Regenerative Medicine and Dentistry
https://www.sciltp.com/journals/rmd

Review

The Current State and Future of Oral Health: A Position Paper Exploring the Role of Regenerative Dentistry

John A. Jansen

Department of Dentistry-Regenerative Biomaterials, Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands; john.jansen@radboudumc.nl

How To Cite: Jansen, J.A. The Current State and Future of Oral Health: A Position Paper Exploring the Role of Regenerative Dentistry. *Regenerative Medicine and Dentistry* **2025**, *2*(1), 6. https://doi.org/10.53941/rmd.2025.100006.

Received: 12 February 2025
Revised: 17 March 2025
Accepted: 20 March 2025
Published: 25 March 2025

Abstract: Regenerative dentistry combines dental science, biology, and technology to develop new therapeutic approaches for treating oral and orofacial problems. It focuses on restoring or regeneration lost or damaged tissues using tissue engineering technology. Current methodologies and methods used in regenerative dentistry are: stem cells, growth factors/biomolecules, tissue engineering and bioactive materials, platelet-rich plasma (PRP), tooth regeneration, and tooth-on-a-chip and organoids. Despite its potential, regenerative dentistry has not met the initial expectations due to unrealistic goals, regulatory challenges, and ethical concerns. Therefore, the field needs a breakthrough discovery with significant clinical impact. It is recommended that future efforts should focus on products with clear clinical need and improving existing materials. In conclusion, regenerative dentistry has great potential, but the research lacks a clear vision and focus. Integration of artificial intelligence (AI) can help guide the field into a new era.

Keywords: regenerative dentistry; tissue engineering; stem cells; scaffolds; growth factors

1. Introduction

Regenerative dentistry is an area of research, development and innovation at the intersection of dental science, biology, and technology. It is expected to make possible a broad range of new therapeutic approaches directed towards the treatment of congenital and acquired oral and orofacial problems. Its focus is on the restoration or regeneration of lost or damaged tissues using physiological principles and the intrinsic self-healing capacity of natural tissues. Therefore, it is making use of the tissue engineering principles, which are also used in regenerative medicine and consist of three main components, i.e., cells, morphogenetic signals and scaffolds [1]. In view of this there are a lot of similarities between regenerative dentistry and regenerative medicine, which is e.g., evident by the similar trends in the number of regenerative dentistry and regenerative medicine publications from 1992–2024 (Figure 1). On the other hand, there are also differences between, which are not only dealing with the different tissues (dentin, enamel, cementum, dental pulp, periodontium, craniofacial and alveolar bone, mucosa, saliva producing secretory cells) specialized organs (teeth, salivary glands, temporomandibular joint, maxillary/mandibular bone, and cranium), as focused on in regenerative dentistry. In addition, differences between regenerative dentistry and regenerative medicine exist in the used stem cells and morphogenetic signals.

At its introduction, regenerative dentistry was supposed to redefine the landscape of oral and orofacial care, moving from a model focused on restoration to one focused on regeneration. However, 30 years later, the question can be asked why the initial expectations about the potential of the regenerative dentistry concept seem not to have fulfilled, while funding of research programs did prosper. With the currently available knowledge, it can even be doubted that the predictable regeneration of tissues and organs is not feasible and unrealistic considering the complexity of tissue and organ structures [2]. This position paper examines the current state of regenerative dentistry, its challenges, and its potential future applications.

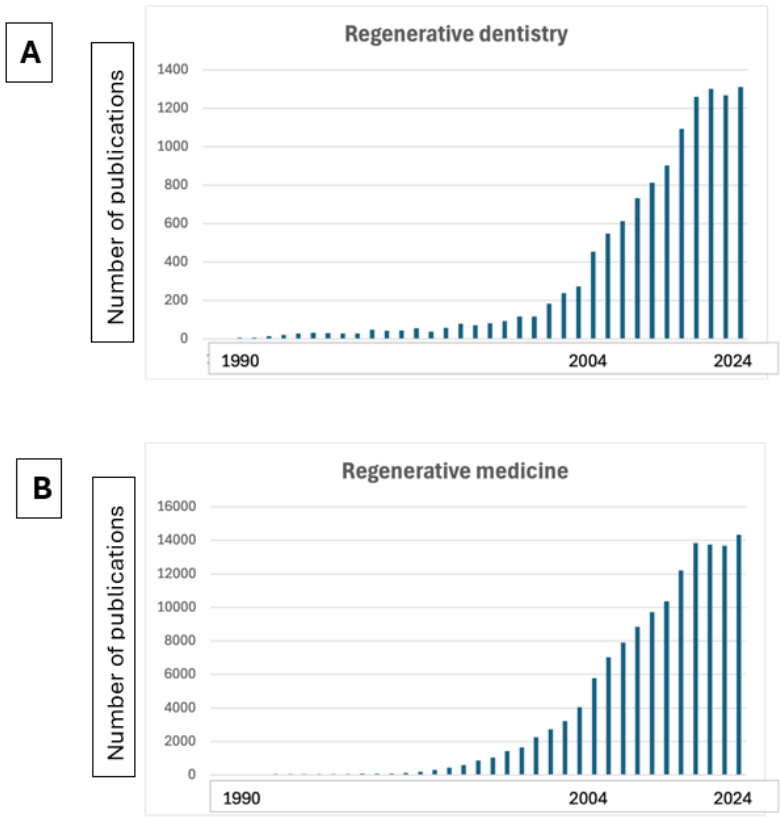

Figure 1. Bar graph showing the similarity in increase in the number of (**A**) regenerative dentistry, and (**B**) regenerative medicine publications from 1990–2024.

2. Current State of Regenerative Dentistry

At its core, regenerative dentistry involves the replacement, repair, or regeneration of damaged, diseased, or lost oral and orofacial tissues, as specifically described above. The current achievements of regenerative dentistry can best be described by potential therapies of which are still in experimental stages or have advanced into early clinical trials.

2.1. Stem Cells

Stem cells are undifferentiated cells capable of differentiating into various specialized cell types, including oral and orofacial tissues [3]. Stem cells can have the ability to differentiate into any cell type including embryonic tissues (pluripotent) or have the potential to differentiate into discrete cell types (multipotent). Stem cells can be divided into three categories: embryonic, adult and induced pluripotent stem cells. This last category are genetically manipulated cells derived directly from a non-pluripotent adult somatic cell [4]. Stem cells for regenerative dentistry can be isolated from extraoral and intraoral tissues, e.g., bone marrow, adipose tissue, dental pulp, periodontal ligament, exfoliated deciduous teeth, and periapical tissue [5–8]. These cells have been used in various pre-clinical and clinical experiments to induce e.g., periodontal, endodontic and bone regeneration [5,6]. Although, preclinical studies in various animal models were successful, these results could not be replicated in phase 1 and 2 clinical trials. The clinical data were not or only slightly better or could not confirm the presence of viable regenerated tissue than if no cells were used and the used scaffold material seemed more relevant for the final study outcome [8,9]. An extensive review of human clinical trials with mesenchymal stem cell therapy for dental tissue regeneration has recently been published by Ivanovski et al. [10]. Several reasons have been suggested for the unfavorable outcome of the clinical trials, e.g., the more favorable biological environment in experimental animals, insufficient nutrient and oxygen supply, heterogenicity of the used cell population [10–12].

In addition to dental stem cells, iPSCs have also been used for differentiation into ameloblasts and odontoblast [13,14]. While, preclinical studies were successful, no clinical trials have been performed till now.

2.2. Growth Factors/Biomolecules

Growth factors are proteins capable of stimulating cell proliferation, differentiation, and migration and are known to play a role in tissue healing. Growth factors are signaling molecules, which act by binding to specific cell receptors. In regenerative dentistry, several growth factors have been explored to promote tissue healing and regeneration, particularly for dental tissues such as alveolar bone, periodontal ligament, dental pulp, and mucosal tissue [15–17]. The key growth factors used are: platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), bone morphogenetic proteins (BMPs), transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), stromal cell-derived factor-1 (SDF-1), and keratinocyte growth factor (KGF). Growth factors, as used to promote tissue healing or regeneration can be produced by different techniques. For example, they can be retrieved from natural tissues [18]. The process of extracting these growth factors usually involves the isolation of specific tissues or cells, followed by purification techniques to concentrate the growth factors. Also, growth factors can be produced using recombinant DNA technology [19]. This process comprises the introduction of a gene encoding for a specific growth factor into a host cell, which subsequently will express the growth factor protein. Common host cells used are bacterial cells (e.g., *E. coli*) and mammalian cells (e.g., Chinese hamster ovary cells). After their expression, growth factors need to be purified from the host cells before they can be applied into the body tissue that has to be regenerated. A third method to deliver growth factors to a tissue defect is using genetically modified cells. Using gene therapy techniques, primary cells can be genetically modified to overexpress the secretion of specific growth factors. Such cells can be incorporated in a scaffold material and implant at a tissue defect site to facilitate tissue regeneration [20,21].

RhBMP-2 loaded into absorbable collagen sponge (ACS) is the most widely applied growth factor in craniofacial bone regeneration [22] It was approved by the FDA in 2007 for alveolar ridge and maxillary sinus augmentation. Although, clinical studies indicated that rhBMP-2 were suggested to be a promising alternative to autogenous bone grafts for alveolar ridge and maxillary sinus formation, concerns about safety, required dose and final efficacy have limited its widespread use [23].

A specific class of proteins used for the regeneration of periodontal tissues are enamel matrix derived (EMD) proteins of porcine origin. As reported, a three-dimensional amelogenin matrix is created on the tooth root surface after its application, which supports the migration and attachment of periodontal cells and the formation of alveolar bone. Although, periodontal regeneration and connective tissue attachment has been demonstrated in clinical studies, complete defect resolution is not achieved [24].

Recently, extracellular vesicles (EVs) have gained attention as a possible vehicle for the delivery of growth factors [25]. EVs are biological particles varying 0.1–0.2 μm in size secreted by the cells. Although their clinical efficacy and mechanism of therapeutic effect is still unknown, several preclinical studies reported already about their favorable effect on tissue healing and regeneration [26].

A latest development is the use of GSK3 inhibitor small-molecule drugs to stimulate reparative dentine formation. For localized delivery of these drugs, it is required that they can be prepared as an aqueous solution. Therefore, a new GSK3 inhibitor small-molecule drug, NP928, was developed and incorporated into methacrylate-hyaluronic acid (MA-HA) hydrogel to deliver it as an injectable paste into a tooth defect [27]. The efficacy of his therapy for the restoration of deep tooth lesions into mice has been proven. However, it is not clear if this development will proceed into human clinical trials.

2.3. Dental Tissue Regenerative Materials

In tissue engineering, biomaterials are used for the manufacturing of scaffolds, which provide a structural support in the tissue defect and guide tissue formation. It is preferred that these biomaterials possess additional properties which favor the biological response. This can be achieved by changing the surface composition, surface structure, and geometry of the biomaterials. These biomaterials can be naturally derived (e.g., collagen) or synthetic (metals, polymers, ceramics, composites) [28]. Optimally, the materials induce tissue regeneration by itself without the addition of stem cells or morphogenetic signals.

An example is the use of a biomimetic coating, i.e., the coating of biomaterials with a layer of apatite by immersing them into simulated body fluid (SBF), to promote the osteogenicity of bone graft materials [29]. These biomimetic coatings can be functionalized with growth factors, like rhBMP-2, to enhance their bone regenerative efficacy in large bone defects [30]. The efficacy and safety of such an approach has also been proven in a recent randomized clinical study that demonstrated that *Escheria coli* derived recombinant human bone morphogenetic protein 1 (ErH-BMP2) incorporated in biomimetic calcium phosphate coating functionalized β-TCP resulted in a significant increase in bone volume using a tooth-extraction-socket model [31].

Another example is the regeneration of enamel by using biomimetic enamel matrix proteins. Enamel matrix proteins play an important role in the deposition of enamel during tooth development. Researchers have used biomimetic enamel matrix proteins, composed of modified leucine-rich amelogenin peptide and non-amelogenin analog to regenerate enamel in vitro on extracted human teeth, which showed similar structural and mechanical properties as natural enamel [32]. Although, this development was reported to be an important development for clinical dentistry, no pre-clinical or human clinical data are available.

A specific class of biomaterials are so-called osseoinductive materials, which are materials that can trigger de novo bone formation in a non-osseous tissue site without the incorporation of bone formation stimulating biomolecules [33]. This property is supposed to be evoked by specific physicochemical and geometric features [34]. The abundant bone inducing capacity of tricalcium phosphate (TCP) ceramics with a micron-scale as well as submicron-scale surface structure has been demonstrated in dog studies [35]. In addition, the noninferiority and efficacy of biphasic calcium phosphate ceramic with a needle-shaped surface structure compared with autografted bone has been reported for spinal fusion [36]. However, no clinical studies are available yet where this material has been used for dental and craniofacial application.

Biomaterials and scaffolds can be produced by conventional manufacturing techniques, but a trend in scaffold preparation is three-dimensional (3D) printing [37,38]. This technique is an additive manufacturing process that uses layer-by-layer deposition of biomaterials to create of complex geometric structures. The biomaterials in 3D printing are used as inks and therefore must be flowable. Current 3D printing research is focusing on the development of bioinks, which involves the simultaneous printing of biomaterials and cell/biomolecules and will even allow the bioprinting of bone-like structures [39]. All these experiments are in the pre-clinical phase.

2.4. Platelet-Rich Plasma (PRP)

Platelet-rich plasma and platelet-rich fibrin are concentrated forms of platelets derived from the patient's own blood [40,41]. The alpha granules of these platelets contain biologically active growth factors that can promote tissue healing and regeneration. The most important growth factors released by the platelets are TGF-β, VEGF, PDGF, FGF, and IGF [40,42]. In addition, bioactive molecules, like matrix metalloproteinases and interleukins, are released. PRP can simply be prepared in a dental clinic using a commercially available centrifuge. PRP and PRF are currently used in periodontal therapy to accelerate soft tissue healing, bone regeneration after tooth extractions, sinus floor augmentation, and the treatment of peri-implantitis.

Though widely utilized in pre-clinical and clinical settings, their effectiveness can vary depending on preparation methods and the specific clinical indications. For example, the centrifugation force and the platelet activation method are reported to play and important role in the efficacy of the prepared PRP [43,44]. As recently confirmed in various publications, further research is needed to standardize protocols and measure long-term outcomes [40,41].

2.5. Oral Mucosa

Tissue-engineered oral mucosa (TEOM) is a cell and scaffold-based construct to cover a surgically created mucogingival wound. An extensive review about development and application of TEOMs has been published by Izumi et al. [45]. Several TEOMs, i.e., Ocural®, Sakracy®, Gintuit® are commercially available yet. Gintuit® is even approved by the U.S. Food and Drug Administration. However, limited clinical studies have been performed, which makes that the working mechanism and long-term efficacy of these TEOMs is still unclear.

2.6. Tooth Regeneration

Perhaps the most futuristic goal of regenerative dentistry is the complete regeneration of lost teeth. The feasibility of this ambition has been proven in animal models. Combination of adult and embryonic cells from mice and humans has led to some success in regenerating dental pulp and tooth-like structures [2,6,7].

A new development has been reported by scientists at Kyoto University and the University of Fukui in Japan. They investigated the effect of anti-uterine sensitization-associated gene-1 (USAG-1) on the on the generation of tooth regeneration in mice and found that single systemic administration of USAG-1 induced the formation of supernumerary teeth and ferrets [46]. Researchers claim that USAG-1 treatment can be effective for the treatment of congenital tooth agenesis as well as the induction of a third dentition [47]. However, the safety and efficacy of this treatment in larger animals is not investigated yet. In addition, it is not evident if the regenerated teeth will have similar morphology and function as natural teeth in case of tooth agenesis.

Therefore, the ability to fully regenerate a functional tooth in humans remains a distant goal.

2.7. Tooth-on-a-Chip and Organoids

A tooth-on-a-chip is a microfluidic device that replicates the natural tooth's microenvironment [48–50]. It integrates living stem cells, nutrient and blood flow simulation, and mechanical forces (chewing pressure). The tooth-on-a chip is a lab model that helps researchers to test biomaterials and dental regenerative therapies before their application in humans. The tooth-on-a chip can be integrated with organoids, which are miniaturized 3D structures grown from stem cells. Organoids self-organize into functional units and mimic the physiological properties and tissue structure of embryonic stages, tissues and organs [51]. Organoid technology in dentistry has been used to create tooth germs, dentin-pulp-like organoids, salivary gland organoids, and taste bud organoids [52–55].

Organ-on-a-chip and organoids are supposed to offer a new approach to regenerative dentistry and dental care. Advantages are: (a) more accurate model systems that mimic real tissue behavior better than the traditional two-dimensional (2D) petri dishes, (b) personalized dentistry by using patient-derived cells for disease-specific treatments, and (c) alternative to animal testing [56,57].

3. Challenges and Limitations

Despite the claimed immense potential of regenerative dentistry, till now all research did not meet the initial expectations. This can be attributed to a combination of factors.

3.1. Clinically Relevant Design for the Development of Regenerative Dental Products

First, there is lack of a clear vision what is really needed and of interest to dentists and maxillofacial surgeons. Consequently, the distance between expectation and reality is huge. Also, these unrealistic expectations set patient expectations too high. But the initially suggested clinical application of regenerative dentistry was also far too optimistic as it was not considered that many of the patients can still be effectively treated with conventional methods. An example of this lack of dental need is whole-tooth tissue engineering. Although, this is a scientific challenge and will provide a lot of knowledge about the fundamental principles of tooth development, the clinical potential is low due to high success rate of dental implants [58,59]. In addition, because e.g., tissue-engineering products based on stem cells or 3D-printed scaffolds are radically different from existing products, they do not conform with standing dental practices. The application of these products therefore requires change of these practices, resulting in complex and frequently delayed application procedures during patient treatment. In contrast to e.g., conventional implants and bone graft materials, tissue-engineered products can frequently not be manufactured in stock and require an exact fit of patient treatment with manufacturing and delivery schedules. Evidently, this lack of an 'assembly line' approach, which has made the automobile industry so profitable in the past, is a bottleneck for the application of tissue-engineered products [60].

3.2. Regulatory Considerations

A further complication has been the ambiguity in regulatory approval of dental regenerative products, which hampered significantly the initial development and introduction of tissue engineered products. Tissue engineered products were therapeutic approaches that did not fit easily in the medical device categories of the existing regulatory framework. Broadly, two regulatory pathways were discerned, i.e., medicinal products (e.g., drugs) and medical devices (e.g., implants), which both had their own regulatory regime. In contrast, tissue engineered products are best described as hybrids, composed of a biomaterial combined with cells or biomolecules. During the last decennium, regulations have been adapted and clear and specific regulatory pathways for tissue engineered products have been developed [61]. Still, the regulatory landscape varies significantly between various countries, which still challenges the approval process and market introduction of a new product [62]. Another complication is the need for animal experimental data. Animal testing regulations limit the conduction of animal experiments and the translation of the obtained data to the human clinical situation is very difficult. In view of this, there is urgent need to predictable testing models of tissue engineered products.

3.3. Ethical Concerns

As regenerative dentistry is focused on restoring and regenerating oral and orofacial tissues using stem cells, biomolecules and biomaterials, attention to the ethical consequences of this development on patient safety and accessibility is required. For an extensive description of the ethical issues of this new technology reference can be made to the publications of de Vries et al. [63], Baker HB et al. [64], and de Kanter A-FJ et al. [65]. Briefly, the key ethical dilemmas in regenerative dentistry are:

(1) Should embryonic and iPSCS be used if ethically acceptable dental stem cells are available?
(2) Should experimental regenerative dental treatments be allowed in humans before long-term safety data is available?
(3) How can it be ensured that regenerative dental care is affordable and widely accessible?
(4) Are patients fully aware of the risks involved in the risks of stem-cell and biomolecule based regenerative dentistry?

In view of these ethical concerns, it is important that strict clinical trials are performed that ensures the safety of the treatment, includes measures to prevent that regenerative dentistry becomes a luxury treatment, guarantees the transparent communication with patients about risks and benefits, and meets the regulations of government and regulatory agencies in monitoring regenerative dental technologies.

4. Future Directions

Undoubtedly, regenerative dentistry has made progress throughout the last decennia. However, 30 years after the introduction of the tissue engineering principles, the intrinsic potential of regenerative dentistry is still not blossoming. Therefore, regenerative dentistry is on a turning point and a breakthrough discovery with significant clinical impact is required. Reference can be made to similar events in history where major inventions with high societal impact were driven by sheer need. Remarkably, a lot of them were a consequence of warfare and were subsequently embraced by society. Two examples are canning to preserve food and internet. Canning was invented in 1809 and used to ship large amounts of food by the armies and during search expeditions. Internet was developed during the cold war, when a communication system was needed that could not be affected by a nuclear attack. The number of available computers for military was limited and was limited and great distances had to be traveled to use them. Then, a communication network was suggested with no central command point, so that all surviving points could still communicate with each other if one point was destroyed. Such an urgency driven development is also required for regenerative dentistry to fulfill the promise of the tissue engineering approach to repair, heal or regenerate oral and orofacial tissues.

In view of the above mentioned, it must be noticed that some of the methods currently under investigation in regenerative dentistry are impractical and too costly, like the earlier mentioned stem cell-based whole-tooth regeneration. Future efforts should concentrate on products with a clear clinical need or on existing products that can be improved by incorporating tissue engineering principles.

A problem of priority in research is the dento-gingival junction, which is a critical and functional interface between the teeth and the surrounding gingival tissues. It adheres the gingiva tightly against the tooth and prevents the ingress of microorganisms and injuring agents that can induce an inflammatory periodontal response (periodontal disease), which can result in tooth loss. Periodontal disease is recognized as a worldwide epidemic and major health problem [66]. Periodontal disease is currently the 6th most prevalent disease worldwide, affecting approximately 10% of the global population [67]. If periodontal disease is treated in its early stages, the dento-gingival tissues show a capacity of repair and regeneration, but it should be emphasized that the healing process is primarily the result of the regeneration of the epithelial attachment [68]. However, for moderate to severe periodontitis, natural healing alone is not sufficient and advanced therapy is required. However, the currently used regenerative treatments do not result in a predictable outcome and make complete regeneration of the original dento-gingival structure challenging, especially if severe bone and connective tissue loss has occurred. However, the gingival attachment is not only important around natural teeth but plays also a crucial role around dental implants. Without proper permucosal seal, bacteria can penetrate the peri-implant tissues leading to peri-implantitis, i.e., bone loss around the implant, which affects the long-term success of oral implants. Histopathological studies have indicated that the structure of the gingival attachment around dental implants contrasts compared to natural teeth [69]. Around implants, the gingival (junctional) epithelium attachment is like that around natural tooth, i.e., by hemidesmosomes, but the strength and quality of epithelial attachment differs. Considering the gingival connective tissue, there is a significant difference in attachment between natural teeth and dental implants. Around natural teeth, connective tissue fiber bundles are embedded into the cement layer as present on the tooth surface and extend perpendicularly outward into the connective tissue, providing firmness and strength to withstand mechanical stresses. In contrast, around dental implants, connective tissue fiber bundles align parallel to the implant surface and do not adhere to the implant surface. This parallel orientation results in a less effective barrier to bacterial penetration and reduced mechanical stability. Supposedly, the geometrical structure and the composition of the cement layer have a decisive effect on the specific organization and orientation of the gingival connective tissue fibers [70]. Also, the circulatory supply of the peri-implant gingival tissue is reduced

compared to the periodontium of natural teeth. This reduced vascularization may affect the ability of the tissue to response to inflammation and the heal after inflammation or trauma.

In view of the above mentioned, establishing an effective gingival tissue seal around teeth and dental implants is a vital requirement in periodontology and oral implantology. However, in addition to dentistry, a permanent connection between the internal and external environment of the body exists around percutaneous implants. These devices penetrate through the skin and are applied to the field of energy- and information transmission, perfusion or dialysis catheters, heart-assist leads, external hearing aid implants, and artificial limb attachments. Percutaneous devices show a high failure rate due to infection or marsupialization (epithelial downgrowth along the implant surface), which is attributed to the lack of epithelial and connective tissue attachment at the skin-implant interface [71]. The skin-exit site is the Achilles heel of percutaneous devices and with great consequence for health care cost. Till now, no solution has been found for this problem, and it is not clear how a strong skin-implant seal can be created. Although, compared with percutaneous implants, specific oral conditions, like plaque and the presence of saliva, constitute an additional factor which must be considered, it will be clear that if a solution is found for how to create a bacteria proof gingival seal, these findings can be applied also for percutaneous devices.

Further, the use of genetically modified cells, embryonic stem cells, growth factors/signaling molecules, and material from bovine origin will always be associated with safety and ethical issues. Therefore, another crucial research priority to advance regenerative dentistry is the improvement of the biological behavior and overall therapeutic effectiveness of existing materials. Instead of inventing and developing completely new materials, researchers can create next-generation biomaterials by integrating surface modifications, nanotechnology, biomimetic methods, and biomaterials. Such materials must possess intrinsic regenerative properties, like osteoinductive materials for bone regeneration. This approach can advance the regulatory approval and market introduction of a regenerative product.

In near future artificial intelligence (AI) can play also a transformative role in regenerative dentistry. Integration of AI into regenerative dentistry can help researchers and clinicians to develop more effective therapies, enhance precision and ultimately improve patient outcome. For example, AI can e.g., (1) help in discovering new biomaterials and new drugs that promote dental tissue regeneration, (2) reduce trial and error in laboratory experiments by automation of laboratory research, (3)optimize the design of 3D-printed scaffolds by predicting how materials will interact with biological tissues, (4) help by predictive analysis of the success of regenerative treatments based on patient-specific data (genetic and biological markers) and selecting the best biomaterials or therapies for each patient, (5) help to develop deep learning models to analyze cone beam computer tomograms, MRI and histology images to guide regenerative treatment, and (6) can process large data sets to uncover trends in regenerative dentistry and improving success rates.

Besides the above-mentioned, the following additional recommendations for advancement of regenerative dentistry can be made;

- On-the-shelf availability: dental professionals need to have an easy access to dental regenerative products. They must be readily available in stock
- Cost effectiveness: the cost of the dental regenerative product must be relative to the benefits as they provide, like patient outcome.
- Regulatory clarity: the regulatory framework for a regenerative product must be clear early in the development process. Involvement of regulatory authorities is crucial to understand the requirements and streamline the approval process.
- Upscalability: the production process of the new development must be upscalable to meet industrial demands.
- Tooth-on-a-chip: while the tooth-on-a-chip offers a promising platform for simulating human dental physiology, its direct validation against human clinical situation is still an issue. Dentistry can play an important role in the validation process of innovative microphysiological tissue models. A lot of the dental regenerative procedures are of low risk and allow the retrieval of biopsies of the regenerated tissue. An example is maxillary sinus elevation, which involves the placement of a bone graft material into the sinus to increase bone volume in the maxilla allowing the placement of dental implants. Usually, the graft material is installed and then after a healing period, the dental implants are placed. However, a bone biopsy can be taken before implant installation and bone ingrowth, as induced by the graft material, can be assessed [72]. The effectiveness of newly developed bone graft materials can first be evaluated in a tooth-on-a-chip model and subsequently the in vivo bone formation capacity of the graft material can be validated in the simus lift procedure. This will enhance the relevance and applicability of findings from tooth-on-a-chip studies. Similar validation studies can be done for soft tissue regeneration.

5. Conclusions

Regenerative dentistry has a great clinical potential, but currently the research field lacks a clear vision and focus where it must be heading. Consequently, the introduction of applicable innovative regenerative treatments is too limited. Dental regenerative dentistry needs a breakthrough like immunotherapy that has revolutionized cancer treatment during the last decennium [73]. Perhaps artificial intelligence (AI) can be the game changer and guide regenerative dentistry into a new era, as it is offering advanced solutions in the development of new techniques and materials. The importance for the integration of AI for the dental research community is already reflected in the recently published Canadian National Oral Health Strategy [74]. In this strategy, AI is a core element to address research priorities.

Funding

This research received no external funding.

Conflicts of Interest

The author declares no conflict of interest.

References

1. Langer, R.; Vacanti, J.P. Artificial organs. *Sci. Am*. **1995**, *273*, 130–133.
2. Nor, J.E. Tooth regeneration in operative dentistry. *Oper. Dent.* **2006**, *31*, 633–642. https://doi.org/10.2341/06-000
3. Han, J.; Menicanin, D.; Gronthos, S.; et al. Stem cells, tissue engineering, and periodontal regeneration. *Aust. Dent. J.* **2014**, *59* (Suppl. 1), 117–130. https://doi.org/10.1111/adj.12100.
4. Takahashi K.; Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* **2006**, *126*, 663–667, https://10.1016/j.cell.2006.07.024.
5. Zhang, W.; Yelick, P.C. Craniofacial tissue engineering. *Cold Spring Harb. Perspect. Med.* **2018**, *8*, a025775. https://doi.org/10.1101/cshperspect.a025775.
6. Yelick, P.C.; Sharpe, P.T. Tooth bioengineering and regenerative dentistry. *J. Dent. Res.* **2019**, *98*, 1173–1182. https://doi.org/10.1177/0022034519861903.
7. Zhang, W.; Yelick, P.C. Tooth repair and regeneration: Potential of dental stem cells. *Trends Mol. Med.* **2021**, *27*, 501–511. https://doi.org/10.1016/j.molmed.2021.02.005.
8. Meijer, G.J.; de Bruijn, J.D.; Koole, R.; et al. Cell based bone tissue engineering in jaw defects. *Biomaterials* **2008**, *29*, 3053–3061. https://doi.org/10.1016/j.biomaterials.2008.03.012.
9. Prins, H.J.; Schulten, E.A.J.M.; Ten Bruggenkate, C.M.; et al. Bone regeneration using the freshly isolated autologous stromal vascular fraction of adipose tissue in combination with calcium phosphate ceramics. *Stem Cells Transl. Med.* **2016**, *5*, 1362–1374. https://doi.org/10.5966/sctm.2015-0369.
10. Ivanovski, S.; Han, P.; Peters, O.A.; et al. The therapeutic use of dental mesenchymal stem cells in human clinical trials. *J. Dent. Res.* **2024**, *103*, 1173–1184. https://doi.org/10.1177/00220345241261900.
11. Meijer, G.J.; de Bruijn, J.D.; Koole, R.; et al. CA. Cell-based bone tissue engineering. *PLoS Med.* **2007**, *4*, 260–264. https://doi.org/10.1371/journal.pmed.004009.
12. Wu, V.; Helder, M.N.; Bravenboer, N.; et al. Bone tissue regeneration in the oral and maxillofacial region: A review of the application of stem cells and new strategies to improve vascularization. *Stem Cells Int.* **2019**, *2019*, 6279721. https://doi.org/10.1155/2019/6279721.
13. Cai, J.; Zhang, Y.; Chen, S.; et al. Generation of tooth-like structures from integration-free human urine induced pluripotent stem cells. *Cell Regen.* **2013**, *2*, 6. https://doi.org/10.1186/2045-9769-2-6.
14. Xie, H.; Dubey, N.; Shim, W.; et al. Functional odontoblastic-like cells derived from human iPSCs. *J. Dent. Res*. **2018**, *97*, 77–83. https://doi.org/10.1177/0022034517730026.
15. Larsson, L.; Decker, A.M.; Nibali, L.; et al. Regenerative Medicine for periodontal and peri-implant disease. *J. Dent. Res.* **2016**, *95*, 255–266. https://doi.org/10.1177/0022034515618887.
16. Herford, A.S.; Miller, M.; Signorino, F. Maxillofacial defects and the use of growth factors. *Oral Maxillofac. Surg. Clin.* **2017**, *29*, 75–78. https://doi.org/10.1016/j.coms.2016.08.006.
17. Kim, S.G.; Malek, M.; Sigurdsson, A.; et al. Regenerative endodontics: A comprehensive review. *Int. Endod. J.* **2018**, *51*, 1367–1388. https://doi.org/10.1111/iej.12954.
18. Reddy, A.H. Role of morphogenetic proteins in skeletal tissue engineering and regeneration. *Nat. Biotechnol.* **1998**, *16*, 247–252. https://doi.org/10.1038/nbt0398-247.

19. Hinsenkamp, M.; Collar, J.F. Growth factors in orthopaedic surgery: Demineralized bone matrix versus recombinant bone morphogenetic proteins. *Int. Orthop.* **2015**, *39*, 137–147. https://doi.org/10.1007/s00264-014-2562-0.
20. Nie, W.B.; Zhang, D.; Wang, L.S. Growth factor gene-modified mesenchymal stem cells in tissue regeneration. *Drug Des. Devel. Ther.* **2020**, *14*, 1241–1256. https://doi.org/10.2147/DDDT.S243944.
21. Blum, J.S.; Barry, M.A.; Mikos, A.G. Bone regeneration through transplantation of genetically modified cells. *Clin. Plast. Surg.* **2003**, *30*, 611–620. https://doi.org/10.1016/s0094-1298(03)00079-8.
22. Ahmad, P.; Della Bella, E.; Stoddart, M.J. Applications of bone morphogenetic proteins in dentistry: A bibliometric analysis. *BioMed Res. Int.* **2020**, *2020*, 5971268. https://doi.org/10.1155/2020/5971268.
23. Freitas, R.M.; Spin-Neto, R.; Marcantonio Junior, E.; et al. Alveolar ridge and maxillary sinus augmentation using rhBMP-2; A systematic review. *Clin. Implant Dent. Rel. Res.* **2015**, *10* (Suppl. 1), 192–201. https://doi.org/10.1111/cid.12156.
24. Miron, R.J.; Sculean, A.; Cochran, D.L.; et al. Twenty years of enamel matrix derivative: The past, the present and the future. *J. Clin. Periodontol.* **2016**, *43*, 668–683. https://doi.org/10.1111/jcpe.12546.
25. Nagelkerke, A.; Ojansivu, M.; van der Koog, L.; et al. Extracellular vesicles for tissue repair and regeneration: Evidence, challenges and opportunities. *Adv. Drug Deliv. Rev.* **2021**, *175*, 113775. https://doi.org/10.1016/j.addr.2021.04.013.
26. Lim, K.M.; Kim, S.; Yeom, J.; et al. Advanced 3D dynamic culture system with transforming growth factor β3 enhances production of potent extracellular vesicles with modified protein cargoes via upregulation of TGF-β signaling. *J. Adv. Res*. **2023**, *47*, 57–74. https://doi.org/10.1016/j.jare.2022.09.005.
27. Alaohali, A.; Salzlechner, C.; Zaugg, L.K.; et al. GSK3 inhibitor-induced dentinogenesis using a hydrogel. *J. Dent. Res.* **2022**, *101*, 45–63. https://doi.org/10.1177/00220345211020652.
28. Temenoff, J.; Mikos, A. *Biomaterials: The Intersection of Biology and Materials Science*, 2nd ed.; Pearson Prentice Hall: Saddle River, NJ, USA, 2023.
29. Kokubo, T.; Ito, S.; Huang, Z.T.; et al. CaP-rich layer formed on high strength bioactive glass-ceramic A-W. *J. Biomed. Mater. Res.* **1990**, *24*, 331–343. https://doi.org/10.1002/jbm.820240306.
30. Wei, L.; Yu, D.; Wang, M.; et al. Dose effects of slow-release bone morphogenetic protein-2 functionalized β-tricalcium phosphate in repairing critical-sized bone defects. *Tissue Eng. Part A* **2020**, *26*, 120–129. https://doi.org/10.1089/ten.TEA.2019.0161.
31. Wei, L.; Sun, Y.; Yu, D.; et al. The clinical efficacy and safety of ErhBMP-2/BioCaP/β-TCP as a novel bone substitute using the tooth-extraction-socket-healing model: A proof-of-concept randomized clinical trial. *J. Clin. Periodontol.* **2025**, *52*, 299–309. https://doi.org/10.1111/jcpe.14084.
32. Fang, Z.; Guo, M.; Zhou, Q.; et al. Enamel-like tissue regeneration by using biomimetic enamel matrix proteins. *Int. J. Biol. Macromo.* **2021**, *183*, 2131–2141. https://doi.org/10/1016/j.ijbiomac.2021.06.028.
33. Hosseini, F.; Nair, L.S.; Laurencin, C.T. Inductive materials for regenerative engineering. *J. Dent. Res.* **2021**, *100*, 1011–1019. https://doi.org/10.1177/00220345211010436.
34. Davison, N.L.; Su, J.; Yuan, H.; et al. Influence of surface microstructure and chemistry on osteoinduction and osteoclastogenesis by biphasic calcium phosphate discs. *Eur. Cell Mater.* **2015**, *29*, 314–329. https://doi.org/10.22203/ecm.v029a24.
35. Duan, R.; Barbieri, D.; Luo, X.; et al. Variation of the bone forming ability with the physicochemical properties of calcium phosphate bone substitutes, *Biomater. Sci.* **2017**, *6*, 136–145. https://doi.org/10.1039/c7bm00717e.
36. Stempels, H.W.; Lehr, A.M.; Delawi, D.; et al. Efficacy of biphasic calcium phosphate ceramic with a needle-shaped surface topography versus autograft in instrumental posterolateral spinal fusion. *Spine* **2024**, *49*, 1323–1331. https://doi.org/10.1097/BRS.0000000000005075.
37. Tian, Y.; Chen, C.X.; Xu, X.; et al. A review of 3D printing in dentistry: Technologies, affecting factors, and applications. *Scanning* **2021**, *2021*, 9950131. https://doi.org/10/1155/2021/9950131.
38. Kantaros, A. 3D printing in regenerative medicine: Technologies and resources utilized. *Int. J. Mol. Sci.* **2022**, *23*, 14621. https://doi.org/10.3390/ijms232314621.
39. Mota, C.; Camarero-Espinosa, C.; Baker, M.B.; et al. Bioprinting: From tissue and organ development to in vitro models. *Chem. Rev.* **2020**, *120*, 11032–11092. https://doi.org/10.1021/acs.chem.rev.9b00789.
40. Xu, J.; Gou, I.; Li, H.; et al. Platelet-rich plasma and regenerative dentistry. *Aust. Dent. J.* **2020**, *6*, 131–142. https://doi.org/10.1111/adj.12754.
41. Lang, S.; Loibl, M.; Hermann, M. Platelet-rich plasma in tissue engineering: Hype and Hope. *Eur. Surg. Res.* **2018**, *59*, 265–275. https://doi.org/10.1159/000492415.
42. van den Dolder, J.; Mooren, R.; Vloon, A.P.G.; et al. Platelet-rich plasma: Quantification of growth factor levels and the effect of growth and differentiation of rat bone marrow cells. *Tissue Eng.* **2006**, *12*, 3067–3073. https://doi.org/10.1089/ten.2006.12.3067.

43. Croise, B.; Pare, A.; Joly, A.; et al. Optimized centrifugation preparation of the platelet rich plasma; literature review. *J. Stomatol. Oral Maxillofac. Surg.* **2020**, *121*, 150–154. https://doi.org/10.1016/j.jormas.2019.07.001.
44. Macozza, A.D.; McCarthy, M.B.; Chowaniec, D.M.; et al. Platelet-rich plasma differs according to preparation methods and human variability. *J. Bone Joint Surg. Am.* **2012**, *94*, 308–310. https://doi.org/10.2106/JBJS.K.00430.
45. Izumi, K.; Yortchan, W.; Aizawa, Y.; et al. Recent trends and perspectives in reconstruction and regeneration of intra/extra-oral wounds using tissue engineered oral mucosa equivalents. *Jpn. Dent. Sci. Rev.* **2023**, *59*, 365374. https://doi.org/10.1016/j.jdsr.2023.10.002.
46. Murashima-Suginami, A.; Kiso, H.; Tokita, Y.; et al. Anti-USAG-1 therapy for tooth regeneration through enhanced BMP signaling. *Sci. Adv.* **2021**, 7, eabf1798. https://doi.org/10.1126/sciadv.abf1798.
47. Ravi, V.; Murashima-Suginami, A.; Kiso, H.; et al. Advances in tooth agenesis and tooth regeneration. *Regen. Ther.* **2023**, *22*, 160–168. https://doi.org/10/1016/j.reth.2023.01.004.
48. Svanberg, S.; Hirth, E.; Dittrich, P.S. "Periodontal ligament-on-a chip" as a novel tool for studies on the physiology and pathology of periodontal tissues. *Adv. Healthcare Mater.* **2024**, *13*, 2303942. https://doi.org/10.1002/adhm.202303942.
49. Franca, C.M.; Tahayeri, A.; Rodrigues, N.S.; et al. The tooth-on-a chip: A microphysiologic model system mimicking the biologic interface of the tooth with biomaterials. *Lab Chip* **2020**, *20*, 405–413. https://doi.org/10.1039/c91c00915a.
50. Soares, D.G.; Bordini, E.A.F.; Benton Swanson, E.; et al. Platform technologies for regenerative endodontics from multifunctional biomaterials to tooth-on-a chip strategies. *Clin. Oral Investig.* **2021**, *25*, 4749–4779. https://doi.org/10.1007/s00784-021-04013-4.
51. Rodriguez y Baena, A.; Casasco, A.; Monti, M. Hypes and hopes of stem cell therapies in dentistry: A review. *Stem Cell Rev. Rep.* **2022**, *18*, 1294–1308. https://doi.org/10.1007/s12015-021-10326-4.
52. Nakao, K.; Morita, R.; Saji, Y.; et al. The development of a bioengineered organ germ method. *Nat. Methods* **2007**, *4*, 227–230. https://doi.org/10.1038/nmeth1012.
53. Jeong, S.Y.; Lee, S.; Choi, W.; et al. Fabrication of dentin-pulp-like organoids using dental pulp stem cells. *Cells*, **2020**, *9*, 642. https://doi.org/10.3390/ce.s9030642.
54. Gao, X.; Wu, Y.; Liao, L.; et al. Oral organoids: Progresses and challenges. *J. Dent. Res.* **2021**, *100*, 1–10. https://doi.org/101177/0022034520983808.
55. Aihara, E.; Mahe, M.M.; Schumacher, M.A.; et al. Characterization of stem progenitor cell cycle using murine circumvallate papilla tastebud organoid. *Sci. Rep.* **2015**, *5*, 17185. https://doi.org/10.1038/srep17185.
56. Li, F.C.; Kishen, A. 3D organoids for regenerative endodontics. *Biomolecules* **2023**, *13*, 900. https://doi.org/10.3390/biom13060900.
57. Franca, C.M.; Balbibot, G.S.; Cunha, D.; et al. In vitro models of biocompatibility testing for restorative dental materials: From 2D cultures to organs-on-a chip. *Acta Biomater.* **2022**, *150*, 58–66. https://doi.org/10.1016/j.actbio.2022.07.060.
58. Alghamdi, H.S.; Jansen, J.A. The development and future of dental implants. *Dent. Mater. J.* **2020**, *39*, 167–172: https://doi.org/10.4012/dmj.2019-140.
59. Rocuzzo, A.; Imber, J.C.; Marruganti, C.; et al. Clinical outcomes of dental implants in patients with and without history of periodontitis: A 20-year prospective study. *J. Clin. Periodontol.* **2022**, *49*, 1346–1356. https://doi.org/10.1111/cpe.13716.
60. Mason, C. Automated tissue engineering: A major paradigm shift in health care. *Med. Device Technol.* **2003**, *14*, 16–18.
61. Oberweis, C.V.; Marchal, J.A.; Lopez-Ruiz, L.; et al. A worldwide overview of regulatory frameworks for tissue-based products. *Tissue Eng. Part B Rev.* **2020**, *26*, 181–196. https://doi.org/10.1089/ten.TEB.2019.0315.
62. Amaral, C.; Paiva, M.; Rodrigues, A.R.; et al. Global regulatory challenges for medical devices: Impact on innovation and market access. *Appl. Sci*. **2024**, *14*, 9304. https://doi.org/10.3390/app14209304.
63. de Vries, R.B.; Oerlemans, A.; Trommelmans, L.; et al. Ethical aspects of tissue engineering: A review. *Tissue Eng. Part B Rev.* **2008**, *14*, 367–373. https://doi.org/10.1089/ten.teb.2008.0199.
64. Baker, H.B.; McQuilling, J.P.; King, N.M.P. Ethical considerations in tissue engineering research: Case studies in translation. *Methods* **2016**, *15*, 135–144. https://doi.org/10.1010/j.ymeth.2015.08.010.
65. de Kanter, A.J.; Jongsma, K.R.; Verhaar, M.C.; et al. The ethical implications of tissue engineering for regenerative purposes: A systematic review. *Tissue Eng. Part B Rev*. **2023**, *29*, 167–180. https://doi.org/10.1089/ten.TEB.2022.0033.
66. Patini, R.; Staderini, E.; Lajolo, C.; Lopetuso, L.; et al. Relationship between oral microbiotia and periodontal disease: A systematic review. *Eur. Rev. Med. Pharmacol. Sci.* **2018**, *21*, 5775–5788. https://doi.org/10.26355/eurrev_201809_15903.
67. Frencken, J.E.; Sharma, P.; Stenhouse, L.: et al. Global epidemiology of dental caries and severe periodontitis —A comprehensive review. *J. Clin. Periodontol.* **2017**, *44*, 94–105. https://doi.org/10.1111/jcpe.12677.
68. Schroeder, H.E. *Pathobiologie Oraler Strukturen*, 3rd ed.; Karger: Basel, Switzerland, 1996.
69. Lindhe, J.; Berglundh, T. The interface between the mucosa and implant. *Periodontology 2000* **1998**, *17*, 47–54. https://doi.org/10.1111/j.1600-0757.1998.tb00122.x.
70. Bruckmann, C.; Walboomers, X.F.; Matsuzaka, K.; et al. Periodontal ligament and gingival fibroblast adhesion to dentin-like textured surfaces. *Biomaterials* **2005**, *26*, 339–346. https://doi.org/10.1016/j.biomaterials.2004.02.031.

71. Abdallah, M.N.; Badran, Z.; Ciobanu, O.; et al. Strategies for optimizing the soft tissue seal around ossointegrated implants. *Adv. Healthc. Mater.* **2017**, *6*, 1700549. https://doi.org/10.1002/adhm.201700549.
72. Farre-Guasch, E.; Bravenboer, N.; Helder, M.N.; et al. Blood vessel formation and bone regeneration potential of the stromal vascular fraction seeded on a calcium phosphate scaffold in the human maxillary sinus floor elevation model. *Materials* **2018**, *11*, 161. https://doi.org/10.3390/ma1101061.
73. Rui, R.; Zhou, L.; He, S. Cancer immunotherapies: Advances and bottlenecks. *Front. Immunol.* **2023**, *14*, 1212476, https://doi.org/10.3389/fimmu.2023.1212376.
74. Rock, L.D.; Akada, G.; Al-Waeli, H.; et al. Canada's First National Oral Health Research Strategy (2024–2030). *J. Dent. Res.* **2025**, *104*, 113–118. https://doi.org/10.1177/00220345241299360.