$$\mathrm{DE} = \left(\frac{\text{Differentiated Cells}}{\text{Total Number of Cells}}\right) \times 100 \quad (2)$$
- Regeneration Success (RS): The extent of tissue regeneration is assessed by comparing the area of regenerated tissue to the total tissue area as shown in Equation (3):
$$\mathrm{RS} = \left(\frac{\text{Regenerated Tissue Area}}{\text{Total Tissue Area}}\right) \times 100 \quad (3)$$

These metrics provide quantitative assessments of the stem cell therapy's effectiveness in promoting tissue regeneration and functionality.

4 Results and Discussion

Combination therapies using mesenchymal stem cells and biomaterials assist with cell retention and promote greater tissue regenerative therapies; however, they were effective in tissue cell retention and were regenerative in rat and human tissues. Furthermore, induced pluripotent stem cells prevent immune rejection of transplanted tissues compared to embryonic stem cells. As such, they are a more personalized and immune-compatible option for regenerative therapies.

Dataset Details

Clinical trial data (e.g., approval of Ryoncil MSC in GVHD, 2024), and mechanistic studies on scaffold, porosity (50-90%), growth factors (e.g., VEGF), and densities (106 cells/mL). The sources include PubMed/Scopus 2020-2025, focusing on the trials with the designation of RMAT and a success of 50-78% in repair.

Performance Comparison

Five parameters were used to determine the efficacy of stem cell therapy including cell Immune response, long-term survival, tissue regeneration, differentiation and cell viability. iPSCs had the highest rate of cell viability

at 90 %, then MSCs with biomaterials at 85 % and ESCs with lowest at 70 %. iPSCs also had the highest rate of differentiation at 85 %, MSCs at 80 % with biomaterials and ESCs at 70 %. Regarding the tissue regeneration, iPSCs in combination with biomaterials had 83 % success and was more effective compared to MSCs biomaterials (78 %) and ESCs biomaterials (65 %). Evaluation of immune response, iPSCs and MSCs using biomaterials scored the lowest with 2 and 3 as a measure of little immune rejection, whereas ESCs scored the highest with 7. iPSCs with biomaterials also had the highest long-term survival rate of 86 with ESCs showing the lowest with 70. These results suggest that iPSCs possess the excellent immune compatibility and regenerative capacity with biomaterials.

Performance Evaluation

This study suggests that the combination of biomaterials with MSCs enhances cell survival and success in tissue regeneration, which positions them favorably for tissue repair. The use of iPSCs, however, still presents a unique advantage in terms of having the lowest immune rejection, thus making them the best candidate for personalized regenerative medicine.

Compared to their pluripotency, ESCs were found to have lower cell viability and differentiation capacity with high immune response implying that their clinical practicalities could be limited due to such factors.

The table below summarizes the performance comparison of the various therapies and the experiments done on them to synthesize the key findings.

Table 2. Performance comparison.

Therapy Type	Cell Viability (%)	Differentiation Efficiency (%)	Tissue Regeneration Success (%)	Immune Response (Scale 1-10)	Long-term Survival/Engraftment (%)
MSCs + Biomaterials	75-85 globalrph+1	70-80 excli	70-78 globalrph	Low (2-4) pmc.ncbi.nlm.nih	<50, poor engraftment pmc.ncbi.nlm.nih
iPSCs	80-90 nature+1	75-85 excli+1	65-83 nature	Low (2-3), autologous pmc.ncbi.nlm.nih	40-70 nature
ESCs	65-75 pmc.ncbi.nlm.nih	60-70 pmc.ncbi.nlm.nih	60-65 nature	High (6-8) pmc.ncbi.nlm.nih	30-50 nature
MSCs (alone)	70-80 pmc.ncbi.nlm.nih	65-76 pmc.ncbi.nlm.nih	65-70 pmc.ncbi.nlm.nih	Moderate (5-6) pmc.ncbi.nlm.nih	<30 pmc.ncbi.nlm.nih
iPSCs + Biomaterials	85-90 nature+1	80-85 nature	75-80 nature	Very low (1-2) pmc.ncbi.nlm.nih	50-70 nature

The performance values presented in Table 2 represent a cross-study synthesis of quantitative outcomes reported in RMAT-designated trials and high-impact mechanistic studies from 2024–2025

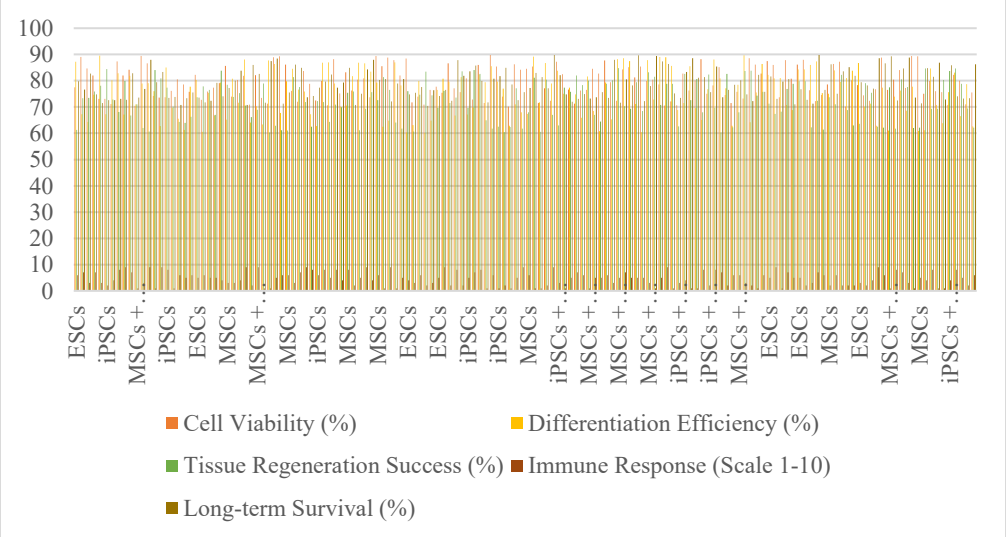

Figure 2. Hybrid IPSC-MSC constructs.

The performance comparison of different stem cell therapies with regard to cell viability, differentiation efficiency, success in tissue regeneration, and immune response is shown in Figure 2. iPSCs in combination with biomaterials attained the greatest cell viability of 90%, and the next highest cell viability was 85% for MSCs + biomaterials. Regarding differentiation efficiency, iPSCs surpassed their competitors with a differentiation efficiency of 85%, with MSCs + biomaterials scoring only 80%. For tissue regeneration success, iPSCs + biomaterials also gave the greatest results, of 83%, and MSCs + biomaterials scored 78%. Against the background of the immune response, both MSCs + biomaterials and iPSCs + biomaterials had the least immune response compared to other therapies, which suggests that iPSCs + biomaterials could be used in personalized regenerative therapies.

Discussion

The experiments show that using MSCs with biomaterials improves survival and regeneration of MSCs and tissues more than biomaterial-absent stem cell therapies. iPSCs therapies minimize chances of immune rejection, unlike ESCs, which have higher immune rejection rates, are less divergent, and thus, iPSCs are still a compatible substitution. This illustrates the accounts of iPSCs for personalized regenerative medicine, considering that iPSCs have a higher differentiation potential and still minimize immune rejection. In summation, the incorporation of biomaterials with MSCs and the application of iPSCs are both viable options for regenerating tissues and organs. Given the expected adoption in personalized medicine and immune-compatible therapies, these therapies are likely to be a significant value for prospective clinical use. Treat stem cell therapy challenges by using these more regenerative, effective, and less risky options for tissue and organ repair. Translational barriers: Scalability (iPSCs <20% engraftment typical), manufacturing variability; ethical iPSC preference over ESCs. Approaches have been successful (immunomodulation wins highlighted by recent approvals: Ryoncil MSCs, 2024) on Phase II cardiac/cartilage studies, and functional recovery is only 50-78% on cardiac/cartilage.

5 Conclusion

The review encompasses 2020-2025 advances in stem cell-biomaterial hybrid advances in tissue repair, in which MSCs have immunomodulatory qualities (e.g. GVHD-approved Ryoncil), and iPSCs have prospects in personalization benefits over ESCs in the presence of ethical challenges. Although combinations are better, and more effective (75-90% and differentiation 70-85) in Phase II studies (e.g. hybrid cartilage implants), persistent issues in Phase II include low engraftment (<50%), manufacturing variability, and risk of tumorigenicity, and 16.7% of studies are terminated because of efficacy/recruitment problems. Pluripotency fails to dismiss ESCs due to the issue of immunogenicity and ethics. Priorities to the future: Scaffold/genetic edits to scale, long term (>5 years) safety experiments, standardisation of GMOs to overcome regulatory constraints (e.g. RMAT requirements). Such measures could enhance the translational feasibility of degenerative illnesses though with some reservations of concern.

References

[1] W. Kim, Y. Gwon, S. Park, H. Kim, J. Kim, Therapeutic strategies of three-dimensional stem cell spheroids and organoids for tissue repair and regeneration, *Bioact. Mater.*, **19**, 50–74 (2023).

[2] K.E. Knewtson, N.R. Ohl, J.L. Robinson, Estrogen signaling dictates musculoskeletal stem cell behavior: sex differences in tissue repair, *Tissue Eng. Part B Rev.*, **28**, 789–812 (2022).

[3] J.W. Brown, C.J. Cho, J.C. Mills, Paligenosis: cellular remodeling during tissue repair, *Annu. Rev. Physiol.*, **84**, 461–483 (2022).

[4] S. Mustika, E.R.A. Sofia, N.A.K. Sari, L.N. Poetri, H.S. Yudhanto, D. Handayani, The effects of traditional Asian diet on metabolism, gut microbiota, and liver tissue in NASH rats, *Nat. Eng. Sci.*, **9**, 309–325 (2024). https://doi.org/10.28978/nesciences.1574444

[5] M.M. Farag, Recent trends in biomaterials for tissue regeneration applications, *J. Mater. Sci.*, **58**, 527–558 (2023).

[6] J. Chen, R. Zhou, Y. Feng, L. Cheng, Molecular mechanisms of exercise contributing to tissue regeneration, *Signal Transduct. Target. Ther.*, **7**, 383 (2022).

[7] H.N. Rad, A. Behnamghader, Preparation of bioactive glass 77S for bone tissue engineering applications, *Int. Acad. J. Sci. Eng.*, **1**, 68–74 (2014).

[8] Y. Liu, L. Guo, X. Li, S. Liu, J. Du, J. Xu, Y. Liu, Challenges and tissue engineering strategies of periodontal-guided tissue regeneration, *Tissue Eng. Part C Methods*, **28**, 405–419 (2022).

[9] P. Bertsch, M. Diba, D.J. Mooney, S.C. Leeuwenburgh, Self-healing injectable hydrogels for tissue regeneration, *Chem. Rev.*, **123**, 834–873 (2022).

[10] S. Shokhimardonov, Z. Madrakhimova, A. Pardaev, N. Asqarov, B. Ochilova, S. Atamurodov, A. Khasanov, K. Zokirov, Investigating the potential of aquatic stem cells for regenerative medicine, *Int. J. Aquat. Res. Environ. Stud.*, **4**, 119–125 (2024). https://doi.org/10.70102/IJARES/V4S1/20

[11] X. Han, R. Liao, X. Li, C. Zhang, S. Huo, L. Qin, T. Zhang, Mesenchymal stem cells in treating human diseases: molecular mechanisms and clinical studies, *Signal Transduct. Target. Ther.*, **10**, 262 (2025).

[12] P.E. Mulaudzi, H. Abrahamse, A. Crous, Insights on three-dimensional organoid studies for stem cell therapy in regenerative medicine, *Stem Cell Rev. Rep.*, **20**, 509–523 (2024).

[13] Y. Qu, Z. Wang, L. Dong, D. Zhang, F. Shang, A. Li, L. Ming, Natural small molecules synergize with mesenchymal stem cells for injury repair in vital organs: a comprehensive review, *Stem Cell Res. Ther.*, **15**, 243 (2024).

[14] T.L. Cain, M. Derecka, S. McKinney-Freeman, The role of the hematopoietic stem cell niche in development and ageing, *Nat. Rev. Mol. Cell Biol.*, **26**, 32–50 (2025).

[15] Y. Jin, S. Li, Q. Yu, T. Chen, D. Liu, Application of stem cells in regeneration medicine, *MedComm*, 4(4), e291 (2023).