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# Programmable hydrogel matrices for oral and maxillofacial organoids: Engineering mechanobiological and biochemical niches to reverse tissue senescence

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## Abstract

Age-related degeneration of oral and maxillofacial tissues, associated with extracellular matrix sclerosis and the senescence-associated secretory phenotype (SASP), poses an escalating challenge in the context of global population aging. Conventional static biomaterials and two-dimensional *in vitro* culture systems cannot adequately recapitulate this dynamic pathological microenvironment, and animal models are limited by interspecies differences that hinder translational fidelity. Organoid technology can recapitulate key aspects of tissue-specific architecture, cellular heterogeneity, and functional organization, thereby providing physiologically relevant three-dimensional models for aging research and regenerative medicine. These models not only enable disease modeling and pathogenesis studies to investigate senescence mechanisms that are difficult to resolve in conventional *in vivo* models and support high-throughput screening of anti-aging compounds, but also provide a basis for organoid transplantation in functional tissue regeneration. As an emerging and promising regenerative strategy, organoid-based therapy therefore offers new opportunities for reconstructing aging oral and maxillofacial tissues. However, its clinical potential remains constrained by the lack of programmable matrices capable of dynamically mitigating key features of the senescent microenvironment. This review examines the emergence of programmable hydrogels as tunable active matrices for oral and maxillofacial organoid engineering within senescent microenvironments. We analyze material-based strategies for modulating senescence-associated phenotypes, including mechanobiological approaches, such as tunable stress relaxation to attenuate pathological mechanical memory, and biochemical interventions that target reactive oxygen species via nanozyme catalysis and modulate SASP signaling through spatiotemporal delivery control. We further evaluate the application of these matrices for lineage-specific tissue reconstruction across the dentin–pulp complex, periodontal tissue, temporomandibular joint, salivary gland, and mucosal barrier. Finally, we discuss how integrating spatiotemporal multi-omics, microfluidic organ-on-a-chip platforms, and artificial intelligence-assisted

bioprinting may advance organoid engineering, while highlighting key translational barriers related to neurovascularization, safety, standardized manufacturing, and regulatory compliance.

**Keywords:** Programmable hydrogels; Organoids; Senescence; Oral and maxillofacial organoids; Tissue engineering

## 1. Introduction

As global life expectancy continues to rise, population aging and its associated degenerative diseases have become a major public health challenge. According to recent systematic analyses, the age-standardized prevalence of major oral conditions reached 45,900 cases per 100,000 population globally in 2021, affecting over 3.69 billion individuals, with this disease burden projected to increase further among older populations by 2035 (Figure 1).[1] Within the oral and maxillofacial region, age-related degeneration manifests as progressive physical deterioration of anatomical structures compounded by chronic low-grade inflammation and impaired endogenous regenerative capacity, driven by the persistent accumulation of senescent cells and their senescence-associated secretory phenotype (SASP).[2]

Researchers have long relied on two-dimensional (2D) monolayer cell culture and animal models to study the molecular mechanisms of aging and develop regenerative interventions (Figure 1). However, these conventional platforms have inherent limitations that constrain their translational utility.[3,4] Static 2D culture lacks the three-dimensional (3D) architecture and physiological cell-matrix interactions needed to reproduce the complex intercellular paracrine signaling and mechanobiological cues that govern cellular senescence *in vivo*.[3] Animal models, meanwhile, exhibit well-documented interspecies differences from humans in pharmacokinetics, local immune networks, wound healing biology, and genetics, which collectively contribute to the high attrition rates of candidate anti-aging therapeutics in late-stage clinical trials.[4]

Organoid technology has advanced regenerative medicine by enabling stem cells to self-organize into 3D miniature organs that recapitulate the multicellular architecture and physiological functions of native human tissues.[5,6] In the oral and maxillofacial context, organoids derived from dental pulp stem cells (DPSCs), periodontal ligament stem cells, salivary gland progenitors, and oral mucosal epithelial cells have shown potential for *in vitro* disease modeling and tissue regeneration.[6]

Organoids have been increasingly deployed along three interconnected therapeutic axes.[7,8] The first is disease modeling and pathogenesis studies. Organoids recapitulate key hallmarks of aging, including epigenetic drift, mitochondrial dysfunction, and SASP-mediated paracrine senescence propagation at a resolution and experimental tractability that is difficult to achieve in living organisms, enabling genetic manipulation, live imaging, and multi-omics profiling within a physiologically relevant 3D human tissue context.[9] The second is high-throughput drug screening: patient-derived organoids cultured in 3D can be arrayed for parallel testing of candidate senolytic and senomorphic compounds, providing efficacy and toxicity data in human-specific microenvironments that better predict clinical outcomes than conventional 2D monolayer screens.[10] The third is organoid transplantation and regenerative therapy: organoids can be engrafted as living grafts into damaged or degenerated tissues, where they integrate with host vasculature and contribute to functional recovery, as demonstrated across multiple organ systems.[11] As reviewed by Soto-Gamez *et al.*[7] and Tao *et al.*[8], these three strategies form the backbone of organoid-based approaches to aging-related diseases.

However, the therapeutic potential of organoids in aging diseases is limited by the extracellular matrix (ECM) substitutes in which they are cultured. Current organoid culture still depends heavily on murine sarcoma-derived basement membrane extracts such as Matrigel, whose ill-defined biochemical composition, substantial batch-to-batch variability, and inherent animal-derived components raise concerns about immunogenicity and pathogen contamination during clinical translation.[12] Moreover, these static matrices cannot provide the spatiotemporally dynamic biomechanical cues needed to mimic the evolving ECM during tissue senescence, including progressive pathological stiffening and persistent oxidative stress.[12]

In parallel, programmable hydrogels have evolved from inert structural scaffolds toward dynamic, stimuli-responsive matrices (Figure 1). These engineered polymer networks can sense pathological cues in the aging microenvironment, such as elevated reactive oxygen species (ROS), acidic pH, and matrix metalloproteinase (MMP) overexpression, and respond through programmed

structural changes, tunable stress relaxation, and spatiotemporally controlled therapeutic delivery.[13–15] Dynamic hydrogel mechanics, including viscoelasticity, stress relaxation rate, and stimuli-responsive topological remodeling, can directly modulate organoid development, stem cell fate specification, and tissue-level morphogenesis through mechanotransduction-mediated chromatin remodeling.[16] By uniting biomechanical responsiveness with biochemically programmed drug delivery in a single synthetic matrix, programmable hydrogels serve two functions at once: providing the physical niche for organoid self-organization while actively remodeling the pathological senescent microecology to favor regeneration. The convergence of programmable hydrogel engineering with organoid biology thus creates a therapeutic strategy for reversing tissue senescence—one that harnesses the dynamic responsiveness of synthetic matrices to counteract microenvironmental drivers of aging (matrix stiffening, oxidative stress, SASP-mediated inflammation) while sustaining organoid viability, lineage-specific differentiation, and functional maturation.[16]

Our review systematically examines the programmable hydrogel-organoid composite regenerative system targeting the senescent oral and maxillofacial microenvironment. We first analyze the material-driven mechanisms by which programmable hydrogels remodel the senescent microecology and counteract senescent cell fates, focusing on two core dimensions: biomechanical modulation and targeted biochemical response. We then discuss the translational applications of this composite system within five specific oral and maxillofacial microenvironments: the dentin–pulp complex, periodontium, temporomandibular joint (TMJ), salivary glands, and oral mucosa.[17] Finally, we assess how interdisciplinary technologies, including multidimensional spatiotemporal omics, dynamic microfluidic organ-on-a-chip systems, and machine learning (ML), are beginning to inform the design of these materials, while also addressing the immune-oncology crosstalk and regulatory hurdles that currently limit clinical standardization. Our aim is to provide a critical synthesis of current strategies and to identify key technological and translational challenges facing the field.

## 2. Design of programmable hydrogels targeting the senescent microenvironment

Programmable hydrogels sense pathological cues—elevated ROS, acidic pH, and MMP overexpression—and respond through dynamic changes in matrix mechanics and drug release kinetics, making them well-suited for supporting organoids in the aging oral and maxillofacial environment. However, designing a hydrogel that counteracts senescence first requires identifying the factors that drive the aging extracellular milieu. Two pathological axes dominate the senescent microecology of oral and maxillofacial tissues, and they reinforce each other (Figure 2). Biochemically, age-related mitochondrial dysfunction elevates ROS, which triggers lipid peroxidation, activates nuclear factor (NF)-κB, and promotes the sustained secretion of SASP factors, including MMPs and pro-inflammatory chemokines, that degrade the ECM and maintain chronic inflammation.[2,14] Mechanically, advanced glycation end product (AGE)-mediated non-enzymatic collagen crosslinking increases matrix stiffness, transmitting persistent tension to resident stem cells through integrin clusters, focal adhesion kinase,

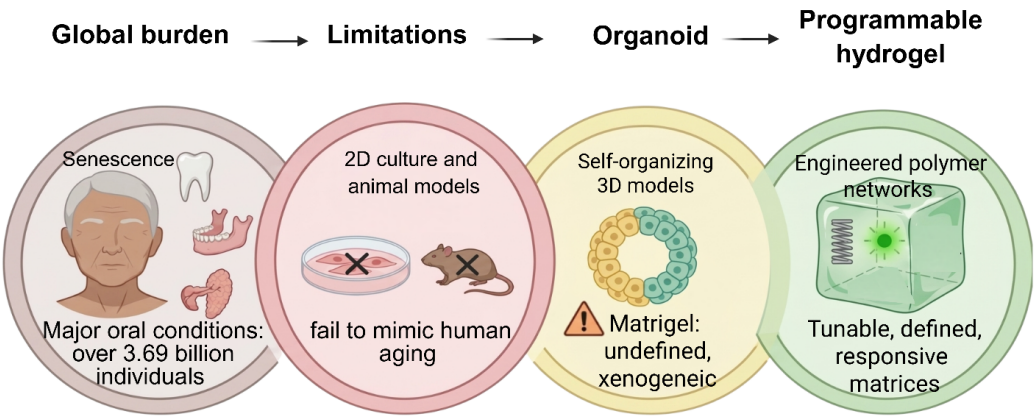


**Figure 1.** The clinical requirement for programmable hydrogels in oral and maxillofacial organoids for anti-aging
Abbreviations: 2D: Two-dimensional; 3D: Three-dimensional. Created with BioRender.com. Jinling Liu (2026) https://BioRender.com/4wtimai

and Piezo1 channels.[17] The biochemical and mechanical axes do not operate independently. They reinforce each other. SASP-mediated ECM breakdown amplifies aberrant mechanotransduction; the resulting mechanical stress drives yet more senescence and SASP secretion. The tissue becomes trapped in a degenerative spiral. Programmable hydrogel research has attacked this problem from two complementary directions—mechanical and biochemical, though rarely both at once. Mechanical strategies dissipate pathological stiffness, intercept Piezo1–Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) signaling, and erase mechanical memory at the chromatin level. Biochemical strategies scavenge mitochondrial ROS through nanozyme catalysis, neutralize SASP components via logic-gated release, and reprogram local immune function. Notably, few hydrogel systems combine these two arms into a single matrix. We regard this integration gap as one of the field's more consequential blind spots. Because matrix stiffening is the first physical barrier an implanted organoid confronts, we begin there.

### 2.1. Mechanobiological intervention

Excessive AGE-mediated non-enzymatic crosslinking lies at the root of the senescent ECM pathology. As these crosslinks accumulate within the native collagen network, the matrix undergoes irreversible stiffening and loses the viscoelasticity that healthy tissue depends on.[18] Piezo1—a mechanosensitive ion channel on resident stem cells—detects this elevated stiffness and responds with sustained calcium ion ($Ca^{2+}$) influx.[19] Notably, the downstream consequences unfold even without exogenous inflammatory cytokines: Piezo1-activated calcium/calmodulin-dependent protein kinase II signaling drives mitochondrial fission through dynamin-related protein 1 phosphorylation, pushing stem cells toward senescence.[20] When stem cells reside for prolonged periods on rigid pathological substrates, YAP/TAZ remains trapped in the nucleus. There, it reorganizes chromatin and imprints a durable mechanical memory. This mechano-epigenetic phenomenon was first documented in skeletal muscle stem cells.[21] Evidence now suggests it is broadly conserved across mesenchymal lineages, and there is no reason to assume that oral and maxillofacial tissues are exempt. As a result, even when re-seeded onto a soft matrix, these mechanically conditioned cells show impaired recovery of regenerative potential and lineage-specific differentiation capacity.[21]

To address this aberrant mechanotransduction at its source, next-generation programmable hydrogels have moved beyond conventional static covalent networks. By incorporating supramolecular host–guest interactions or dynamic reversible hydrogen bonding, these materials exhibit enhanced viscoelasticity and stress relaxation properties.[22] Such dissipative dynamic networks can absorb and buffer aberrant cytoskeletal traction forces generated during cell spreading, thereby intercepting the transmission of pathological stiffness signals to the nucleus.[23] Single-cell multi-omics and epigenetic analyses further indicate that stress relaxation in dynamic hydrogels functions as a mechano-epigenetic modulator: by downregulating enhancer of zeste homolog 2 (EZH2) expression, these materials facilitate erasure of the repressive histone modification histone H3 lysine 27 trimethylation (H3K27me3), thereby reactivating tissue-specific regenerative gene clusters silenced by mechanoaging.[24]

### 2.2. Biochemical responsive networks to oxidative stress and senescence-associated secretory phenotype

In the biochemical dimension, the senescent microecology is driven first by mitochondrial ROS. Supraphysiological ROS levels damage membrane lipids, promote ferroptosis in resident stem cells, and induce leakage of mitochondrial DNA into the cytosol, where it activates the cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) innate immune pathway and drives macrophages toward a pro-inflammatory M1 phenotype.[25] Nanozyme-integrated hydrogels intercept this cascade at its origin by catalyzing the breakdown of ROS before downstream inflammatory signals can propagate. Glycyrrhizic acid-based hydrogels functionalized with cell membrane coatings achieve mitochondrial-targeted ROS scavenging, attenuating the cGAS–STING–NF-κB axis within the mitochondrial compartment.[26] Cerium (Ce)-zoledronic acid nanocomposites embedded in phenylboronic acid-modified hyaluronic acid networks exploit $Ce^{3+}/Ce^{4+}$ reversible valence conversion to replicate the dual cascade activities of superoxide dismutase and catalase.[27] At the level of single-atom catalysis, chitosan-based hydrogels incorporating manganese-nitrogen-carbon single-atom nanozymes (Mn-NC SAzymes) use $Mn\text{-}N_4$ coordination to inhibit the ROS-driven mitogen-activated protein kinase (MAPK) pathway, reducing chondrocyte apoptosis and cartilage matrix degradation.[28] Black phosphorus@cerium oxide nanozymes extend scavenging to target the interleukin 6/signal transducer and activator of transcription 3 pro-inflammatory and pro-ferroptotic axis through suppression of human antigen R-mediated mRNA stabilization.[29] These systems differ in catalytic mechanism, such as membrane-targeted delivery, metal valence cycling, single-atom coordination, and heterostructure engineering, but share the same logic: eliminating ROS at the source before the signal cascades into inflammation. These systems, however, do not address the SASP that has already accumulated in the tissue.

The ROS scavenging curbs the oxidative drive of new SASP production, but the chemokines and MMPs secreted by senescent cells persist in the microenvironment, sustaining local immune suppression and ECM breakdown. Strategies for this residual burden span a continuum. At one end, passive neutralization: a pure DNA immunosuppressive hydrogel exploits its polyanionic backbone to physically trap free pro-inflammatory chemokines through steric hindrance and electrostatic adsorption, limiting macrophage and neutrophil infiltration.[30] At the other end, active elimination: hydrogels crosslinked with ROS-cleavable thioketal or Schiff base bonds depolymerize selectively within the SASP-rich microenvironment, releasing therapeutic payloads on demand.[31,32] A further step removes the senescent cells themselves—macrophage-derived vesicles co-modified with arginine–glycine–aspartic acid (RGD) peptides and anti-programmed death-ligand 1 antibody activate natural killer cell cytotoxicity against senescent fibroblasts through photodynamic stimulation.[33] These two approaches complement rather than compete with each other. Trapping provides immediate damage control; elimination changes the cellular composition of the tissue. But even after the SASP burden is cleared, immune cells chronically conditioned by the senescent microenvironment do not spontaneously recover.

Macrophages are locked into a glycolytic M1-like phenotype, while T cells exhibit impaired effector function. Other immune cell populations are progressively reshaped following prolonged exposure to the senescent microenvironment. None of these populations spontaneously reverts to a pro-regenerative state once ROS and SASP are removed. Restoring tissue homeostasis, therefore, demands active reprogramming. Astragalus polysaccharides inhibit immune cell ferroptosis through the nuclear factor erythroid 2-related factor 2/heme oxygenase-1/solute carrier family 7 member 11 axis while driving M2 macrophage polarization, thereby shifting the local balance from inflammation to repair.[34] A peptide composite hydrogel (Fmoc-DDT@Fos) that provides sustained release of fostamatinib similarly inhibits ferroptosis and reshapes macrophage polarization, attenuating cartilage matrix degradation in the TMJ.[35] These strategies rescue immune cells from ferroptotic death and reorient their phenotype. α-Ketoglutarate (α-KG) reprograms macrophages at the metabolic-epigenetic interface: derived from glutamine metabolism, it serves as an obligate cofactor for ten-eleven translocation methylcytosine dioxygenase 2, driving DNA hydroxymethylation at anti-inflammatory gene promoters and shifting macrophages toward a pro-resolving phenotype.[36] Composite hydrogels (3-aminophenylboronic acid-silk fibroin/poly[vinyl alcohol]) that release microvesicles derived from interferon-γ-stimulated cells in response to ROS cues provide context-dependent immune modulation within the senescent microenvironment.[37] These approaches intervene at three levels, including preventing immune cell death, restoring oxidative metabolism, and erasing senescence-associated epigenetic marks, though their integration within a single programmable matrix remains to be demonstrated.

### 2.3. Dynamic topological remodeling and spatiotemporal decoupled delivery

The mechanobiological and biochemical strategies described above each target a single pathological axis of the senescent microenvironment. In aging oral and maxillofacial tissues, however, matrix stiffening and SASP-driven inflammation form a self-reinforcing positive feedback loop (Figure 2) that a one-dimensional intervention alone cannot disrupt.[38–40] Therefore, we examine hydrogel designs that integrate dynamic topological matrix remodeling with spatiotemporally programmed delivery, progressing from externally tunable physical networks to materials capable of cell-driven adaptation, sequential logic, and ultimately molecular computation.

DNA-based crosslinking matrices such as DyNAtrix exploit Watson–Crick base pairing to tune stress relaxation time from seconds to hours simply by adjusting hybridization chain length or introducing base mismatches, without altering network elasticity.[41] At a finer spatial scale, photoresponsive supramolecular assemblies reversibly modulate cell adhesion ligand (RGD) spacing between 1.8 and 2.6 nm, approaching the 60–70 nm threshold required for integrin clustering, and thereby enable dynamic control over focal adhesion kinase maturation.[42] For deeper tissue applications, visible-light-responsive tetrafluoroazobenzene has replaced ultraviolet (UV) triggers, overcoming the limited penetration depth and cytotoxicity of UV while enabling non-destructive, reversible photoisomerization-driven topological changes for programmed drug release.[43] Photo-triggered secondary grafting with polyethylene glycol and alginate further permits spatial patterning of stress relaxation rates within a single 3D matrix, creating local mechanical heterogeneity to guide cell migration and lineage specification. Compared to DNA-based strategies, which offer precise molecular-level tunability but require aqueous environments and are susceptible to nuclease degradation, photoresponsive systems provide spatiotemporal control through a non-contact stimulus; however, both classes depend on externally applied triggers and cannot autonomously sense or adapt to evolving tissue states.

A different design philosophy closes the feedback loop entirely. Instead of responding to external triggers, these living composite hydrogels remodel in response to signals secreted by the cells they house. The cell-programmed adaptive contraction (CPAC) mechanism illustrates the

concept. Mesenchymal stem cells (MSCs) embedded within microgel-based composites secrete alkaline phosphatase (ALP), which triggers a hydrophilic-to-hydrophobic phase transition in the surrounding microgels, producing a mechanically heterogeneous network. Critically, where the matrix stiffens and how much, depends on the number and metabolic activity of the resident cells. The result is a bidirectional feedback loop. The matrix is no longer a passive substrate; it becomes an active participant in tissue remodeling.[24] This marks a conceptual departure from externally tunable materials: rather than responding to an operator-applied stimulus, the hydrogel remodels in response to the functional state of its embedded cells. Current CPAC systems, however, remain limited to a single enzymatic input (ALP). Extending this principle to multi-signal integration and to the diverse cell types of the oral and maxillofacial region remains an open challenge.

Beyond structural remodeling, a second demand arises: temporal precision. In the senescent microenvironment, controlling inflammation and promoting tissue regeneration are temporally distinct tasks. They cannot be accomplished simultaneously. Programmable hydrogels must therefore coordinate therapeutic cargo delivery with the right sequence and timing, suppressing inflammation first, then triggering repair. A microspheres-in-gel sequential logic gate system addresses this need through a two-phase design: MMP-13, which is abundant in the SASP-rich milieu, triggers degradation of the outer hydrogel layer to release anti-inflammatory exosomes (Phase 1). Subsequently, the exposed inner microspheres provide sustained release of pro-regenerative extracellular vesicles (EVs) (Phase 2), achieving spatiotemporal decoupling of inflammation mitigation and tissue reconstruction.[44] This design represents a form of sequential logic: the Phase 1 → Phase 2 transition follows a fixed, pre-programmed order. An inherent constraint is that Phase 2 proceeds regardless of whether inflammation has been resolved, because the system lacks feedback sensing of local inflammatory status, a limitation that motivates the conditional logic strategies discussed below.

To enable conditional rather than pre-programmed responses, hydrogels incorporating molecular Boolean logic gates process multiple environmental inputs and trigger drug release or matrix remodeling only when a defined combination of pathological cues is present. Dual aptamer sequences integrated into multi-armed DNA hydrogels have been employed to construct "AND" and "OR" gates that recognize ATP together with target molecules, triggering network disassembly and payload release exclusively when the programmed combination of stimuli is simultaneously detected.[45] While aptamer-based gates offer a generalizable recognition framework that can, in principle, be adapted to different targets by swapping the aptamer sequence, their sensitivity is limited by the binding affinity of the aptamer to its ligand. In a complementary approach that addresses this sensitivity ceiling, clustered regularly interspaced short palindromic repeats–CRISPR-associated protein 12a trans-cleavage activity embedded in DNA hydrogels enables exponential signal amplification for trace disease-associated nucleic acids, coupling matrix liquefaction directly to molecular detection, and the matrix itself serves as both sensor and actuator.[46] Multi-branched DNA nanostars with regulated sticky-end pairing logic extend this paradigm: they undergo phase transitions in response to multiplexed environmental inputs, and the underlying topological interlocking (e.g., HEX-dimers) simultaneously enhances mechanical toughness.[47] At the highest level of molecular integration reported to date, cytokine-responsive DNA origami plasmonic nanoantennas operate a set of Boolean logic operations, AND, OR, NOT, and INHIBIT, within hydrogels, with output monitored in real time by surface-enhanced Raman scattering.[48] Counterion-regulated metal-ion coordination strategies (e.g., $SP^{-}Mn^{+}Xy^{-}$) add a temporal encoding dimension, yielding hydrogel systems whose logic modules can be switched over time.[49] The rational design of these increasingly complex stimulus-responsive networks has begun to benefit from supervised ML models, including random forests and decision trees for high-throughput material screening, although this direction remains at an early stage.[49] Across all these Boolean systems, one practical consideration matters especially for oral and maxillofacial applications: are the required molecular inputs (ATP, specific nucleic acids, cytokines) present at diagnostically informative concentrations in saliva, gingival crevicular fluid, or local tissue exudates? This question has received little attention.

In summary, the programmable hydrogel toolbox has grown well beyond the static scaffolds of a decade ago. The field now commands matrices that dissipate pathological stiffness while erasing the underlying mechanical memory, that intercept oxidative stress at its mitochondrial origin while reprogramming the immune milieu, and that integrate these mechanical and biochemical functions within spatiotemporally coordinated, logic-gated delivery platforms. This progression from single-axis intervention to multi-input, conditional responsiveness marks a genuine advance; yet several challenges remain. Few systems combine all three tiers of functionality within a single matrix. The molecular inputs required for Boolean logic gates (ATP, pathogen-derived nucleic acids, cytokine signatures) have been validated largely in defined buffer conditions, not in the complex, enzyme-rich fluids of the oral cavity. The long-term stability of DNA- and peptide-based dynamic networks under the mechanical and microbiological demands of the oral environment remains largely unexplored. Addressing these gaps requires

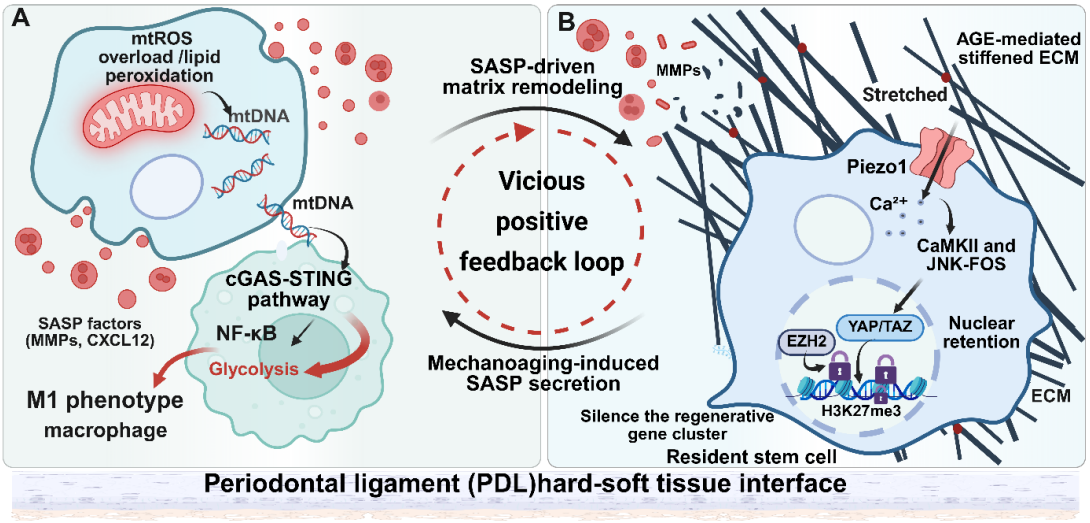


**Figure 2.** The pathological microenvironment of oral and maxillofacial aging: a vicious cycle of biochemical and mechanical collapse. (A) Biochemical and immune collapse. Age-related mitochondrial dysfunction leads to mitochondrial (mt) reactive oxygen species (ROS) overload, lipid peroxidation, and subsequent mtDNA leakage. This abnormal mtDNA overactivates the cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING)–nuclear factor (NF)-κB innate immune pathway[25], forcing macrophage metabolism to shift to glycolysis and driving polarization to a pro-inflammatory M1 phenotype.[26,50] Simultaneously, senescent resident cells secrete numerous senescence-associated secretory phenotype (SASP) factors, including matrix metalloproteinases (MMPs) and chemokine ligand (C–X–C motif chemokine ligand [CXCL12])[2,12], creating a highly destructive microecological network. (B) Mechanical and epigenetic drift. Advanced glycation end products (AGE)-mediated non-enzymatic cross-linking leads to progressive stiffening of the extracellular matrix (ECM).[19] This pathological, rigid mechanical stretch of the Piezo1 channel residing on stem cells triggers a sustained $Ca^{2+}$ influx. This abnormal mechanical transduction activates the calmodulin-dependent protein kinase II (CaMKII) and c-Jun N-terminal kinase (JNK)-FBJ murine osteosarcoma viral oncogene homolog (FOS) axis, resulting in nuclear retention of Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ), and ultimately enhancer of zeste homolog 2 (EZH2) methyltransferase catalyzes the repressive histone H3 lysine 27 trimethylation (H3K27me3) histone modification, silencing the regenerative gene cluster, and locking cells in "mechanical memory".[19–21,24] (Central) malignant positive feedback loop. These two axes reinforce each other: SASP-driven matrix remodeling (e.g., MMP-mediated ECM degradation) further disrupts the physical structure, which, in turn, induces greater mechanical aging and subsequent SASP secretion. Created with BioRender.com. Jinling Liu (2026) https://BioRender.com/u6d0vwn

closer integration between materials chemistry and oral microbiology, together with accelerated screening pipelines that test matrix formulations against clinically relevant multi-species biofilms and masticatory loading regimes. The following section examines how the design principles described above are currently being applied and where they fall short across four oral and maxillofacial organoid systems. To the best of our knowledge, the most under-explored question is not whether these matrices function in controlled settings, which they clearly do, but whether they can maintain performance under the extreme mechanical and enzymatic stresses of the oral cavity over clinically relevant time scales.

## 3. Senescence reversal and functional reconstruction of oral and maxillofacial-specific organoids

The hard and soft tissues of the oral and maxillofacial region, from dental pulp and periodontium to jawbone and salivary glands, exhibit considerable developmental heterogeneity. This diversity arises from coordinated interactions among cranial neural crest cells (CNCCs), ectoderm, and mesoderm. Capturing such lineage-specific architecture *in vitro* calls for 3D organoid models.[6,51]

With aging and chronic inflammatory stress, resident progenitor cells in these tissues undergo epigenetic drift, with genome-wide DNA hypermethylation and aberrant histone modifications accumulating. Programmable matrices may counteract this senescence-associated epigenetic silencing through mechanotransduction-mediated chromatin remodeling, as discussed in Section 2.[52] Notably, the mechanical drivers of this silencing differ sharply across oral tissues, reflecting the distinct anatomical demands and loading environments of each niche.

Specifically, the dentin–pulp complex, enclosed within rigid mineralized walls, is subject to hydrostatic pressure. The periodontal complex sustains shear and tensile forces at the hard–soft interface. The TMJ fibrocartilage

undergoes cyclic compression. The salivary glands and mucosal barriers are continuously subjected to fluid shear stress.[17] Conventional rigid scaffolds and cell suspension injections cannot meet the distinct mechanical dissipation requirements of these niches. The consequence is mechano-apoptosis, compromised organoid viability, and impaired functional integration with host tissue.[53] To address these tissue-specific requirements, programmable hydrogels can be tailored as lineage-specific delivery vehicles by modulating viscoelastic stress relaxation, enzyme-responsive degradation, and topographical biochemical cues.[39] The following subsections address each niche in turn (Figure 3), and the corresponding hydrogel-organoid strategies are systematically summarized in Table 1.

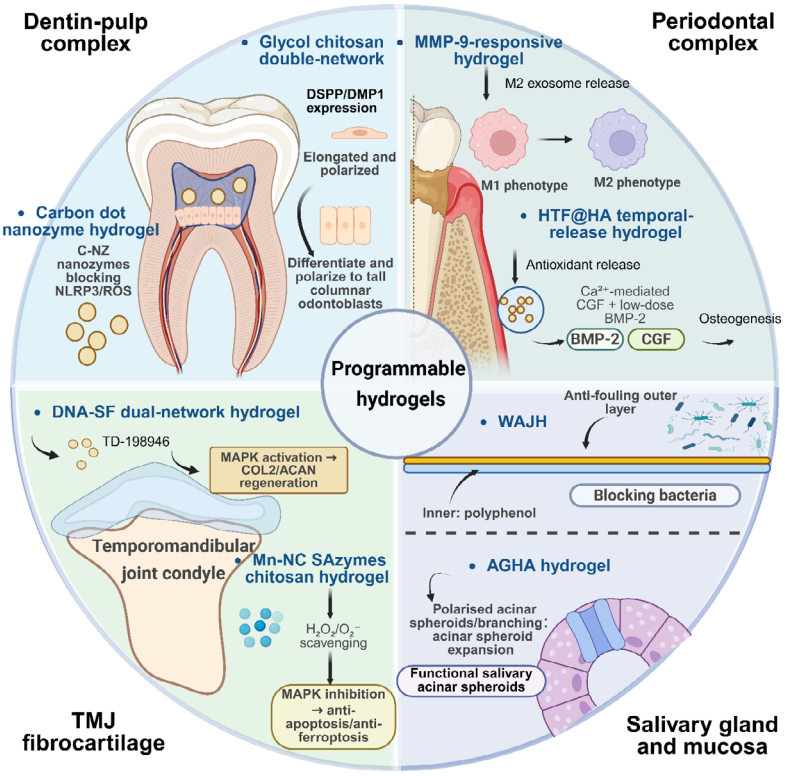


**Figure 3.** Programmable hydrogel-organoid system for lineage-specific reconstruction. The central radial diagram illustrates the active programmed microecological interventions for four different oral and maxillofacial niches. (Top left: Dentin–pulp complex) In the confined cavity, an injectable glycol chitosan double-network hydrogel supports dental pulp stem cell odontogenic differentiation and mineralization, while an integrated carbon quantum dot nanozyme (C-NZ) hydrogel catalytically quenches mitochondrial reactive oxygen species (ROS) and blocks NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome assembly.[54,55] (Top right: Periodontal complex) At the hard–soft tissue interface, a matrix metalloproteinase (MMP)-9-responsive hydrogel releases M2 macrophage-derived exosomes upon enzymatic cleavage of peptide crosslinkers within the inflammatory microenvironment, driving M1-to-M2 macrophage polarization and transitioning the local immune milieu from inflammation to regeneration.[56] In parallel, a temporally programmed injectable hydrogel (HTF@HA) exploits boronate ester hydrolysis under acidic and oxidative conditions during the early inflammatory phase to release antioxidant factors, followed by calcium-phosphate-mediated sustained delivery of concentrated growth factors and low-dose bone morphogenetic protein-2 (BMP-2) during the repair phase for coordinated alveolar bone regeneration.[57] (Bottom left: Temporomandibular joint [TMJ] fibrocartilage). To withstand cyclic compressive loading of the TMJ condyle, digital light processing three-dimensional-bioprinted DNA-silk fibroin (SF) dual-network hydrogels sustain the release of glucosamine and the chondrogenic small molecule TD-198946 under dynamic loading, activating mitogen-activated protein kinase (MAPK) signaling to promote hyaline-like fibrocartilage regeneration.[58] Concurrently, manganese-nitrogen-carbon single-atom nanozymes (Mn-NC SAzymes) anchored within a chitosan hydrogel catalyze ROS decomposition via Mn-$N_4$ coordination, inhibiting the MAPK apoptotic cascade, and ferroptosis to protect the cartilage matrix.[28] (Bottom right: salivary gland and mucosa) At the mucosal barrier, a Janus wet-adhesive hydrogel (WAJH) deploys an antifouling agar/polyacrylamide double-network outer face that blocks bacterial ingress, while its polyphenol-rich inner face achieves strong wet-tissue adhesion and continuous ROS scavenging to sustain epithelial integrity.[59] Within the salivary gland, a fully chemically defined thermo-ionic hydrogel composed of hyaluronic acid, alginate, and gelatin (AGHA) matches the low elastic modulus of native glandular tissue, enabling expansion of functional acinar spheroids from human salivary stem/progenitor cells without xenogeneic components.[60] Created with BioRender.com. Jinling Liu (2026) https://BioRender.com/u1e8mlj

### 3.1. Dentin–pulp complex: Reversing senescence in confined microenvironments

The dentin–pulp complex is enclosed within rigid mineralized dentinal walls, creating a confined microenvironment with limited collateral blood supply and elevated hydrostatic pressure. DPSCs, derived from CNCCs, possess multipotent differentiation capacity, particularly toward neurogenic and angiogenic lineages. Under aging or inflammatory stress, the combination of mechanical confinement and oxidative damage, which are mutually reinforcing, drives DPSC senescence. The confined cavity limits vascular clearance of ROS, compounding mitochondrial oxidative stress. At the epigenetic level, single-cell multi-omics studies have shown that reduced expression of the nuclear pore complex protein (nucleoporin 62) triggers nuclear receptor-binding SET domain protein 2-mediated aberrant histone H3 lysine 36 dimethylation, thereby silencing proliferative gene programs.[61] Conventional root canal therapy using inert materials (e.g., gutta-percha) provides only passive physical obturation and does not restore the sensory and immune functions supported by intrapulpal nerve fibers and capillaries.

To address this combined mechanical and biochemical challenge, dual-network (DN) glycol chitosan-based programmable hydrogels with rapid stress relaxation have been developed for *in situ* injection within the root canal. Upon swelling in the confined cavity, these hydrogels dissipate accumulated hydrostatic pressure through dynamic sliding of polymer segments, reducing the risk of mechanical ischemia and anoikis in implanted organoids.[54]

For the oxidative stress component, nanozyme-functionalized hydrogels, such as carbon quantum dot nanozymes covalently anchored within gelatin methacryloyl (GelMA) networks, have been developed to provide sustained catalytic scavenging of $H_2O_2$ and superoxide anions in the dental pulp inflammatory microenvironment.[55] This ROS clearance inhibits the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome assembly and Caspase-1-mediated pyroptosis in macrophages, steering polarization toward a pro-angiogenic M2 phenotype that supports early vascularization of the regenerating pulp.

Functional pulp regeneration additionally requires directing DPSCs to polarize into columnar odontoblasts capable of forming organized dentinal tubule networks. This process depends on anisotropic ECM topological cues that isotropic hydrogels cannot provide. Decellularized porcine dental pulp ECM hydrogels preserve lineage-specific biochemical motifs (e.g., laminin, fibronectin) and provide a biomimetic niche for DPSC culture.[62] Temperature-gradient ice-templating during hydrogel crosslinking creates anisotropic microchannel architectures that physically guide DPSC cytoskeletal elongation.[63] This directional alignment activates YAP-dependent mechanotransduction, which drives polarized expression of odontoblast markers—dentin sialophosphoprotein (DSPP) and dentin matrix protein 1 (DMP1)—at the apical membrane.[64]

Biochemical chemotaxis strategies have also been developed: peptide motifs derived from bone-forming peptide-1 and amelogenin have been grafted onto self-assembling peptide hydrogels (L-gel/D-gel), enabling the recruitment of residual endogenous stem cells within the pulp cavity through activation of the transforming growth factor-β/Smad and extracellular signal-regulated kinase 1/2 pathways.[65] For severely necrotic teeth, MMP-20-sensitive crosslinkers have been designed to achieve on-demand release of pro-angiogenic and neurotrophic proteins (e.g., S100 calcium-binding protein A7, Copine 7) in coordination with capillary ingrowth.[66]

Vascular endothelial growth factor-loaded temperature-sensitive chitosan/β-glycerophosphate hydrogels provide sustained pro-angiogenic signals to support pulp tissue regeneration.[67] In addition, DPSC-derived EVs enriched with microRNA-1246 have been explored for paracrine modulation of the local microenvironment[68], and digital light processing (DLP)-based bioprinting strategies are being developed to fabricate pre-vascularized pulp constructs that conform to root canal anatomy.[69] These approaches have been validated in microfluidic "tooth-on-a-chip" platforms that maintain organoid viability under continuous perfusion over extended culture periods.[69]

Collectively, these strategies tackle three core obstacles to functional pulp regeneration: pathological pressure dissipation, redox restoration, and odontoblast polarization. Systematic validation at the organoid level, however, has not kept pace. What the field lacks is a set of standardized benchmarks that would allow rigorous comparison across studies.

Dental pulp organoids have been derived from three classes of starting cells: DPSCs from permanent third molars, stem cells from human exfoliated deciduous teeth, and induced pluripotent stem cell (iPSC)-derived CNCCs, each yielding organoids with distinct mineralization kinetics, DSPP expression, and neurogenic propensity.[70,71] Comparing hydrogel performance across these disparate systems is hindered by the absence of standardized reporting benchmarks. Core necrosis, for instance, is predictable under the confined root canal geometry given the diffusion limit of oxygen; yet organoid diameter and viability relative to this limit are rarely reported. Odontoblast polarization, the fraction of cells acquiring columnar morphology with basal nuclei and apical DSPP/DMP1 localization, can

be tracked through Wnt family member 6 upregulation in DPSC-derived organoid-like microspheroids[71], but it is seldom quantified. Similarly, the presence of dentinal tubule-like structures can be assessed by scanning electron microscopy or polarized light imaging[72], and neurovascular coupling can be assessed by co-localized CD31-positive endothelial networks and β-III-tubulin-positive neurites within the same organoid. Trans-dentinal barrier function, meanwhile, can be quantified as permeability coefficients across integrated dentin discs in tooth-on-a-chip platforms.[73] At present, no consensus protocol exists for reporting these metrics across laboratories, leaving the field without a rigorous basis for comparing how matrix design parameters translate to functional pulp regeneration.

### 3.2. Periodontal complex: Bridging hard–soft interfaces under mechanical stress

While the dentin–pulp complex poses challenges of confined-space regeneration, the periodontal complex presents a different mechanical problem, the need to bridge hard and soft tissues under dynamic loading. The periodontal complex, situated at the interface between the tooth root and alveolar bone, is subject to high-frequency masticatory shear and tensile stresses. Periodontal ligament stem cells (PDLSCs) are highly mechanosensitive, and under aging or pathogenic stress, chronic aberrant mechanical loading drives their senescence, impairing their capacity for oriented collagen fiber assembly.[74,75] These mechanically senescent PDLSCs, in turn, secrete SASP factors that amplify local tissue damage.

This SASP-driven inflammation exacerbates local redox imbalance, promoting NLRP3 inflammasome assembly, inflammatory pyroptosis, and polarizing macrophages toward a glycolysis-dependent M1 phenotype.[76] Concurrent iron overload and lipid peroxidation trigger ferroptosis and defective macrophage efferocytosis, contributing to osteoclast overactivation and alveolar bone resorption.[77,78]

Conventional rigid bone grafts or collagen membrane barriers function as passive physical barriers and do not dissipate aberrant shear stress at the hard–soft interface or reverse PDLSC mechanosenescence.[79] To address this, dual DLP and direct ink writing 3D bioprinting have been used to fabricate hard–soft biphasic gradient hydrogels incorporating decellularized ECM.[80,81] These constructs provide rigid support on the alveolar bone side and a viscoelastic, stress-relaxing network on the periodontal ligament side. By dampening aberrant mechanotransduction through Piezo1 channels on PDLSCs, the constructs release YAP/TAZ nuclear retention, thereby restoring the cells' capacity for directional collagen assembly and osteogenic/cementogenic differentiation.[82] The negatively charged, immunosuppressive pure DNA gel has been shown to neutralize free pro-inflammatory chemokines within periodontal pockets through steric hindrance and electrostatic adsorption, limiting neutrophil and macrophage infiltration.[30]

More targeted interventions employ dynamically crosslinked hydrogels with disulfide or ester bonds that release engineered EVs in response to elevated ROS or acidic pH.[15,83] M2-macrophage-derived EVs carrying miR-23a-3p inhibit NIMA-related kinase 7 to suppress the NLRP3 inflammasome and restore the mitochondrial fusion/fission balance, shifting macrophage metabolism from glycolysis to oxidative phosphorylation (OXPHOS) and promoting a pro-angiogenic, pro-osteogenic M2 phenotype.[83–85] Sustained release of α-KG from microenvironment-responsive hydrogels further suppresses osteoclast overactivation, contributing to bidirectional immune correction.[86,87]

For the temporally complex repair of large periodontal defects, spatiotemporally decoupled bilayer hydrogel systems with "IF-THEN" Boolean logic have been developed.[57,88] The outer, MMP-sensitive layer undergoes rapid depolymerization upon implantation, releasing curcumin nanoparticles to quench the initial oxidative burst and suppress M1 macrophages.[56]

Once the outer layer has dissolved, the inner crosslinked microspheres provide sustained release of bone morphogenetic protein-2 and the anti-fibrotic drug pirfenidone during the remodeling phase, inhibiting excessive fibrosis and activating osteogenic pathways to support coordinated alveolar bone mineralization and perpendicular collagen fiber insertion.[89] Recent microfluidic and 3D culture studies indicate that stem cells encapsulated within dynamically perfused DN hydrogels can maintain anisotropic elastic fiber architecture under simulated occlusal loads.[82,90]

These gradient hydrogel systems provide a programmable platform for addressing the mechanical complexity of the hard–soft periodontal interface, though organoid-level validation of multi-lineage structural outcomes remains largely absent. Defining what such validation should measure is a prerequisite for progress.

Engineering a periodontal organoid demands reconstructing the compartmentalized cementum–periodontal ligament (PDL)–alveolar bone interface, a task that requires coordinated multi-lineage differentiation beyond what single-cell-type cultures provide.[91] Primary PDLSCs, gingival MSCs, and dental follicle progenitor cells have each been used; the choice of source affects both differentiation capacity and matrix deposition. Meaningful cross-study comparison requires attention to several parameters that are currently under-reported. Multi-

lineage differentiation efficiency tops the list. A single construct should simultaneously express cementogenic markers (cementum attachment protein, cementum protein 1), osteogenic markers (runt-related transcription factor 2, osteocalcin), and ligamentogenic markers (periostin, tenomodulin). Collagen fiber architecture matters no less. The native cementum–PDL interface exhibits a sharp mineralization gradient from unmineralized ligament collagen to mineralized cementum, with Sharpey fibers inserting at oblique angles that optimize load transfer during mastication.[92,93] This structurally graded, oriented architecture has not been reproduced in any organoid model. Fiber orientation at the cementum-analog surface is rarely measured by polarized light microscopy or second-harmonic generation imaging. Regional heterogeneity in fiber insertion density and angle directly governs the mechanical response under occlusal loading[93,94], yet it is almost never characterized. Mechanical integrity under simulated occlusal loading, including resistance to delamination at the cementum–PDL boundary, constitutes another critical gap. Most studies report material properties in isolation; organoid-level structural and mechanical validation trails far behind. We would argue that the field does not lack innovative materials. Rather, it lacks standardized organoid-level assays to determine which of these materials actually deliver physiologically meaningful regeneration.

### 3.3. Temporomandibular joint: Counteracting compression-induced senescence

Unlike the periodontal ligament, which operates in a tensile and shear environment, the TMJ operates under cyclic compression, requiring distinct matrix design strategies. The TMJ features fibrocartilage (enriched with type I and type II collagen) covering the condylar surface, and is subjected to cyclic compressive stress and shear friction.[95] With aging and mechanical wear, the TMJ undergoes osteoarthritic degeneration (OA), characterized by ROS overload, chondrocyte ferroptosis, and progressive functional decline of resident stem cell populations.[96]

As in other oral tissues, mechanical stress activates Piezo1 in chondrocytes, triggering $Ca^{2+}$ influx that suppresses anabolism via phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin complex 1 signaling pathway and accelerates degradation of type II collagen (COL2) and aggrecan (ACAN). *In vivo* conditional knockout studies indicate that Piezo1 and Piezo2 play distinct and potentially opposing roles in TMJ homeostasis: chondrocyte-specific deletion of both channels protects against post-traumatic OA, whereas in jawbone development, the two isoforms collectively regulate morphogenesis. This suggests that dysregulated Piezo1/2 coordination, rather than elevated Piezo1 activity alone, contributes to dual cartilage-bone degeneration during TMJ aging.[97,98] Conventional homogeneous scaffolds fail to dissipate the high-frequency cyclic loads of the TMJ and are prone to mechanical failure under these conditions.[99,100] In the healthy TMJ, *Lgr5*$^{+}$ secretory cells in the perichondrium release Wnt inhibitors (e.g., Sclerostin) that maintain chondrocyte quiescence; however, this protective niche is depleted during aging.[101]

To recreate this niche, decellularized perichondrium hydrogels retaining sclerostin have been shown to suppress hyperactivated Wnt/β-catenin signaling and prevent osteoblast-like hypertrophy of senescent chondrocytes.[58] DLP 3D bioprinting of DNA-silk fibroin DN hydrogels has been employed to mimic the nonlinear viscoelastic energy dissipation of native fibrocartilage. Sustained release of glucosamine and the chondrogenic small molecule TD-198946 from the hydrogel backbone under dynamic loading activates MAPK signaling in implanted organoids, promoting hyaline cartilage regeneration within eight weeks.[58]

Complementary biochemical and metabolic reprogramming approaches include poly(lactic-co-glycolic acid) (PLGA) microspheres loaded with p16-siRNA co-encapsulated with synovial MSC (SMSC) organoids in a composite hydrogel, reducing MMP-13 accumulation through p16 knockdown.[102] Microgel systems delivering miR-24 mimics target thousand-and-one amino acid protein kinase 1 to shift senescent chondrocyte metabolism from glycolysis to OXPHOS, partially rescuing chondrogenic capacity.[103] Mn-NC SAzymes anchored in chitosan-based hydrogels have been explored for sustained ROS scavenging in the joint cavity, inhibiting the ROS-driven MAPK apoptotic pathway, and supporting dual cartilage-subchondral bone regeneration.[28,104]

The TMJ fibrocartilage organoids have been generated from primary SMSCs, mandibular condylar chondrocytes, and iPSC-derived chondroprogenitors. Spatially organized fibrocartilage assembloids, fabricated by seeding MSC spheroids into dual-architecture polymeric scaffolds, have recently been shown to recapitulate the fibrous, proliferative, and hyaline-like zones of native TMJ condylar cartilage.[105] Jawbone-like organoids containing osteoblast-osteocyte networks within self-produced mineralized matrices have likewise been established from iPSC-derived CNCCs.[51] Despite these advances, the metrics used to evaluate TMJ organoid quality vary widely. Chondrogenesis efficiency, the percentage of organoids staining positive for COL2 and ACAN, is the most commonly reported parameter, but is insufficient alone. The type I collagen/COL2 ratio distinguishes fibrocartilage from hyaline cartilage identity,

yet is rarely quantified; the Dufour assembloid platform demonstrated native-like spatial collagen patterns without providing quantitative ratios. Zonal architecture poses a further challenge. Native TMJ fibrocartilage contains a superficial lubricin-rich (PRG4) zone and a deep COL2/ACAN-rich zone; *Lgr5*$^{+}$ positive secretory cells maintain this zonation through Wnt inhibition[102], but PRG4/COL2 gradients have not been demonstrated in organoid models. Dynamic mechanical properties such as compressive modulus and coefficient of friction under cyclic loading, though direct functional correlates of matrix quality, are the least commonly assessed. The heterogeneity of current readouts precludes rigorous cross-study comparison.[101]

### 3.4. Salivary glands and mucosa: Restoring epithelial polarity and barrier function

Beyond the load-bearing tissues of the TMJ, the salivary glands and oral mucosa represent fluid-exposed epithelial barriers with distinct requirements for polarity, secretion, and microbial defense. As the main defense barrier against exogenous microbial invasion and physical and chemical stimulation, the stratified squamous epithelium of oral salivary glands and mucosa undergoes age-related deterioration, involving oxidative stress, chronic inflammation, and impaired tissue homeostasis associated with basement membrane degradation.[106]

Within the salivary gland microenvironment, aging or head and neck radiotherapy compromises human salivary epithelial stem/progenitor cells (hS/PCs), impairing acinar self-organization. Accumulation of cytotoxic free radicals disrupts endoplasmic reticulum and mitochondrial function, impairing secretory pathways. Conventional Matrigel-based organoid culture, with its variable composition and xenogeneic origin, is poorly suited to address this pathological loss of polarity and introduces immunogenicity concerns.[107]

Fully chemically defined (xeno-free) synthetic hydrogels now address this need. A thermo-ionic dual-crosslinked hydrogel composed of hyaluronic acid, alginate, and gelatin (AGHA) matches the low elastic modulus of native salivary gland tissue at the level of physical mechanosensing.[60] For branching morphogenesis, MMP-sensitive crosslinking peptides (e.g., gel-ink writing-bismaleimide) embedded in hyaluronic acid matrices allow epithelial cells to locally remodel the matrix by secreting MMPs and promoting Rho-associated coiled-coil containing protein kinase (ROCK)-mediated cytoskeletal tension. This mechanobiological cascade drives apical translocation of the Golgi marker (Golgi matrix protein of 130 kDa [GM130]) and aquaporin-5 (AQP5), supporting the polarized architecture required for fluid secretion in salivary gland organoids.[108,109]

For radiation-induced salivary gland injury with irreversible denervation, bilayer microporous scaffolds of PLGA and polycaprolactone loaded with Wnt family member 3A activate the PI3K-AKT signaling pathway, promoting the expansion of salivary epithelial stem cells and the secretion of tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta (14-3-3 protein ζ)-enriched EVs (3D Wnt-enriched EVs) that reduce cleaved calpain I-mediated apoptosis.[110]

For the oral mucosal barrier, aging involves a "microbiome-SASP-aging" feedback loop in which microbial metabolic byproducts and pro-inflammatory secretions from senescent cells promote chronic, hard-to-heal ulceration. A Janus wet-adhesive hydrogel, inspired by the asymmetric multilayered architecture of the oral mucosa, has been developed to establish a dual barrier in this moist and microbially rich environment.[59] The outer layer, composed of an agar/polyacrylamide DN, provides low-adhesion, antifouling properties that limit pathogen penetration. The inner layer, facing the mucosal wound, uses a polyphenol-rich network that achieves strong wet-tissue adhesion while scavenging ROS.[59] This antioxidant environment promotes epithelial integrity and supports mucosal stem cell proliferation.

A parallel spatiotemporally decoupled strategy applies the same logic to mucosal repair: the lower layer releases curcumin rapidly during the early inflammatory phase, while the upper layer sustains pirfenidone release to limit late-stage fibrosis.[111] For chemotherapy-induced oral mucositis, salivary amylase-responsive hydrogels release stromal cell-derived factor 1, which binds C–X–C chemokine receptor type 4 to establish a chemotactic gradient that recruits endogenous repair cells.[112,113]

At the systems level, the microfluidic "oral mucosa-on-a-chip (OMoC)" incorporates decellularized mucosal matrix blended with hyaluronic acid/sodium alginate and maintains stratified squamous epithelial architecture under simulated salivary flow.[114] For these fluid-exposed tissues, programmable hydrogel systems integrate chemically defined matrices, asymmetric barrier topologies, and stimuli-responsive delivery into a single platform. Translating these innovations to durable functional recovery in vivo remains a central challenge.[115] Rigorous functional benchmarking, as outlined below, would help the field track progress toward this goal.

Salivary gland organoids have been derived from primary hS/PCs and, more recently, from iPSC-derived salivary gland progenitors. A foundational study established long-term murine and human organoid cultures that express acinar (AQP5, Muscle, intestine, and stomach expression 1), ductal (keratin 5, keratin 7), and myoepithelial (actin alpha 2) markers and exhibit functional calcium influx with swelling upon cholinergic stimulation.[116] Cross-platform

evaluation is hampered by inconsistent reporting practices. Acinar structure formation, the percentage of organoids with polarized apical GM130 and AQP5 localization, reaches over 60% when ROCK is inhibited in protease-degradable hyaluronic acid hydrogels[108], yet it is not uniformly reported. Quantified fluid secretion upon pilocarpine stimulation, a direct functional readout demonstrated by Yoon *et al.*[116], is rarely measured across hydrogel platforms. Other under-reported parameters include maintenance of secretory capacity beyond four weeks, transepithelial electrical resistance (TEER) as a barrier integrity measure, and stratified squamous epithelial architecture confirmed by cytokeratin profiling, as shown in the decellularized matrix-hyaluronic acid-alginate OMoC platform.[114] Chemically defined matrices, such as the thermo-ionic AGHA hydrogel, support functional acinar spheroid expansion without xenogeneic components.[60] Most current studies report histological architecture or transcriptional markers, but rarely both, and functional secretion data are the least commonly reported metric of all.

## 4. Multiscale characterization and intelligent fabrication for organoid engineering

Programmable hydrogel systems for complex senescent microenvironments require characterization strategies that capture transient cell-material interactions during dynamic matrix remodeling, rather than relying solely on conventional endpoint assays.[117] Spatiotemporal multi-omics, organ-on-a-chip technologies, and artificial intelligence (AI)-assisted design each offer complementary capabilities for addressing these characterization and manufacturing challenges (Figure 4).[118]

### 4.1. Spatiotemporal multi-omics deconstructs hydrogel-cell interaction trajectories

Integrating single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics into 3D hydrogel culture systems resolves cell population dynamics that remain invisible in bulk assays. At the subcellular resolution, these multi-omics

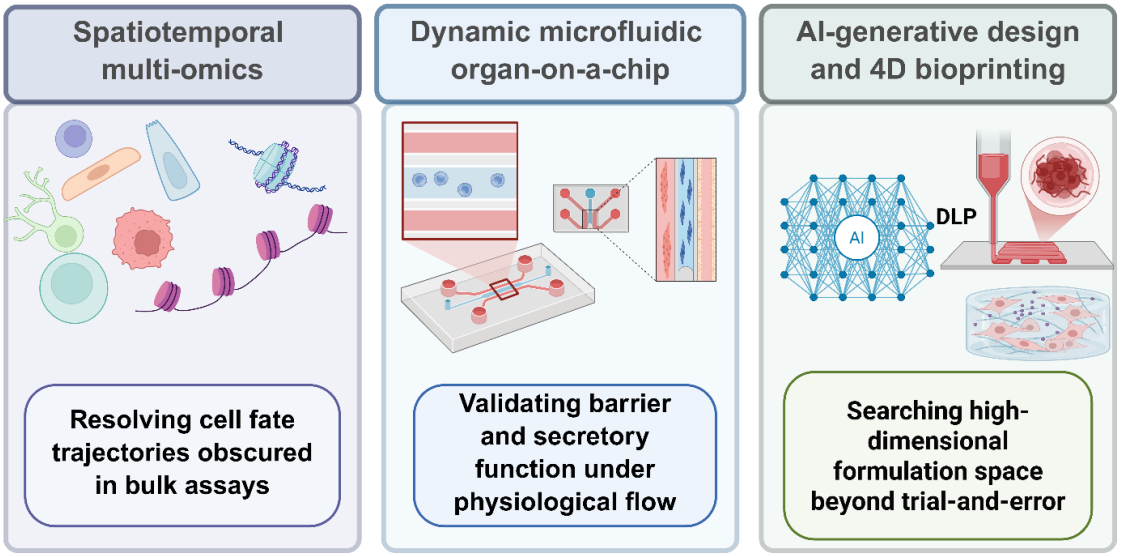


**Figure 4.** Next-generation characterization and manufacturing technologies for programmable hydrogel-organoid systems. The three-panel schematic illustrates complementary technology tracks that together move organoid engineering beyond conventional black-box *in vitro* culture. Left: Spatiotemporal multi-omics (scRNA-seq, omni-assay for transposase-accessible chromatin-seq, and spatial transcriptomics) resolves cell-state transitions and chromatin accessibility dynamics that remain invisible in bulk endpoint assays.[119,120] Center: Microfluidic organ-on-a-chip platforms, including tooth-on-a-chip[67] and oral mucosa-on-a-chip[114], enable real-time functional validation of barrier integrity and secretory output under physiological flow and polymicrobial conditions. Right: Artificial intelligence (AI)-assisted generative design (Bayesian optimization, multilayer perceptron/support vector machine surrogate models) and digital light processing (DLP)-based four-dimensional (4D) bioprinting of shape memory polymer scaffolds represent emerging approaches for navigating the high-dimensional hydrogel formulation space[121,122]; neither has been demonstrated in an oral or maxillofacial environment to date. Dashed circular arrows denote the proposed closed-loop feedback: multi-omics data inform machine learning-driven formulation design, optimized hydrogels are validated on-chip, and chip-derived functional readouts refine subsequent omics analyses; a cycle that, if realized, would shift organoid culture from empirical optimization toward mechanism-guided engineering. Created with BioRender.com. Jinling Liu (2026) https://BioRender.com/6iuajyu

tools map the spatial coordinates of stem cell differentiation clusters within transparent polymer networks and track their fate trajectories in response to microenvironmental cues, from matrix stiffening to local ROS gradients.[123]

For example, tomo-seq spatial omics has been applied to construct a stem cell niche atlas of oral mucosal organoids, identifying gradients of fibroblast growth factor ligands across the hydrogel depth that can guide spatial chemokine loading strategies. For epigenetic profiling, *in situ* omni-assay for transposase-accessible chromatin-seq enables quantitative assessment of chromatin accessibility dynamics without disrupting the hydrogel network.[124]

Multi-omics profiling has established correlative links between hydrogel matrix properties and the epigenomic landscape of resident cells. As discussed in Section 2.1, stress relaxation in dynamic hydrogels can function as a mechano-epigenetic modulator.[24] Direct causal relationships between specific matrix parameters, stress relaxation half-time, RGD ligand spacing, and crosslinker density, and defined epigenetic outcomes have not been established through controlled perturbation, leaving these mechanistic insights largely correlative. High-resolution tools now permit single-cell joint profiling of chromatin accessibility and the transcriptome in organoid systems: scEpiChem simultaneously measures drug-chromatin

**Table 1. Programmable hydrogel strategies, mechanisms of senescence reversal, and representative applications in oral and maxillofacial organoid engineering**

| Strategy category (design principle) | Representative hydrogel system | Mechanism of senescence reversal | Oral/ maxillofacial tissue niche | Organoid type | References |
|---|---|---|---|---|---|
| Mechanobiological modulation | Glycol chitosan DN hydrogels with rapid stress relaxation | Dissipates pathological hydrostatic pressure via dynamic polymer segment sliding; reduces mechanical ischemia and anoikis of implanted organoids in confined root canals | Dentin–pulp complex | DPSC-derived odontoblast organoids | 54 |
| | DLP/DIW 3D-bioprinted dECM biphasic gradient hydrogels (rigid bone side / viscoelastic PDL side) | Dampens aberrant shear stress at the hard–soft interface; relieves Piezo1–YAP/TAZ nuclear retention in PDLSCs; restores directional collagen fiber assembly | Periodontal complex | PDLSC/GMSC-derived multi-lineage organoids | 80–82 |
| | DNA-silk fibroin DN hydrogels with nonlinear viscoelastic energy dissipation | Mimics native fibrocartilage mechanics under cyclic compression; sustained glucosamine/TD-198946 release activates MAPK-driven hyaline chondrogenesis | TMJ fibrocartilage | SMSC/chondrocyte-derived fibrocartilage assembloids | 58 |
| | Thermo-ionic dual-crosslinked hydrogel (hyaluronic acid/ alginate/gelatin) | Matches native salivary gland elastic modulus; MMP-degradable peptides (GIW-bisMI) enable ROCK-mediated apical GM130/AQP5 polarization for secretory function | Salivary gland | hS/PC-derived acinar organoids ($AQP5^+$/$MIST1^+$) | 60,108,109 |
| Biochemical intervention | C-NZ/GelMA nanozyme hydrogels; Mn-NC SAzyme chitosan hydrogels | Catalytic $H_2O_2$/superoxide scavenging via $Ce^{3+}$/$Ce^{4+}$ valence cycling or Mn-$N_4$ single-atom coordination; inhibits the NLRP3 inflammasome assembly and the ROS–MAPK apoptotic pathway | Dentin–pulp complex; TMJ cavity | DPSC organoids; SMSC chondrogenic organoids | 28,55 |
| | Is-pDNA gel (immunosuppressive DNA hydrogel); ROS-cleavable thioketal hydrogels | Passive chemokine trapping via polyanionic steric hindrance/ electrostatic adsorption; on-demand anti-inflammatory EV release upon ROS-triggered depolymerization | Periodontal complex; TMJ | PDLSC organoids with M2 macrophage co-culture | 30–32 |
| | α-KG-loaded metabolic-epigenetic hydrogels; APS composite microneedle systems | TET2-dependent DNA hydroxymethylation at anti-inflammatory gene promoters; Nrf2/ HO-1/SLC7A11 ferroptosis inhibition; glycolytic (M1) → oxidative (M2) macrophage metabolic reprogramming | Periodontal complex; oral mucosa | Multi-lineage organoids with immune co-culture | 34–36 |

(*Cont'd...*)

**Table 1. (*Continued*)**

| Strategy category (design principle) | Representative hydrogel system | Mechanism of senescence reversal | Oral/ maxillofacial tissue niche | Organoid type | References |
|---|---|---|---|---|---|
| Spatiotemporal logic-gated delivery | MMP-13/MMP-9-responsive bilayer hydrogels with sequential "IF-THEN" logic | Phase 1: MMP-sensitive outer layer degrades → rapid curcumin/anti-inflammatory exosome release; Phase 2: exposed inner microspheres → sustained BMP-2/pirfenidone pro-regenerative delivery | Periodontal complex (large bone defects) | DFPC/PDLSC-derived cementum-PDL-bone organoids | 44,56,57,88,89 |
| | Aptamer-crosslinked multi-armed DNA hydrogels; CRISPR-Cas12a DNA hydrogels | AND/OR Boolean gate processing of ATP + cytokine inputs triggers conditional network disassembly and drug release; CRISPR-Cas12a trans-cleavage enables exponential signal amplification for trace nucleic acid detection | Multi-tissue platform (saliva/gingival crevicular fluid applicable) | Cross-tissue organoid screening platform | 45–48 |
| | WAJH (Agar/PAAm DN outer face + polyphenol-rich inner face) | Asymmetric bifunctionality: the antifouling outer layer blocks bacterial ingress, and the polyphenol inner face achieves strong wet-tissue adhesion and sustained ROS scavenging to maintain epithelial integrity | Oral mucosal barrier (moist, microbially rich environment) | Stratified squamous epithelial organoids (OMoC platform) | 59,111,114 |

Abbreviations: APS: Astragalus polysaccharides; AQP5: Aquaporin 5; bisMI: Bismaleimide; BMP-2: Bone morphogenetic protein-2; C-NZ: Carbon quantum dot nanozyme; CRISPR-Cas12a: Clustered regularly interspaced short palindromic repeats-CRISPR-associated protein 12a; dECM: Decellularized extracellular matrix; DFPCs: Dental follicle progenitor cells; DIW: Direct ink writing; DLP: Digital light processing; DN: Dual-network; DPSC: Dental pulp stem cell; GelMA: Gelatin methacryloyl; GIW: Gel-ink writing; GM130: Golgi matrix protein of 130 kDa; GMSCs: Gangiva-derived mesenchymal stem cells; $H_2O_2$: Hydrogen peroxide; HO-1: Heme oxygenase-1; hS/PCs: Human salivary stem/progenitor cells; Is-pDNA: Immunosuppressive pure DNA; MAPK: Mitogen-activated protein kinase; MIST1: Muscle, intestine, and stomach expression 1; MMP: Matrix metalloproteinase; Mn-NC SAzyme: Manganese-nitrogen-carbon single-atom nanozymes; Mn-NC: Manganese-nitrogen carbon nanozyme; NLRP3: NOD-like receptor family pyrin domain containing 3; Nrf2: Nuclear factor erythroid 2-related factor 2; OMoCs: Oral mucosa-on-a-chip; PAAm: Polyacrylamide; PDL: Periodontal ligament; PDLSCs: Periodontal ligament stem cells; ROCK: Rho-associated coiled-coil containing protein kinase; ROS: Reactive oxygen species; SLC7A11: Solute carrier family 7 member 11; SMSCs: Synovial mesenchymal stem cells; TET2: Ten-eleven translocation methylcytosine dioxygenase 2; TMJ: Temporomandibular joint; WAJH: Janus wet-adhesive hydrogel; α-KG: α-ketoglutarate.

binding and multimodal epigenomic profiles[125], while scRICA-seq jointly profiles RNA isoforms and chromatin accessibility in retinal organoids.[119] A key challenge remains: no published study has used multi-omics readouts, for instance, identifying an under-represented differentiation trajectory by scRNA-seq, to drive a second round of hydrogel formulation adjustment and experimentally validate improved organoid outcomes. Establishing this feedback would move organoid culture beyond empirical optimization toward mechanism-guided engineering.

### 4.2. Dynamic fluid boundaries of microfluidic organ-on-a-chip systems

Oral and maxillofacial tissues, including the periodontal complex, salivary glands, and TMJ, exist in environments with dynamic fluid shear, interstitial pressure, and polymicrobial communities that static culture systems cannot replicate.[120–126] The integration of programmable hydrogels with microfluidic organ-on-a-chip platforms allows for continuous perfusion and controlled pressure gradients, providing a more physiologically relevant testing environment.[127]

The "gingival crevice-on-chip" model uses a micropillar array to contain cell-laden hydrogel while perfusing multi-species oral biofilms (including *Streptococcus mutans*) through adjacent microchannels.[120] Controlled fluid pressure differentials across reservoirs simulate gingival crevicular fluid flow, enabling the study of host-microbe-hydrogel immune interactions.[120,127]

For dental pulp applications, a "tooth-on-a-chip" incorporating *ex vivo* human dentin slices forms a dentin–pulp barrier, allowing real-time monitoring of hydrogel-delivered agents as they traverse mineralized dentinal tubules.[73] Pump-free droplet microfluidic platforms can also generate thousands of uniformly sized micro-

organospheres for higher-throughput screening of anti-SASP therapeutic candidates.[128]

Microfluidic organ-on-a-chip platforms offer two capabilities beyond those of static culture for hydrogel-organoid systems. First, they enable real-time monitoring of barrier integrity, secretory output, and apoptotic markers in response to hydrogel-delivered agents under physiologically relevant flow and polymicrobial co-culture[114]; the tooth-on-a-chip platform described above exemplifies this capability.[73] Second, chip-based platforms could serve as standardized testbeds for comparing multiple hydrogel formulations against the same organoid batch, reducing the batch-to-batch organoid variability that confounds conventional well-plate comparisons.[129] Head-to-head benchmarking of different hydrogel formulations for the same organoid type on a single chip has not yet been reported, leaving the field unable to identify which matrix parameters most strongly govern organoid function under dynamic physiological conditions.

### 4.3. Artificial intelligence-assisted material design and bioprinting

Empirical optimization of hydrogel formulations for organoid systems is inherently difficult. Organoid function reflects the interaction of multiple material parameters over weeks of culture, and the relationship between any single parameter (e.g., stiffness, degradation rate) and the organoid phenotype is rarely monotonic. ML offers a more efficient means of searching this high-dimensional design space than trial-and-error, but its application to organoid culture remains nascent. To date, most ML-guided hydrogel studies have focused on predicting material properties rather than organoid functional outcomes.

The design space for multi-stimuli-responsive hydrogels spans crosslinking density, macromolecular entanglement, ligand occupancy, and enzymatic degradation kinetics. ML-assisted materials discovery has gained traction as an alternative to exhaustive empirical screening.[130] For example, deep generative networks trained on experimental mechanical datasets have enabled inverse design of hydrogel composites with user-specified stress and displacement fields, capturing structure-property relationships that conventional screening would miss.[131] In work directly relevant to bioprinting, a Bayesian optimization framework was developed to predict the viscosity of heterogeneous bioink formulations. Using multilayer perceptron and support vector machine surrogate models, the framework guided iterative sampling toward hyaluronic acid methacrylate/GelMA hybrid compositions with target extrusion rheology.[132] Compared to random screening, this active-learning strategy cut the experimental burden substantially while still identifying printable formulations. Critically, these demonstrations have been limited to in-process rheological endpoints; predicting how a hydrogel formulation will shape organoid differentiation or secretory function remains beyond the reach of current ML approaches.

On the fabrication side, digital micromirror device-driven stereolithography enables rapid photopolymerization of photosensitive polymers with lower shear stress on encapsulated cells than extrusion-based printing. This approach can produce anisotropic architectures that approximate the microscale features of cortical and cancellous bone.[133] 4D bioprinting extends this capability by incorporating stimuli-responsive materials (shape memory polymers, degradable microgel bilayers, and dynamic covalent networks) into bioinks, so that printed constructs undergo programmed shape changes in response to temperature, pH, or enzymatic activity.[134] Such constructs could, in principle, conform to irregular tissue defects or trigger staged cargo release, though no demonstration in a physiologically relevant oral or maxillofacial environment has yet been reported.

## 5. Future perspectives

Global population aging has made age-related degeneration of oral and maxillofacial tissues an increasingly urgent clinical problem: over 3.69 billion individuals are affected by oral conditions worldwide, with the disease burden projected to rise substantially among older populations by 2035.[1] Conventional 2D culture and animal models cannot adequately recapitulate the dynamic, mechanically active microenvironment that drives this degeneration. 2D systems lack the 3D mechanobiological cues governing cellular senescence, while interspecies differences limit the translational utility of animal data.[3,4] Organoid technology sidesteps these limitations. Patient-derived stem cells self-organize into functional 3D tissue surrogates that serve three purposes at once: disease modeling, drug screening, and transplantation-based regeneration.[7,8] The clinical reach of oral and maxillofacial organoids, however, remains handcuffed to Matrigel and other static matrices. These substrates fail twice over. They do not reproduce the dynamic biomechanics of aging ECM. They do not satisfy the compositional definition required for regulatory approval.[12] Programmable hydrogels break this bottleneck. These engineered polymer networks detect pathological cues (elevated ROS, acidic pH, MMP overexpression) and respond through tunable stress relaxation, stimuli-responsive degradation, and spatiotemporally controlled therapeutic release.[13,14] The outcome is twofold: a physical niche for organoid self-organization and concurrent remodeling of the senescent microecology toward regeneration.

This review has examined the programmable hydrogel-organoid system across two mechanistic dimensions

and four tissue-specific application domains. On the mechanobiological front, dynamic hydrogels with tunable viscoelasticity and stress-relaxation dissipate aberrant cytoskeletal traction forces. In doing so, they intercept the Piezo1–YAP/TAZ axis that transmits pathological stiffness signals to the nucleus and imprints durable mechanical memory through EZH2-mediated H3K27me3 deposition on regenerative gene clusters.[20,23] On the biochemical front, nanozyme-integrated hydrogels harness $Ce^{3+}$/$Ce^{4+}$ valence cycling and Mn-$N_4$ single-atom catalysis to achieve superoxide dismutase/catalase-mimetic ROS scavenging within the mitochondrial compartment. Logic-gated delivery platforms add a second biochemical layer: spatiotemporally decoupled release of anti-inflammatory and pro-regenerative cargo, triggered by MMP activity and local pH shifts.[26,27,43] Across the four niches examined (dentin–pulp complex, periodontal attachment, TMJ fibrocartilage, salivary gland, and mucosal barrier), one design principle cuts across all contexts. Matrix mechanics and biochemical programming must be tailored to the tissue-specific biophysical environment. A confined root canal demands hydrostatic pressure dissipation. The cementum-PDL interface requires shear damping. The TMJ cavity calls for cyclic compression resistance. The mucosal surface needs an asymmetric wet-adhesive barrier. The organoid-level functional benchmarks proposed in Section 3 (neurovascular coupling, oriented collagen fiber insertion angle, zonal chondrogenesis, secretory polarity) are meant to supply the rigorous cross-study framework the field currently lacks. Setting such benchmarks across laboratories with different equipment, expertise, and cell sources will be difficult, but the absence of shared standards can now be scientifically addressed.

The strategies surveyed here span mechano-epigenetic modulation via stress-relaxing dynamic hydrogels, ROS-scavenging nanozymes, SASP-neutralizing biochemical systems, spatiotemporally programmable logic-gated delivery, tissue-specific organoid engineering across four oral and maxillofacial niches, and emerging multi-omics and microfluidic characterization technologies. These advances confirm that programmable hydrogels tackle pathological features of the senescent oral microenvironment that static matrices leave untouched. Translating these demonstrations from the bench to the clinic, however, means confronting interconnected challenges in vascularization, oncological safety, manufacturing standardization, and computational design (Figure 5).

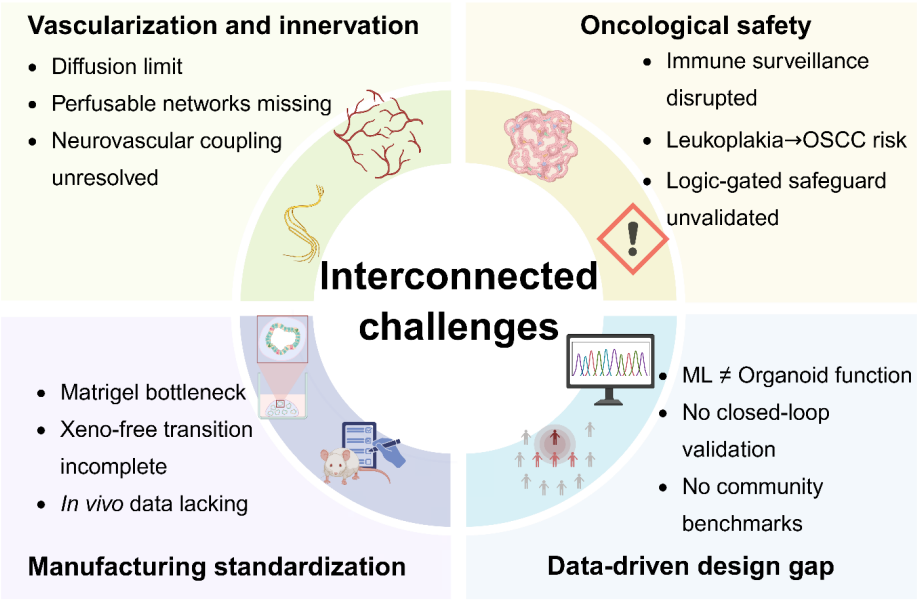


**Figure 5.** Four interconnected challenges for the clinical translation of programmable hydrogel-organoid systems in oral and maxillofacial regeneration. Top left: Vascularization and innervation: diffusion limit, absence of perfusable networks, and unresolved neurovascular coupling.[135–137] Top right: Oncological safety, such as disrupted immune surveillance, leukoplakia-to-oral squamous cell carcinoma (OSCC) risk, and unvalidated logic-gated safeguards.[138,139] Bottom left: Material and translational barriers, such as the Matrigel bottleneck, incomplete xeno-free transition, and lack of *in vivo* data.[12,40,140] Bottom right: Data-driven design gap, such as machine learning cannot yet predict organoid functional outcomes, no closed-loop validation, and no community benchmarks.[121,141] Created with BioRender.com. Jinling Liu (2026) https://BioRender.com/qv6z8ea

One physical constraint dominates. Organoids beyond several hundred microns in diameter lack a pre-connected, perfusable vascular network. Without perfusion, core hypoxia and necrosis follow. This diffusion limits the dentin–pulp complex, in which organoids are confined within rigid mineralized walls that offer scant collateral blood supply. Emerging 4D bioprinting approaches that use shape memory polymers aim to pre-construct hierarchical vascular architectures within hydrogels.[136,137] However, key challenges remain. The first is achieving large-scale dynamic deformation without mechanically damaging encapsulated organoids via compression or shear forces. Functional restoration of dental pulp and oral mucosa also requires coordinated neurovascular regeneration.[142] Neovascular networks lacking innervation tend to undergo fibrotic degeneration. One potential strategy is to integrate piezoelectric or photoelectric materials that deliver localized microcurrent stimulation to promote coordinated neurovascular bundle development.[143] However, this concept remains in its early stages of development.

The second concern is oncological safety. SASP-targeting and senolytic strategies, applied over long periods in the oral microenvironment, could inadvertently promote tumorigenesis.[138] The oral cavity differs from sterile internal organs. It faces chronic microbial and mechanical stress. Senescent cells residing in this environment, especially in pre-malignant conditions such as oral leukoplakia, may accumulate mutations and epigenetic alterations. Clearing these cells pharmacologically or via hydrogel-mediated delivery risks disrupting immune surveillance of carcinogenic clones, potentially accelerating malignant transformation to oral squamous cell carcinoma.[139] Conditional logic-gated materials that activate senolytic activity only when senescence biomarkers are present, and malignancy markers are absent, could mitigate this risk.[140] However, this concept remains theoretical and requires preclinical validation in appropriate oral carcinogenesis models.

Standardized, xeno-free manufacturing is the third prerequisite for clinical translation. Matrigel-based cultures fail to meet regulatory requirements due to their ill-defined biochemical composition, substantial batch-to-batch variability, and inherent xenogeneic components. As a result, their suitability for clinical translation is increasingly limited under evolving regulatory standards. The Food and Drug Administration Modernization Act 3.0 (2025) promotes alternatives to mandatory animal testing. The National Institutes of Health's investment in Standardized Organoid Model Centers signals growing institutional momentum.[144,145] Several fully defined synthetic matrices discussed above (DNA-based dynamic hydrogels [DyNAtrix], thermo-ionic AGHA hydrogels, recombinant silk fibroin systems) already offer viable alternatives to Matrigel. What remains missing is the systematic evaluation of their long-term *in vivo* degradation products, potential immunogenicity, and tissue-specific host responses. The organoid-level functional benchmarks proposed in Section 3 (neurovascular coupling in pulp, collagen fiber insertion angle in the periodontium, fluid secretion in salivary glands, TEER in the mucosa) could also serve as standardized quality attributes for regulatory assessment.

Artifical intelligence-driven biomaterial design promises faster hydrogel formulation. Applied to organoid engineering, however, it faces fundamental barriers: small and heterogeneous training datasets, validation confined to simplified *in vitro* conditions, no community-wide benchmarks, and no independent replication of ML-predicted formulations.[141] The critical step forward is not further tuning in-process rheological endpoints. It is closing the gap between ML-predicted material properties and actual organoid functional outcomes. This will require community data sharing, high-throughput automated platforms that capture biological alongside material endpoints, and physics-informed ML architectures that embed known constraints from polymer science and cell biology.[146]

## 6. Conclusion

We believe the single most consequential move the community could make is to build a shared, open-access database linking hydrogel formulations to quantitative organoid functional outcomes, a resource analogous to the Protein Data Bank in structural biology. Without it, ML-driven materials design stays a theoretical exercise.

Three near-term priorities emerge: First, building perfusable, innervated vascular networks inside implantable organoids; second, developing conditional safety mechanisms that block oncogenic escape during oral senolytic therapy; third, constructing standardized, benchmarked datasets that enable AI to predict organoid functional outcomes rather than relying solely on material properties. Progress on each front will decide whether programmable hydrogel-organoid systems graduate from proof-of-concept to meaningful clinical intervention for the aging oral and maxillofacial patient.

Programmable hydrogels and oral organoid biology are no longer advancing along separate trajectories. The central question is no longer whether a material can merely fill a defect, but whether it can reverse or mitigate the damage already imposed by cellular senescence. Addressing this challenge will require close collaboration among polymer chemists, developmental biologists, immunologists, and computational scientists to achieve three shared objectives. Although the individual components are already emerging, their successful integration into a coherent therapeutic platform remains a critical task.

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## Conflict of interest

The authors declare they have no competing interests.

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