Regenerative Dentistry - Updates And Upcoming Trends

ABSTRACT

Regenerative dentistry is shifting clinical practice from mechanical repair to biologically driven restoration of dental tissues. Advances in stem cell biology, biomaterials, and molecular signaling now support regeneration of enamel, dentin, pulp, periodontal ligament, and alveolar bone. Dental-derived mesenchymal stem cells show strong differentiation, angiogenic, and immunomodulatory capabilities, while modern biomaterials like hydrogels, nanocomposites, bioactive glasses, and smart adhesives enhance remineralization and tissue integration.

Biologics such as enamel matrix derivatives, platelet concentrates, and growth factors enable predictable pulp revitalization, and stem cell–scaffold constructs promote regeneration of the pulp–dentin complex. Periodontal regeneration benefits from photobiomodulation, advanced grafts, hydrogels, and hyaluronan-based systems, with emerging roles for mesenchymal stem cells–derived microRNAs.

Rapid developments in 3D bioprinting, decellularized scaffolds, nanodelivery platforms, exosome-based therapies, and AI-driven design are accelerating translation into patient-specific solutions. Together, these innovations outline a paradigm shift toward therapies capable of restoring natural tooth form and function, potentially reducing reliance on traditional fillings, root canals, and periodontal surgery.

BACKGROUND

Regenerative dentistry is rapidly reshaping contemporary dental practice by shifting the focus from repair and replacement to biological restoration of damaged oral tissues.[2] Unlike conventional approaches that rely on artificial materials and invasive procedures, regenerative therapies harness the body’s innate healing mechanisms to rebuild enamel, dentin, pulp, periodontal ligament, and alveolar bone.[2]

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This paradigm is driven by advances in stem cell biology, biomaterials science, tissue engineering, and bioactive signaling technologies. Central to regenerative dentistry is the use of dental-derived stem cells—such as dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), stem cells from human exfoliated deciduous teeth (SHED), stem cells from apical papilla (SCAPs), and dental follicle progenitor cells (DFPCs).[1,2] These cells possess the capacity for self-renewal and multipotent differentiation into odontoblast-like cells, periodontal fibroblasts, and other dental-specific phenotypes.[2]

In addition to direct tissue regeneration, stem cells exert potent paracrine effects through the release of cytokines, growth factors, and extracellular vesicles that modulate inflammation, promote angiogenesis, and stimulate resident cell activity.[2] Their immunomodulatory properties further create a favorable microenvironment for predictable tissue repair.[2]

The development of advanced biomaterials has significantly enhanced the outcomes of cell-based therapies. Hydrogels, nanocomposites, biodegradable polymers (PLA, PGA, PLGA), bioactive ceramics, and electrospun nanofibers provide scaffold architectures that mimic the extracellular matrix, support cell adhesion and proliferation, and promote differentiation.[1,2] These materials can be functionalized with growth factors such as BMPs, VEGF, PDGF, FGF, and TGF-β to guide regeneration of dentin, pulp tissue, alveolar bone, and periodontal structures.[2] Collectively, these biomaterial–cell–signaling combinations aim to recreate the natural architecture, mechanical properties, vascularity, and sensory functions of healthy dental tissues.[2]

Recent innovations are speeding the transition of regenerative dentistry from laboratory research toward clinical translation. Notable advancements include 3D bioprinting of patient-specific scaffolds and dental tissues, gene-editing technologies such as CRISPR-Cas9 to enhance regenerative potential or correct developmental defects, and nanotechnology-based platforms for targeted drug or growth factor delivery. Bioreactors capable of mimicking physiological conditions allow pre-conditioning of engineered tissue constructs before implantation.[1] Alongside these, exosome-based, cell-free therapies have emerged as a promising alternative to stem cell transplantation, offering reduced immunogenicity and simplified clinical application.[1,2]

The field is also moving toward personalized regenerative strategies**.** Biobanking of dental stem cells, integration of genetic profiling, and AI-driven diagnostics enable treatment protocols tailored to a patient's biological responsiveness and risk profile.

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Personalized scaffolds, nano-carriers, and biologically matched growth factor systems are expected to minimize complications and enhance treatment predictability.[2]

Collectively, regenerative dentistry is poised to transform future clinical practice by transitioning from mechanical repair to biological replacement. Key updates including dental stem cell therapy, biomimetic scaffolds, exosome-based treatments, smart materials, and minimally invasive biological techniques suggest that traditional fillings, root canals, and implants may eventually give way to solutions that regenerate natural tooth structures. As these technologies mature, they promise more durable, functional, and patient-centered outcomes, marking a significant leap forward in the management of complex dental diseases.This review will provide an overview of the recent advancements and upcoming trends to regenerative dentistry.[1,2]

RESTORATIVE DENTISTRY APPLICATIONS

Bioactive Glasses

Bioactive glass–based materials facilitate the formation of hydroxyapatite and support dentin remineralization through sustained release of calcium, phosphate, and other therapeutic ions. Their capacity to promote enamel and dentin repair has been widely documented. Baino et al. emphasized their broad adaptability and regenerative applications in dentistry,[3] while Hench's historical review outlines their evolution from discovery to clinical translation.[4] Recent systematic assessments further validate their strong remineralization profile.[5]

CPP-ACP and Other Remineralizing Systems

Casein phosphopeptide–amorphous calcium phosphate (CPP-ACP) formulations have shown measurable benefits in preventing early erosive damage and enhancing mineral redeposition in demineralized enamel and dentin.[6,7] These biomimetic systems regulate mineral equilibrium and promote early regenerative activity within the tooth structure.

Fluoridated Biomimetic Techniques

Fluoride-based biomimetic agents aid in remineralization by encouraging the growth of fluorapatite crystals, which provide superior resistance to acidic challenges.[8] Long-term clinical reports support their usefulness in managing dentin hypersensitivity and in promoting mineral gain.[9]

Nanoparticles and Advanced Adhesive Technologies

Recent materials research incorporates zinc-doped polymeric nanoparticles[10] and silver/polydopamine-modified hydroxyapatite fillers[11] to improve the antibacterial behavior and remineralizing efficiency of adhesive systems. Polydopamine itself has

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been extensively evaluated for its ability to drive biomimetic mineral deposition and enhance bond durability.[12,13] Poly(amido amine)–based agents and restorative materials containing calcium phosphate nanoparticles also show favorable outcomes in dentin tissue regeneration.[14]

ENDODONTIC APPLICATIONS

Enamel Matrix Derivatives (EMD)

EMD has been shown to enhance pulp cell differentiation, stimulate mineral deposition, and support biological dentin regeneration.[15] Its signaling properties make it a valuable adjunct in early wound-healing events within the pulp–dentin complex.

Platelet-Rich Plasma (PRP) and Platelet-Rich Fibrin (PRF)

Autologous platelet concentrates provide high concentrations of growth factors that accelerate cell proliferation, angiogenesis, and structural tissue organization during REPs.[16] Their biocompatibility and ease of preparation support increasing clinical adoption.

Growth Factors and BMPs

Bone morphogenetic proteins—particularly BMP-2 and BMP-7—have demonstrated strong odontogenic and angiogenic induction abilities.[17,18] BMP-7 shows specific potential in stimulating intrinsic pulp regenerative processes.[18]

SCAP and Dental Pulp Stem Cells (DPSCs)

Stem cells of the apical papilla (SCAP) exhibit resilience even in necrotic or inflamed periapical environments, making them critical contributors to root development in immature teeth.[19] Dental pulp stem cells (DPSCs) also support tissue-engineering strategies when combined with scaffolds and controlled biological environments.

Scaffold-Assisted Regeneration

Natural polymer matrices, synthetic scaffolds, hydrogels, and bioceramic constructs promote cell attachment, proliferation, and differentiation, bringing the field closer to consistent and predictable pulp regeneration outcomes.[20]

PERIODONTIC APPLICATIONS

Conventional surgical and non- surgical periodontal therapies often result in healing by formation of a long junctional epithelium. Although this leads to improvements in clinical

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attachment level (CAL) and probing pocket depth (PPD), it does not restore the periodontium to its original architecture. Guided tissue regeneration (GTR) and other regenerative approaches aim to overcome this limitation by creating an ideal environment for true regeneration of bone, periodontal ligament, and cementum while preventing epithelial and bacterial migration into the defect.

Recent advances in regenerative periodontics have significantly altered the management of two- and three- wall periodontal defects. Emerging therapies include adjunctive antimicrobial photodynamic therapy (PDT), light- emitting- diode (LED) photobiomodulation therapy, advanced regenerative biomaterials, and mesenchymal stem cell (MSC)- derived microRNA- based approaches.[21,22]

1. Adjunctive Light- and Energy- Based Therapies

1.1 Antimicrobial Photodynamic Therapy (PDT)

Antimicrobial photodynamic therapy involves the use of a photosensitizing agent, such as an optical absorption dye, activated by low- level lasers (LLLs) or LEDs. Upon activation, the photosensitizer releases singlet oxygen—an electronically excited form of molecular oxygen that is highly cytotoxic to periodontal pathogens present in deep periodontal pockets.Beyond its antimicrobial effect, PDT has been shown to promote periodontal ligament stem cell differentiation, thereby enhancing osteoblastic activity and contributing to periodontal regeneration.

1.2 Light- Emitting- Diode Photobiomodulation Therapy

LED photobiomodulation therapy utilizes a combination of low- level lasers, LEDs, and near- infrared light. This therapy is believed to enhance cellular metabolism by increasing adenosine triphosphate (ATP) production and extracellular matrix synthesis, both of which are essential for wound healing and regeneration.Clinical studies have demonstrated that the adjunctive use of PDT and LED photobiomodulation therapy, in combination with allogenic bone grafts and collagen membranes, yields significant improvements at both the cellular and clinical levels. Notable outcomes include enhanced CAL gain and reduction in PPD, particularly in periodontal pockets deeper than 7 mm in patients with Stage III and IV Grade C periodontitis.

2. Regenerative Biomaterials in Periodontics

Regenerative biomaterials are primarily used in the management of periodontal defects such as Class II furcation defects and infrabony defects measuring ≥3 mm. Although complete resolution of complex defects—particularly Class III furcations—remains

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challenging, ongoing research continues to expand the scope of biomaterial-based regenerative therapies.[27]

2.1 Bone Grafts

Bone grafts remain a cornerstone of periodontal regeneration and are classified as follows:[31]

- **Autogenous bone grafts**: These are osteogenic, osteoconductive, and osteoinductive. They are commonly used in intrabony defects, often in combination with platelet-rich fibrin (PRF).
- **Allografts**: Typically demineralized freeze-dried bone allografts (DFDBA), these materials exhibit osteoinductive properties due to exposed collagen and are processed to reduce immunogenicity.
- **Xenografts**: Derived mainly from bovine sources, xenografts are osteoconductive and widely used in periodontal regeneration.
- **Alloplasts**: Synthetic ceramic materials such as calcium phosphates; these are less commonly used compared to other graft types.

2.2 Platelet Concentrates

Platelet concentrates are autologous biomaterials obtained by centrifugation of venous blood under controlled conditions. They are rich in growth factors that promote differentiation of mesenchymal stem cells, enhance wound healing, and exhibit bacteriostatic properties.[25]

- **Platelet-Rich Plasma (PRP)**: Contains a high concentration of platelets but has limitations, including lack of fibrinogen, short working time, and partial xenogenic derivation.
- **Platelet-Rich Fibrin (PRF)**: An improvement over PRP, PRF releases growth factors over an extended period, supports immune response, reduces infection risk, promotes soft-tissue regeneration, and helps maintain space for bone growth.

Recent advancements in platelet concentrates include:

- **Advanced PRF (A-PRF)** – promotes angiogenesis.
- **Concentrated Growth Factor (CGF)** – characterized by a dense fibrin matrix that prevents flap collapse and releases chemokines; mainly used in hard-tissue regeneration.

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- **Injectable PRF (I- PRF)** – enhances fibroblast migration in infrabony defects.
- **Titanium PRF (T- PRF)** – forms a thick fibrin matrix that aids flap stability during wound healing.

Although these newer concentrates show promising results, further long- term clinical studies are required.[25]

Growth Factor–Enhanced Matrix (GEM 21S) is an FDA-approved bone grafting material designed to enhance wound healing and bone regeneration.[31] It consists of recombinant human platelet-derived growth factor-BB (rhPDGF-BB) combined with an osteoconductive β-tricalcium phosphate (β-TCP) scaffold that supports new bone formation. In addition to repairing intrabony and furcation defects, GEM 21S is also being utilized in the treatment of peri-implantitis, a condition that was previously considered to have a poor or hopeless prognosis, by promoting enhanced bone regeneration and improved peri-implant wound healing.[32,33]

3. Bone Putties

Bone putties represent an evolution of combined hydrogel and bone graft approaches. They facilitate bone regeneration and angiogenesis while offering improved handling characteristics. Commonly used bone putties include NovaBone Putty, C- Blast Putty, MaxResorb Inject, DBX Putty, Ostim, and MinerOss Putty. Among these, NovaBone Putty has the strongest clinical evidence, while others require further validation through clinical research.

4. Hydrogels in Periodontal Regeneration

Hydrogels are hydrophilic polymer networks capable of absorbing blood and forming a temporary extracellular matrix (ECM). Their injectable nature makes them suitable for small, deep periodontal defects.[22-24]

4.1 REGROTH Dental Kit

REGROTH is a hydrogel containing 0.3% human fibroblast growth factor- 2 (FGF- 2) in a 3% hydroxypropyl cellulose carrier. It exhibits angiogenic properties and recruits undifferentiated mesenchymal stem cells to deep bone defects.

4.2 Enamel Matrix Derivatives (EMD)

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Enamel matrix derivatives are purified extracts from porcine tooth buds, rich in amelogenins involved in tooth mineralization. Delivered using propylene glycol alginate, EMDs stimulate mesenchymal cells, promote angiogenesis, and inhibit epithelial downgrowth, thereby favoring periodontal regeneration. However, a major limitation is membrane collapse due to insufficient structural support.[26]

4.3 Hyaluronan- Based Hydrogels

Hyaluronan- based hydrogels promote angiogenesis and wound healing and are available as topical gels for both surgical and non- surgical periodontal therapy. While effective in narrow defects, they lack space- maintaining ability and are therefore often combined with bone grafts in wider defects.[28]

Currently, commonly used regenerative materials in clinical practice include Emdogain (EMD), Bio- Oss xenograft, and NovaBone putty due to their availability, affordability, and documented clinical outcomes.[28]

5. Mesenchymal Stem Cell- Derived microRNA Therapy

Recent research highlights the role of mesenchymal stem cell (MSC)- derived microRNAs (miRNAs) in regulating periodontal regeneration at the genetic level. These miRNAs function both intracellularly and extracellularly.[23]

- **Intracellular miRNAs**, such as miR- 31, inhibit bone resorption and promote osteogenesis by increasing alkaline phosphatase activity and regulating osteoblast maturation.
- **Extracellular miRNAs**, transported via exosomes, facilitate angiogenesis by transferring genetic signals to target cells.

MSCs also exert immunomodulatory effects by polarizing macrophages, regulating autophagy, reducing apoptosis, and eliminating damaged tissues, thereby accelerating periodontal repair. The anti- inflammatory properties of miRNAs further contribute to periodontal regeneration.

Despite promising results, challenges remain regarding optimal delivery methods, dosage, and administration techniques, necessitating further clinical research.

6. DPSCs Scaffold-Based Tissue Engineering: Workflow

Workflow of DPSCs Scaffold-Based Tissue Engineering for Periodontal Regeneration.

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Workflow illustrates the sequential steps from DPSC isolation to functional periodontal regeneration, highlighting the cell–scaffold–signal triad (Fig1and2).

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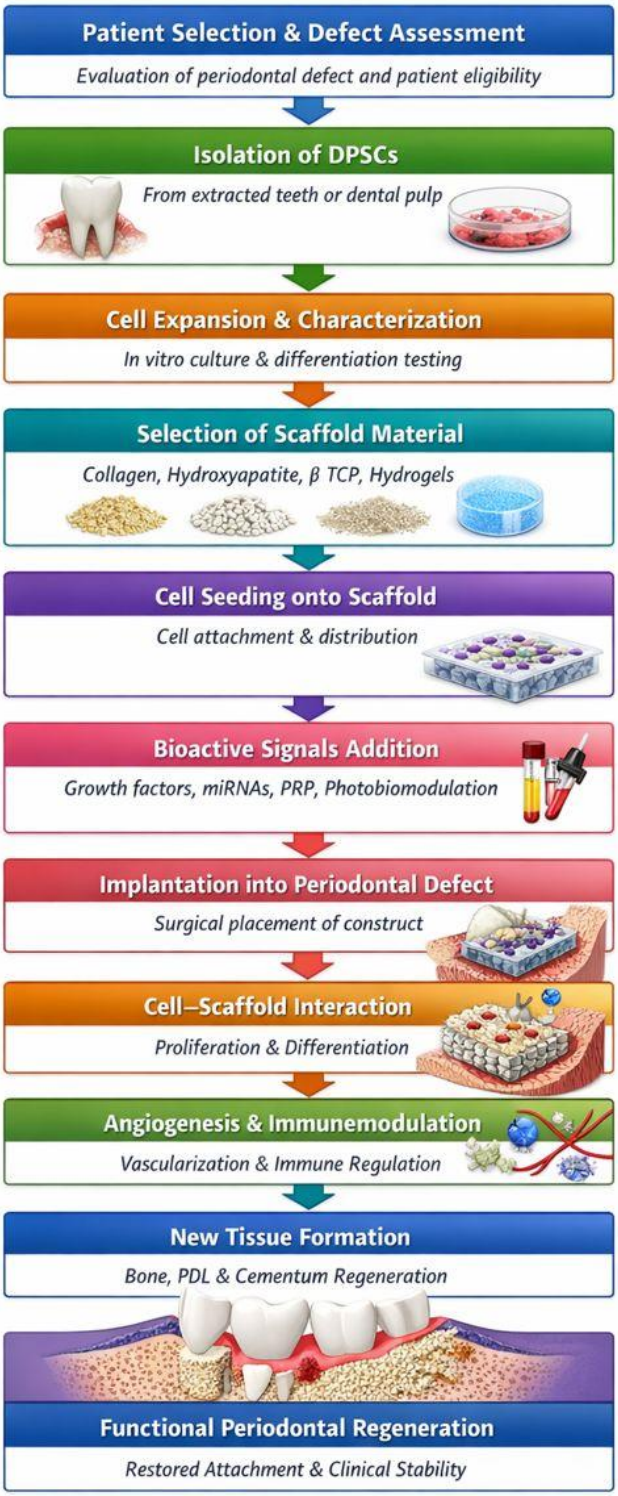

Fig.1 Workflow for DPSC-Based Periodontal Regeneration

DPSCs are a promising cell source for periodontal and bone tissue regeneration due to their high proliferative capacity, self-renewal ability, and osteogenic potential. Scaffold-based tissue engineering integrates cells, biomaterials, and signaling molecules to achieve functional regeneration of periodontal tissues.[29]

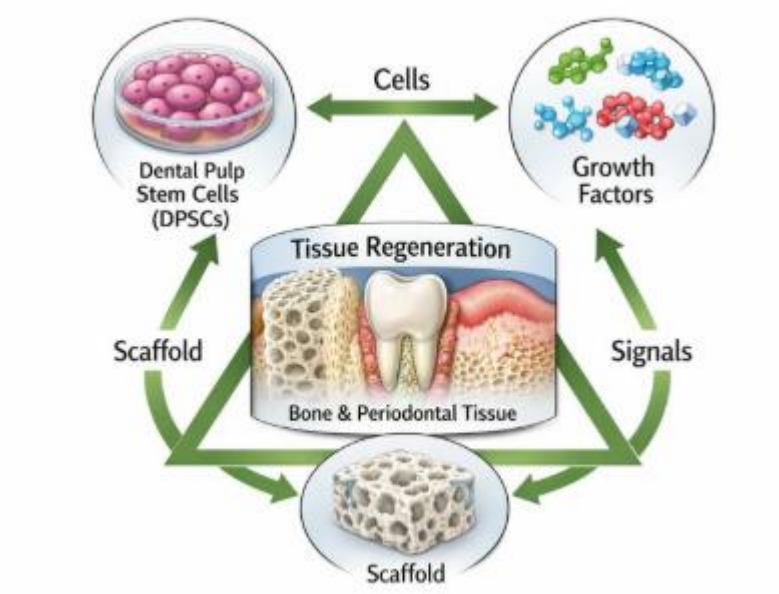

Fig.2 Cell, Scaffold, Signal Triad

UPCOMING AND FUTURE TRENDS

Future - upcoming trends in regenerative dentistry

Regenerative dentistry has moved rapidly from proof-of-concept animal studies to translational research with several parallel technological trajectories likely to shape the field over the next 5–10 years. The coming wave of advances centers on (1) moving from cell-based to cell-free therapies, (2) integrating next-generation biomaterials with advanced manufacturing (3D bioprinting and organoids), (3) leveraging computational and AI tools for personalized regenerative design, and (4) strengthening clinical translation pathways (standardization, manufacturing, and regulation). Below we summarize these trends and the rationale for their future impact.

1. From cell therapies toward cell-free/secretome approaches

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Dental-derived mesenchymal stem cells (DPSCs, PDLSCs, SHED) continue to demonstrate potent regenerative effects in preclinical and early clinical studies; however, practical barriers (cell sourcing, immune concerns, storage/transport, GMP manufacturing) remain.[34,42] As a result, a major near-term trend is the adoption of **cell-free** approaches using extracellular vesicles/exosomes and conditioned media that capture stem cell paracrine activity while avoiding many logistical and safety hurdles of living cell products.[36,39,43] Multiple recent reviews highlight dental stem-cell derived exosomes as modulators of angiogenesis, immunomodulation and osteo/odontogenic signaling — positioning them as attractive off-the-shelf therapeutics for pulp, periodontal and bone regeneration.[36,39,43]

2. Biomaterials and interface engineering: "functional" materials, dECM and smart scaffolds

Biomaterials are evolving from inert fillers to **bioactive, immunomodulatory and instructive scaffolds** that actively guide cell behavior and tissue patterning. Decellularized extracellular matrix (dECM) scaffolds, hybrid hydrogels, and multifunctional membranes are receiving particular attention for reproducing native microenvironments and improving histologic outcomes in regenerative endodontics and periodontal repair.[37,41] The emphasis is on materials that present both biochemical cues (growth factors, miRNAs) and mechanical/architectural guidance for multi-tissue interfaces (cementum–periodontal ligament–alveolar bone) — a requirement for clinically reliable reconstruction.[37,38]

3. 3D bioprinting, organoids and whole-tooth engineering

Advances in 3D bioprinting, microfabrication and organoid biology are rapidly lowering the barrier to complex tissue patterning. Bioprinting strategies now enable spatial deposition of multiple cell types and gradient biomaterials to recreate periodontal and pulp–dentin architectures, and organoid approaches using pluripotent cells hold theoretical promise for whole-tooth morphogenesis.[35,40] Over the next decade, these technologies are likely to shift from academic demonstration to preclinical large-animal evaluation and, eventually, targeted clinical applications (e.g., complex alveolar defects, tooth germ replacements) as manufacturing scale and regulatory pathways mature.[35,40]

4. Computational design and artificial intelligence

AI and computational modeling are emerging as practical tools to accelerate discovery and clinical translation. Applications include automated analysis of stem cell phenotypes

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and imaging, optimization of scaffold microarchitecture and material composition, and predictive modeling of regenerative outcomes.[38] Integrating AI with multi-omic datasets (single-cell transcriptomics, proteomics) can help identify potent regenerative signals and design patient-specific grafts, enabling precision regenerative therapies.

5. Clinical translation, standardization and outcome evidence

While numerous promising studies have been published, systematic evidence comparing regenerative procedures to traditional therapies is now beginning to accumulate; recent meta-analyses highlight the need for standardized protocols and long-term outcome measures.[43,2] Future work must address GMP manufacturing, reproducibility of biologic products (cells/exosomes), regulatory classification, and cost-effectiveness analyses to enable broad clinical adoption.

6. Practical and ethical considerations

Key translational barriers include donor-cell sourcing and consent, product stability and cold-chain logistics, immunogenicity risks for allogeneic constructs, and reimbursement frameworks. Ethical frameworks for emerging interventions (e.g., gene-edited xenogeneic models or organoid-derived teeth) will also require active multidisciplinary engagement as technologies approach clinical use.[35]

Concluding outlook

The near future of regenerative dentistry will be hybrid: combining **cell-free biologics** (exosomes/secretomes) with **smart biomaterials** and **precision manufacturing** (bioprinting) underpinned by **AI-driven** design and standardized clinical pathways. Research priorities for translational success include robust preclinical large-animal validation, harmonized clinical protocols, and early health-economic evaluation to ensure equitable patient access. With these complementary advances, routine clinical applications that restore form and function (beyond prosthetic replacement) appear increasingly feasible within the coming decade.[34-38,40,43]

ABBREVIATIONS

PLA - Poly(lactic acid)
PGA - Poly(glycolic acid)
PLGA - Poly (lactic-co-glycolic acid)
BMPs - Bone morphogenetic proteins

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VEGF - Vascular endothelial growth factor
PDGF - Platelet-derived growth factor
FGF - Fibroblast growth factor
TGF-β - Transforming Growth factor - beta
DPSCs - Dental pulp stem cells
PDLSCs - Periodontal ligament stem cells
SHED - Stem cells from human exfoliated deciduous teeth
SCAPs - Stem cells from apical papilla
DFPCs - Dental follicle progenitor cells
CPP-ACP - Casein phosphopeptide–amorphous calcium phosphate
CRISPR - Clustered Regularly Interspaced Short Palindromic Repeats
PRP - Platelet-Rich Plasma
PRF - Platelet-Rich Fibrin
PDT - Photodynamic therapy
dECM - Decellularized extracellular matrix
HPC - Hydroxypropyl cellulose
MSC - Mesenchymal stem cell
EMD - Enamel Matrix Derivatives
A-PRF - Advanced PRF
CGF - Concentrated Growth Factor
I- PRF - Injectable PRF
DFDBA - Demineralized freeze- dried bone allografts
T- PRF - Titanium PRF
PDT - Photodynamic Therapy
GEM - Growth Factor–Enhanced Matrix
CAL - Clinical attachment level
PPD - Probing pocket depth
GTR - Guided tissue Regeneration
LED - Light- emitting- diode

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