TISSUE ENGINEERING: Part B
Volume 00, Number 00, 2026
Mary Ann Liebert, A Part of Sage

DOI: 10.1177/19373368261420588

termis
Tissue Engineering
& Regenerative Medicine
International Society

REVIEW ARTICLE

Organoid Models of the Oral Mucosa for Precision Medicine

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Patient-derived organoids (PDOs) have emerged as advanced bioengineered platforms for modeling oral mucosal tissues, offering unprecedented opportunities to interrogate disease mechanisms and evaluate therapeutic responses in a clinically relevant context. This article provides a critical and integrative assessment of recent advances in organoid technologies applied to oral mucosal disorders, with particular emphasis on oral squamous cell carcinoma (OSCC), oral lichen planus, and oral mucositis. Despite significant progress in therapeutic development, the clinical management of OSCC remains challenging due to pronounced inter- and intratumoral heterogeneity and unpredictable treatment responses. Conventional two-dimensional (2D) culture systems and traditional animal models often fail to recapitulate the complex cellular architecture, stromal interactions, and microenvironmental cues that govern oral mucosal pathophysiology, thereby limiting their translational predictive value. In contrast, organoid systems preserve key genetic, epigenetic, and phenotypic features of patient tissues, enabling more faithful *ex vivo* modeling of disease progression and therapeutic sensitivity. This article critically evaluates the engineering principles underlying oral organoid generation, including stem cell sources, extracellular matrix scaffolds, and microenvironmental modulation, and discusses their implications for disease modeling, drug screening, and personalized therapeutic stratification. Furthermore, current limitations, such as variability in culture conditions, incomplete immune and vascular components, and challenges in standardization, are examined alongside emerging strategies to enhance organoid complexity and translational relevance. Collectively, this article positions organoid-based platforms as a pivotal component of next-generation tissue engineering approaches for oral health research. By bridging fundamental biological insights with clinically actionable applications, organoid technologies hold substantial promise for advancing precision medicine and improving outcomes in patients with complex oral mucosal disorders.

Keywords: organoids, oral squamous cell carcinoma, personalized therapy, oral mucosal disorders, bioengineering

Impact Statement

This article highlights the critical role of organoid technology in revolutionizing the study and treatment of oral mucosal disorders. By providing patient-specific, physiologically relevant models, organoids overcome the limitations of traditional preclinical models, enabling more accurate disease modeling and drug screening. The insights presented herein are poised to significantly accelerate the development of personalized therapeutic strategies for conditions such as oral squamous cell carcinoma, oral lichen planus, and oral mucositis. Ultimately, this work contributes to the advancement of precision medicine in oral health, promising improved diagnostic capabilities, more effective treatment paradigms, and enhanced patient outcomes.

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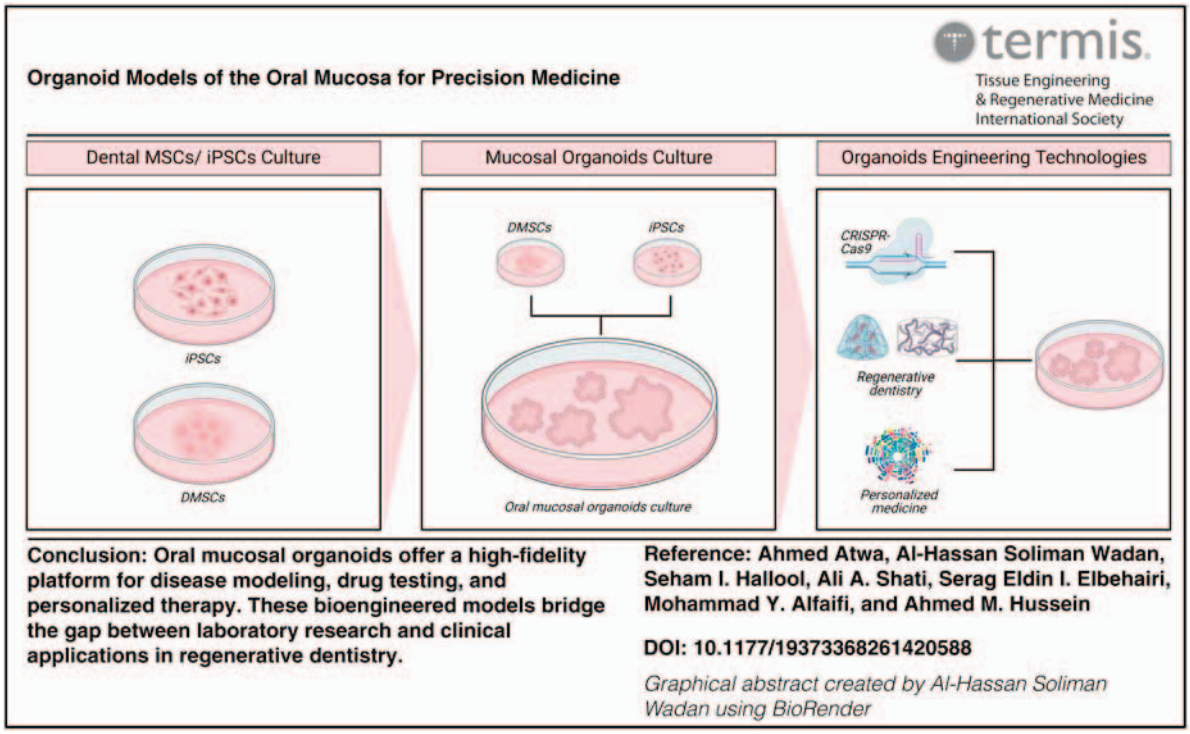

Introduction

In developing countries, cancer significantly negatively impacts the economy and society. Cancerous activities in the mouth, nasal cavity, throat, larynx, salivary glands, and paranasal sinuses are classified as head and neck cancers (HNCs).[1,2] Neoplastic activities of the squamous epithelial cells of the soft lining tissues of the skull and neck often cause tumors of the oral cavity, nasal passages, and pharynx.[3] Oral mucosal diseases affect a large population segment and significantly impact on the quality of life. Chronic discomfort and difficulty eating, swallowing, and speaking are common symptoms of disorders, including conditions such as oral squamous cell carcinoma (OSCC), oral submucosal fibrosis, and oral lichen planus (OLP).[4,5] Treatment of oral mucosal diseases is challenging, partly due to their anatomical location, which complicates surgery or even experimental therapies, and partly due to the high variability in response to treatment. Advanced cases require a combination of surgery, radiotherapy, and chemotherapy.[6] Alcohol and tobacco use are among the leading causes of head and neck tumors, according to the National Cancer Institute.[7] According to the latest updates from the Centers for Disease Control and Prevention, a significant proportion of oropharyngeal tumors, which affect the tonsils, soft palate, and base of the tongue, are caused by the human papillomavirus (HPV). Additionally, men over the age of 50 are twice as likely to develop a head and neck tumor. Treatment for early squamous oral cell carcinoma requires surgery, chemotherapy, or radiation therapy. After cancer surgery, further surgery may be needed to correct the changes.[8–10]

Prior to the introduction of animal studies and human clinical trials, 2D implantation techniques were widely used in more than 70% of laboratory cancer research.[11] Among the many widely recognized advantages of 2D cultures are their cost-effectiveness, technical simplicity, easy availability of nutrients and oxygen, ease of cell handling, ease of observation and analysis, and enhanced cell viability. However, the main limitation of 2D monolayer cell cultures is the absence of the 3D microenvironment inherent in healthy tissue within these systems.[8,12]

Additionally, it has been noted that animal models designed to mimic the interaction between cancer and the immune system, identify therapeutic side effects, or simulate metastatic progression are frequently ineffectual because of biological distinctions between people and animals. Likewise, the use of animals in experimental research is limited by current regulations and ethical standards.[13,14]

As a result, researchers with diverse expertise in cell biology and tissue engineering are working on creating 3D cultures, spheroids, and organoid models that mimic cancer tissue. Tissue engineering is a dynamic and crucial subject within contemporary biomedicine. By merging principles from biology and engineering, this area focuses on producing biological parts that require either repair or replacement. Key elements worked as in tissue engineering include scaffolds, growth factors, and cells.[15,16] By enhancing knowledge of the condition and assisting in the development of more accurate pharmaceutical agents, this initiative seeks to advance more potent cancer therapy strategies. To get a better drug test procedure, it is also critical to precisely position and confirm the platforms. Take into consideration the pathophysiological features of the 3D tumor environment.[17,18]

3D cancer models and *in vitro* organoid technology offer potential advantages over traditional 2D cultures and animal models in studying drug toxicity and sensitivity. However,

this technology has not yet met the criteria necessary for clinical trials. For biologists and bioengineers seeking to understand the complex mechanisms of cancer proliferation and metastasis, recreating the tumor microenvironment in a controlled laboratory setting is compelling.[19–21] This review aims to examine the development of organoid models in oncological research related to oral mucosal disorders such as OLP, OSCC, and OM, for which experimental studies *in vitro 2D cultures and in vivo models are still insufficient. Therefore, we will shed light on them, especially since they express all pathological disorders that target the mucosal layer of the oral cavity tissues.*

Structural and Functional Composition of Oral Mucosal Tissues

The human oral mucosa is classified into three parts: Lining mucosa 60%, which includes buccal, sublingual, and soft palate tissues; masticatory mucosa 25%, which includes gingival and hard palate tissues; and specialized mucosa 15%, which includes the dorsal side of the tongue.[22] An outer layer of stratified squamous epithelium contains oral keratinocytes, and a layer of collagen-based connective tissue called the lamina propria contains fibroblasts, blood vessels, nerve endings, and salivary glands. All these subtypes of tissue exist in living organisms. Around 60% of the oral cavity's surface area is occupied by the lining mucosa, and the epithelial layer is not cornified.[23] The cornified masticatory tissue occupies around 25% of the mouth's interior, whereas the specialized tongue mucosa accounts for about 15%, divided into noncornified and cornified areas, as shown in Figure 1. Stratified squamous epithelium makes up the epithelium, whereas collagen and fibroblasts make up the lamina propria. Laminin and collagen make up the basement membrane, a very thin layer.[24] The exocrine structures, known as salivary glands, are mostly made up of serous acini, ductal, and myoepithelial cells responsible for producing and secreting saliva.[25] Researchers continue to investigate the detailed structure and functions of the salivary and oral mucosal glands.[26]

The oral cavity, due to its position and anatomical features, often faces rapidly shifting and potentially harmful conditions. The main role of the oral mucosa is to safeguard and shield the tissues beneath it. This defense mechanism relies on the physical characteristics of the epithelial layer, the presence of immune cells like Langerhans cells (LCs) and lymphocytes in the epithelium, as well as in the lamina propria.[27] These epithelial cells enhance the oral mucosa's

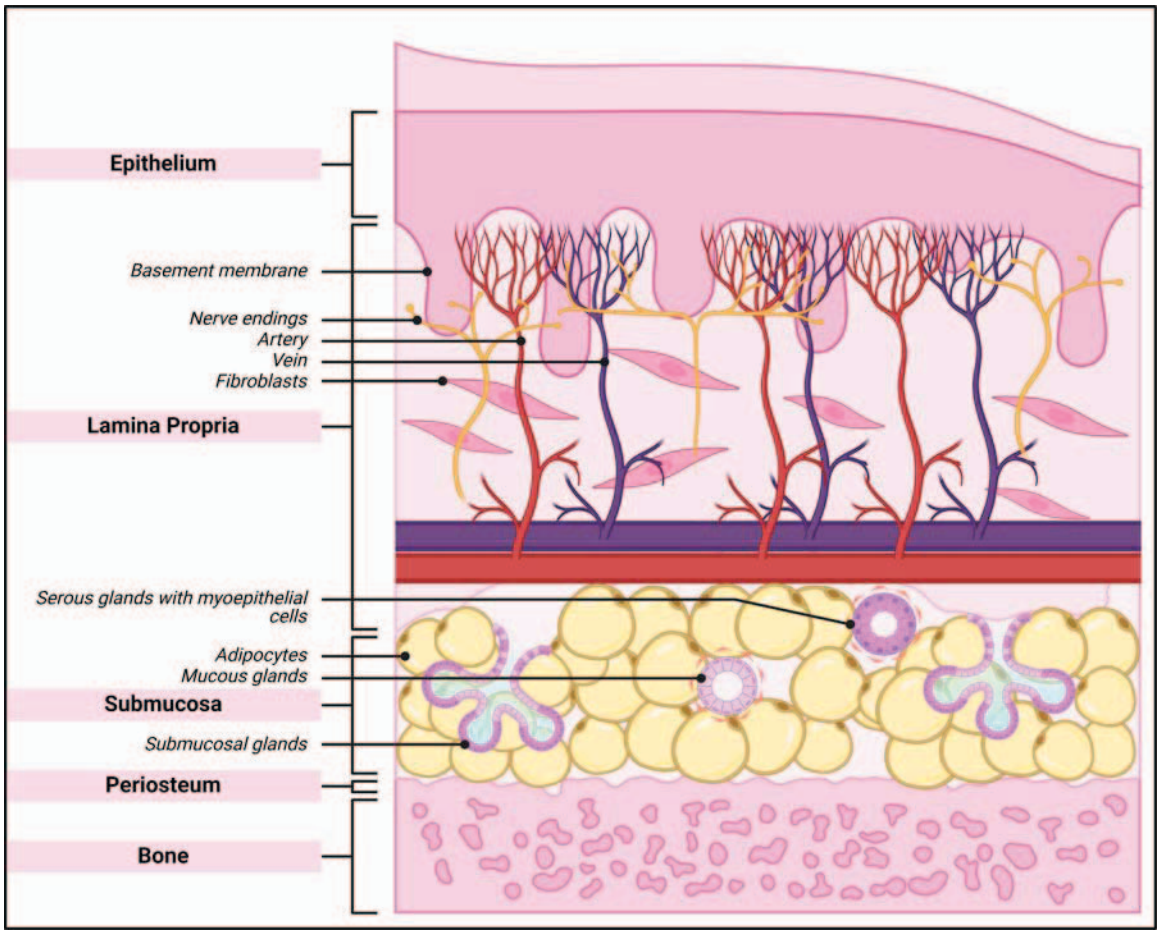

FIG. 1. Schematic cross-sectional representation of the oral mucosa, delineating the epithelial layer, underlying connective tissue, and associated salivary gland structures. The illustration emphasizes the distinction between keratinized and nonkeratinized epithelia, the basement membrane interface, and the spatial distribution of fibroblasts, vascular elements, and glandular components. Created with BioRender.com.

defense by detecting harmful organisms and producing various antimicrobial substances. Beyond protection, the oral mucosa plays vital sensory roles, such as detecting pain, touch, the unique warmth of the mouth, and taste.[28] These functions are typically performed by a variety of specialized nerve endings, cells (Merkel cells), and cytoskeletons (taste buds) located in different regions of the oral mucosa. The human oral mucosa, unlike the skin, is not thought to have a significant thermoregulatory function, although this role may be more important in animals, for example, the tongue of a panting dog.[27]

OLP is a common chronic inflammatory disease of the oral basal epithelium affecting T cells. Immune infiltration, particularly of $CD8^+$ lymphocytes, is a common and associated feature of this disease.[29] The World Health Organization defines OLP as: a chronic inflammatory disorder of unknown etiology, characterized by characteristic relapses and remissions, and presents white, reticulated lesions, which may be accompanied by atrophic, erosive, ulcerated, or plaque-like areas. Lesions are often symmetrical on both sides. Scaling gingivitis may be a characteristic feature.[30] The seriousness of OLP lies in its potential to progress to oral cancer over the course of the disease. For this reason, after years of controversy, OLP is now considered an oral potentially malignant disorder (OPMD).[31]

OM is a common side effect associated with radiation and chemotherapy for HNC. This is due to the induction of cellular damage that contributes to oral mucositis development. Despite the medical advances in cancer therapy, OM is still virtually inevitable in patients being irradiated for neoplasms of the head and neck.[32] Several of these symptoms might be caused by OM, inflammation, and acute damage to the oral mucosa, which occur because of HNC therapy.[33] who believed that around 66% of HNC patients have severe OM, and the frequency of OM in this population surpasses 85%. Oral mucosa that is not keratinized, such as the lateral and ventral tongue, buccal mucosa, and soft palate, is most often affected by OM, which typically starts as erythema and progresses to erosion and ulceration, frequently with a white fibrinous pseudomembrane covering it all. Systemic or local infections may develop because these lesions weaken the mucosal barrier.[34]

OSCC arises from the squamous epithelium of the oral mucosa and usually affects the gingiva, alveolar ridges, oral mucosa, floor of the mouth, palate, and tongue. OSCC is approximately 90% of head and neck squamous cell carcinomas (HNSCC) and is the most common malignant tumor of the oral and maxillofacial region.[35] Worldwide, 389,485 new instances of lip and oral cavity cancer were reported in 2022, with 188,230 fatalities.[36] This information is based on the Global Cancer Observatory (GLOBOCAN). Forecasts indicate that the number of new cases of oral cancer will climb steadily over the next decades, reaching 856,000 in 2035. The 5-year survival rate for locally diagnosed cancer is 80%; however, after the disease has progressed to regional lymph nodes, it decreases to 20%, making this rising trend more concerning.[37] Not only does oral cancer treatment have negative health consequences, but it also has a huge monetary cost, which may be directly or indirectly attributed to the costs of research, treatment, and monitoring, as well as the costs of cancer therapy problems.[38] The following logic chart (Fig. 2) shows a summary of the classification of oral mucosal disease.[39]

Chronic exposure to carcinogenic insults, specifically tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, betel quid alkaloids, and high-risk HPV, accelerates malignant transformation. Mechanistically, these agents drive carcinogenesis by inducing genomic instability, aberrant epigenetic modifications, and dysregulation of the tumor microenvironment, ultimately promoting local invasion and metastasis. The etiological contributions of these factors are summarized in Figure 3.[40]

An additional difficulty in building composite tissues and assembling them in their natural anatomical connection arises when OSCC spreads to various tissues. While bioprinting's use in composite tissue creation is still in its infancy, a small number of encouraging investigations have

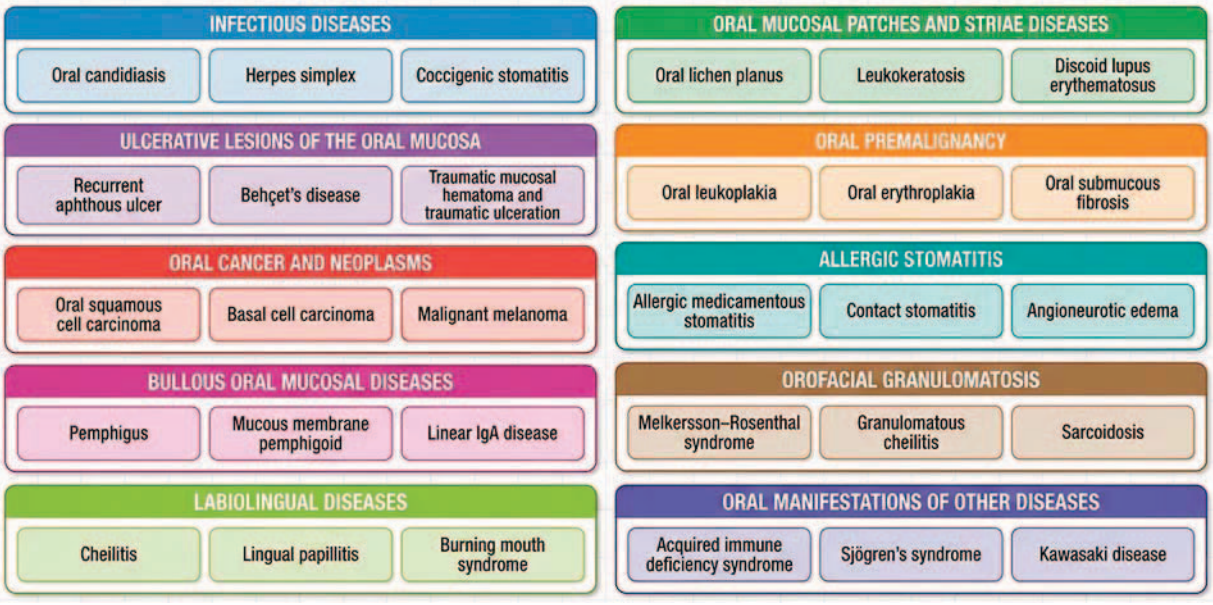

FIG. 2. Logic diagram summarizing the classification of oral mucosal diseases.

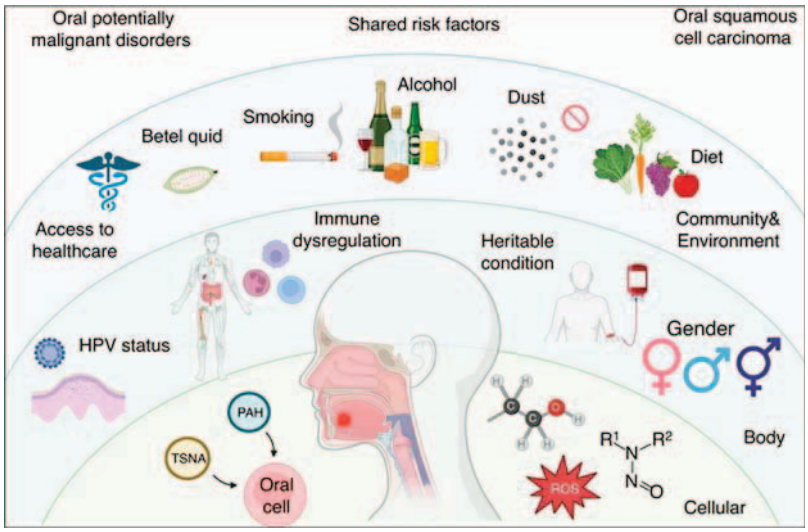

FIG. 3. Proposed mechanistic pathways connecting risk factors to OPMDs and OSCC. Key etiological factors, including tobacco usage, chronic alcohol consumption, betel quid (BQ) mastication, and HPV infection, synergize with host factors such as immunodeficiency and genetic susceptibility to initiate pathogenesis. At the molecular level, exposure generates polycyclic aromatic hydrocarbons (PAHs), reactive oxygen species (ROS), and tobacco-specific nitrosamines (TSNAs). These molecular mediators drive the transition from oral potentially malignant disorders (OPMDs) to oral squamous cell carcinoma (OSCC). Adapted from Almela et al.[38] with permission.

shown that the technique might be used to create hybrid mouth prosthetics.[38] It is believed that 3D bioprinting would make it possible to build hybrid models with various tissues by depositing multicomponent bioinks that include various biomaterials, cells, additives, and biomolecules.[41]

Challenges of Traditional In Vitro and In Vivo Models for Studying Mucosal Disorders

The reproducibility dilemma: Physiological variability in animal models

While *in vivo* animal models remain a cornerstone of biomedical investigation, their predictive validity is frequently compromised by fundamental phylogenetic discrepancies. Inherent anatomical, genetic, and immunological divergences between species often result in a failure to adequately mimic human pathophysiology. This discordance contributes significantly to the 95% attrition rate observed in human clinical trials, highlighting a critical translational bottleneck.[42] These limitations are particularly pronounced in the study of the oral mucosa.[13] The murine oral microenvironment, for example, exhibits distinct keratinization patterns, immune landscape composition, and healing kinetics that do not faithfully reproduce human oral physiology. Specifically, nonhuman models often fail to capture the sophisticated regulatory networks and self-organizing mechanisms inherent to human tooth formation and periodontal regeneration.[43] Furthermore, the variability in xenogeneic immune responses renders the extrapolation of mesenchymal stem cell (MSC)-based regenerative therapy outcomes from animals to humans highly problematic.[44] Our longitudinal observations suggest that standard laboratory strains frequently exhibit inexplicable physiological variability and lack the genetic standardization required for consistent, reproducible data, thereby confounding the determination of therapeutic efficacy.

Inadequacies of 2D cell cultures in recapitulating the tumor microenvironment

Traditional 2D cell cultures, while cost-effective for high-throughput screening, fail to recapitulate the structural complexity and dynamic cellular interactions of the native tissue microenvironment (Fig. 4). By enforcing an

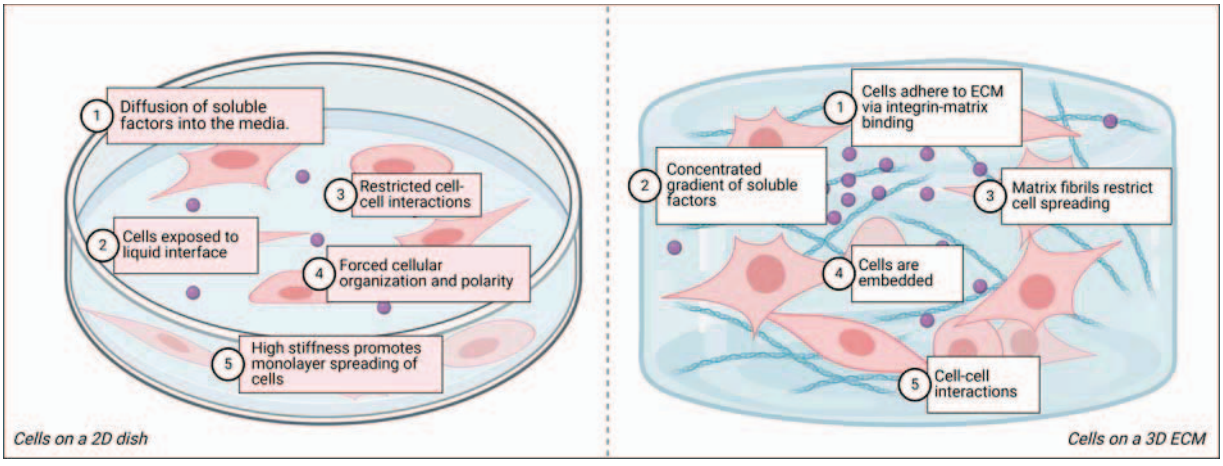

FIG. 4. Comparative analysis of two-dimensional (2D) and three-dimensional (3D) experimental models. Created with BioRender.com.

artificial monolayer geometry, these systems distort cellular morphology, polarity, and cell-matrix interactions.[45] Crucially, 2D systems cannot replicate the stratification of epithelial layers characteristic of the oral mucosa, nor can they simulate the hypoxic cores and nutrient gradients typical of solid tumors.[11] The reliance on immortalized cell lines further compounds this issue; these lines often harbor karyotypic abnormalities and lack the phenotypic diversity of primary patient-derived cells. The establishment of novel cell lines is resource-intensive and prone to selection bias, potentially yielding artifacts driven by atypical growth conditions.[46] Ultimately, the absence of 3D spatial organization alters intracellular signaling cascades, rendering 2D cultures increasingly insufficient for elucidating complex disease mechanisms or validating novel therapeutic targets.[47]

Bridging the gap in oral cancer modeling: from traditional 3D constructs to organoids

Traditional bioengineered oral tissues, exemplified by models like the human tissue–engineered oral mucosal model, have been utilized for initial studies of OSCC,[48] However, current *in vitro* oral cancer models are fundamentally constrained by two significant drawbacks:

1. The inability to accurately reconstitute tumor microenvironment of the native tissue counterpart.
2. The absence of a heterogeneous construct encompassing multiple tissue types in a single unit.

These inherent constraints, which necessitate accounting for substantial inter- and intratissue variability, significantly hinder the clinical translatability of *in vitro* findings to contemporary oral cancer models. To address this structural and cellular complexity deficit, 3D bioprinting has emerged as a promising high-precision manufacturing strategy. This technology has already demonstrated success in creating complex tumor models across various oncology fields, including ovarian, pancreatic, hepatocarcinoma, and breast cancers.[17] Despite this potential, the applications of bioprinting in oral cancer research remain relatively restricted, requiring sustained developmental efforts to fully realize its clinical benefits. Achieving effective synthetic tissue models requires careful consideration of three critical components: the mechanical characteristics, biological makeup, and intrinsic complexity of the target tissue. Consequently, the next logical steps in advancing oral cancer modeling via bioprinting involve creating heterogeneous single oral tissue equivalents and complex composite oral tissue constructions.[15] However, while high-throughput and controlled, these advanced *in vitro* models (including traditional 3D constructs) still face limitations in fully replicating the structural and functional complexity of the native oral mucosa, which often results in poor clinical translatability.[49] For instance, monolayer cell cultures lack the stratified epithelium and essential microenvironmental cues critical for studying disease mechanisms or drug responses. Conversely, *in vivo* models, though offering superior physiological relevance, are encumbered by ethical considerations, high operational costs, and protracted timelines, particularly for investigations into chronic disease progression.[50]

Organoids provide a more realistic and practical depiction than 2D models (Table 1), which have limitations when it comes to simulating the intricate interactions inside the mouth mucosa, while 3D models, although offering advances, still fall short. These developments highlight how organoids might be used more widely in healthcare settings.

Engineering Human-Relevant models: From MSCs to organoids-on-a-chip

While preclinical studies utilizing MSCs have demonstrated therapeutic potential, the translation to human clinical endpoints has yielded inconsistent results. This discrepancy is largely attributable to the inability of current animal models to emulate the complexity of human immune modulation and tissue regeneration.[56] For example, the efficacy of MSC-derived extracellular vesicles (MSC-EVs) in dental regeneration is frequently obscured by species-specific variations in stem cell potency and secretome profiles.[16] To resolve these translational inconsistencies, there is an imperative need for human-relevant *in vitro* systems that integrate biological complexity with mechanical and physiological cues.

Recent bioengineering advances have catalyzed the development of Organ-on-a-Chip (OoC) platforms microfluidic devices that recapitulate the physicochemical microenvironment of human tissues. Unlike static organoids, OoC systems integrate dynamic fluid flow to simulate vascular shear stress and mechanical strain, factors critical for cellular homeostasis.[55] Crucially, modern OoC platforms enable the precise coculture of multiple tissue types (e.g., oral mucosa, immune cells, and vascular endothelium) linked via microfluidic channels. This configuration allows for the study of systemic interorgan crosstalk and the reproduction of complex *in vivo* signaling pathways, such as metastasis or systemic immune responses, in a controlled setting.[57] By combining the regenerative potential

Table 1. Highlights of the Comparative Analysis of Organoid Models Versus Traditional Models

	Organoids	*Traditional 2D models*
Drug screening	In colorectal cancer, patient-derived organoids (PDOs) exhibited an 88% concordance rate with clinical responses to chemotherapy.[51]	Only 5–25% of drugs showing efficacy in 2D cultures succeed in clinical trials.[52]
Genetic stability	PDOs retain >90% of parental tumor mutations even after long-term culture.[6]	In 2D cell lines lose heterogeneity due to clonal selection.[53]
Clinical predictive power	A blind study demonstrated that PDOs predicted chemotherapy responses in stage IV colorectal cancer with 93% accuracy.[54]	Outperforming xenograft models (typically 60–70% concordance).[55]

of dental-derived MSCs with the structural relevance of OoC scaffolds, researchers can now create sophisticated models of oral disorders. These systems not only mimic the multicellular architecture of the oral niche but also facilitate the high-fidelity evaluation of MSC-EV-based therapies, offering a superior alternative to traditional reductionist models.[58,59]

Historical Background of Organoids

A significant milestone in the evolution of organoids was the pioneering research conducted by Henry Van Peters Wilson in 1907. He demonstrated that individual sponge cells could spontaneously arrange themselves into functional structures.[60] This remarkable finding led to further exploration into the possibility of directing cells to autonomously form intricate multicellular assemblies after they were separated from their original tissue.[61] Progress accelerated in the 1950s, as scientists attempted to recreate damaged organs using chick embryos.[62] The following decades saw the emergence of pluripotent stem cells (PSCs), particularly with the extraction of embryonic stem cells (ESCs) from human blastocysts and mouse embryos, which further facilitated the advancement of organoids. In the 1980s, Howard Green built on these earlier developments by culturing human epidermal keratinocytes with mouse embryonic fibroblasts, creating a model that mimicked human skin.[63]

In its relatively short timeline, organoid research has made significant progress (Fig. 5), achieving critical milestones, such as the development of a model for human diseases and insights into various developmental processes thanks to stem cell investigations. The discovery of induced PSCs (iPSCs), which allowed scientists to revert adult cells to a pluripotent state, further transformed the field.[64] From the early 2000s, researchers began exploring the potential of organoids for use as disease models, platforms for drug testing, and subjects for regenerative medicine. Because of these advances, methods for 3D cultures have gained prominence. These systems provide a representation of *in vivo* conditions that surpasses traditional 2D cultures.[65] Since their inception, organoids have been employed in studies related to embryonic development, cancer, and genetic diseases. A visual timeline illustrating the key developments in organoid technology since Wilson's experiments would be beneficial.[63]

Organoids: The Future of Oral Mucosal Disease Modeling

Organoids are miniature, simplified, 3D replicas of organs grown in a lab that serve an identical purpose as their *in vivo* equivalents.[66] They are developed from stem cells from different sources, which can be detailed in (Fig. 6). Making oral mucosal organoids entails separating out the appropriate stem cells, seeding them onto a scaffold or extracellular matrix (ECM) (such as hydrogels or synthetic polymer scaffolds), and then engineering their development into mucosal tissues with the help of targeted growth factors.

Cellular Components and Engineering Strategies for Oral Mucosal Organoid Development

The effective designing and establishment of oral mucosal organoids depends on four essential components: a viable cell source, a biocompatible scaffold, a technique for inducing targeted differentiation, and gene-editing tools. Stem cells have a natural capacity to organize themselves into intricate 3D structures when they encounter specific signaling molecules, such as growth factors and small compounds. Although not always necessary, scaffolds are vital for supporting the structure and functional development of organoids in many instances. A crucial factor in organoid development is the regulation of the stem cell microenvironment, often referred to as the "niche," which affects cellular behavior and maintains a consistent supply of undifferentiated stem cells.

Multiple sources of stem cells have been investigated for constructing oral organoids. These include PSCs, like ESCs obtained from the inner cell mass of blastocysts,[67] and

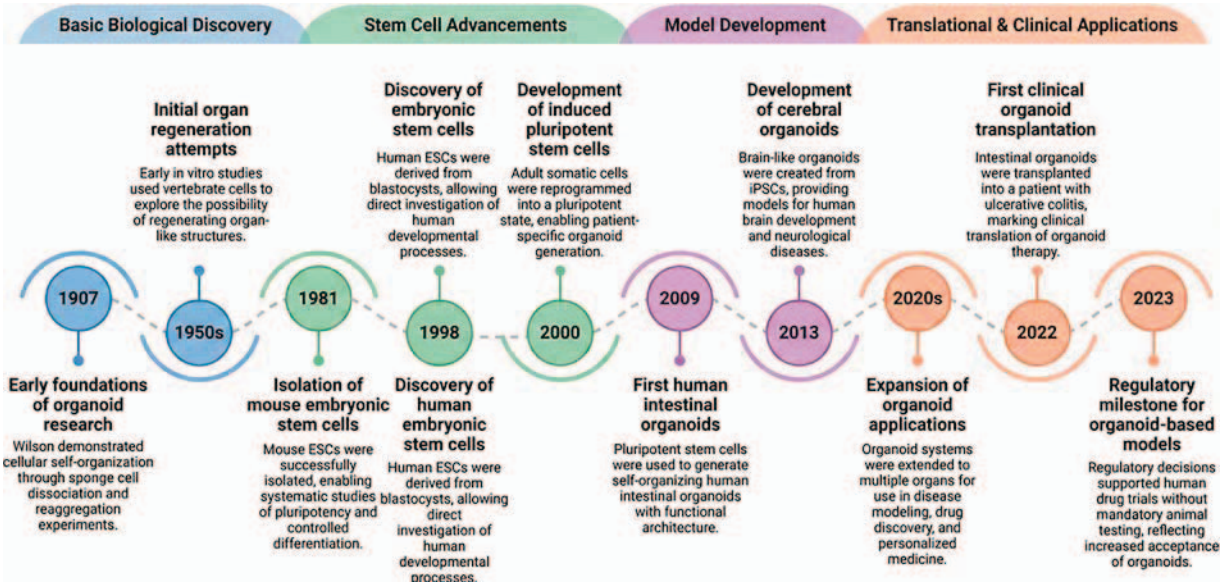

FIG. 5. Timeline illustrates the major milestones in the development of organoid technology.

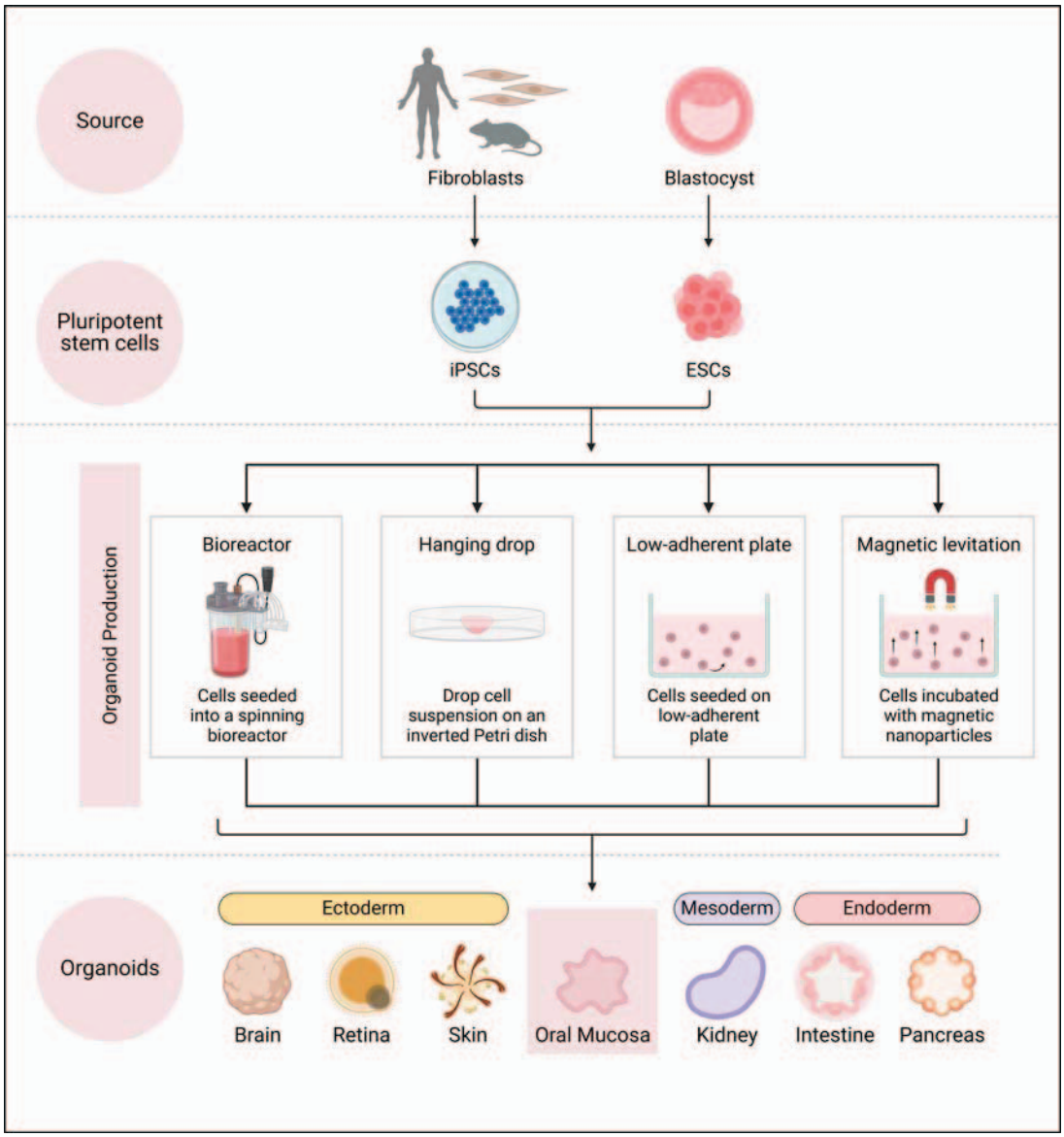

FIG. 6. Biological engineering of oral mucosal organoids using stem cell platforms and gene-editing technologies. Organoids are miniaturized, three-dimensional *in vitro* models that recapitulate key structural and functional features of native tissues. They can be derived from multiple stem cell sources, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult stem cells. To elucidate genetic determinants of disease pathogenesis and to evaluate therapeutic strategies, precise genomic modifications can be introduced using CRISPR-based gene-editing tools. The workflow involves the isolation of appropriate stem cell populations, their encapsulation within an extracellular matrix or scaffold, and the application of defined growth factor cues to direct differentiation toward oral mucosal lineages. Created with BioRender.com.

iPSCs, which are created by reprogramming somatic cells with specific transcription factors.[68] Multipotent adult MSCs also serve as important resources; they exist in tissues and have limited differentiation potential.[69] Gene-editing technologies, especially CRISPR-Cas-9, have expanded the capabilities of organoid systems by allowing for precise genetic alterations that replicate disease-specific mutations. This method supports studies on gene function, disease modeling, and preclinical drug testing.[70]

Selecting the appropriate cell source is a crucial decision, influencing the fidelity, scalability, and clinical relevance of organoids. Historically, somatic cells have been utilized for organoid generation; however, stem cells provide superior capabilities in self-renewal, differentiation, and efficiency, making them the favored choice in most methods.[71] Adult stem cells, often called tissue-specific stem cells, conserve genomic stability and show differentiation tied to their tissue of origin. As a result, they play a vital role in organoid models involving teeth, taste buds, and salivary glands. For example, dental epithelial (DE) cells from the tooth germ can develop into ameloblasts, while dental mesenchymal (DM) cells can transform into odontoblasts under specific conditions. Dental pulp stem cells (DPSCs) are easily accessible and have reproduced the DM environment in tooth germ

organoids.[72–76] Similarly, MSCs from the salivary glands, whether from embryonic or postnatal stages, have shown the ability to self-organize into functional gland structures.[77] Lingual epithelial stem cells, which include Bmi1-positive populations, have formed organoids that mirror the lingual epithelium.[78,79] Despite their benefits, such as specificity to tissue and easier lineage commitment, the wider use of ASCs is often limited by their availability and scalability.[80]

On the other hand, PSCs, including both iPSCs and ESCs, demonstrate strong self-renewal and pluripotency, providing significant benefits for creating organoids. Recent studies have shown that iPSCs can be manipulated to develop DE and DPSCs through a series of differentiation steps or coculturing methods.[81] Salivary gland modeling systems have shown that PSCs can be instructed toward oral ectodermal progenitor fates, which, upon exposure to FGF7 and FGF10, initiate branching morphogenesis and self-organize into duct-like epithelial networks.[54,82] However, several challenges remain, including issues related to tumor formation, incomplete differentiation, and variations in procedures. These must be resolved to facilitate the use of organoids in clinical settings. The combination of adult MSCs and PSCs through hybrid or staged methods shows potential for improving oral tissue engineering, modeling diseases, and advancing regenerative medicine. Ongoing efforts to enhance cell sourcing, scaffold compatibility, gene-editing accuracy, and control over microenvironments will be crucial to unlocking the full capabilities of oral mucosal organoids in fundamental and applied research.

Integrating ECM and Scaffold Technologies for Engineering Oral Mucosa Organoids

An important factor in creating successful organoids is the ability to mimic the natural environment that influences how cells act and make decisions in living organisms. At the core of this microenvironment lies the ECM, which functions as a dynamic instructive scaffold governing cell fate decisions, tissue architecture, and organoid self-organization. Different methods have been used to build this intricate setting, such as hydrogels made from natural ECM, synthetic materials, and decellularized tissues-all of which play a unique role in forming and maintaining the function of oral mucosa organoids.

Natural ECM-based materials

Natural biomaterials like Matrigel and collagen gels play a crucial role in organoid studies because they closely mimic the native basement membrane. Matrigel, which comes from Engelbreth-Holm-Swarm mouse sarcoma, contains a rich blend of ECM proteins such as laminin, collagen IV, and entactin, as well as growth factors that promote the growth and organization of epithelial cells.[83,84] On the other hand, collagen gels enhance structural stability and are compatible with various types of oral epithelial and mesenchymal cells. These natural materials have been vital for creating layered epithelial tissues and gland-like structures. Nonetheless, their biological variability and unclear composition can create obstacles for consistent experimentation and application in clinical settings.[58]

Synthetic scaffolding platforms

Synthetic polymers can be tailored to have specific physical and chemical properties that are essential for developing organoids. For example, materials like poly lactic-coglycolic acid (PLGA) and polycaprolactone have been crafted into scaffolds that create a supportive environment for the crucial interactions between epithelial and mesenchymal cells needed for tooth germ organoid formation.[85] Furthermore, hydrogel systems that include PLGA or hyaluronic acid have aided in the growth of salivary gland organoids by encouraging the creation of branched duct structures.[86,87] Even though synthetic scaffolds show good structural stability and consistent results, they typically need additional functionalization with peptides for cell attachment or signaling molecules to mimic the natural bioactivity of the ECM.

Decellularized ECM scaffolds

Recent improvements in techniques for decellularizing tissues have resulted in the development of acellular ECM scaffolds that retain the complex biochemistry and 3D structure of natural tissues. These biomimetic matrices keep the spatial distribution of ECM proteins and bioactive substances, promoting an ideal setting for stem cells to attach, grow, and differentiate. For instance, when DPSCs and DE cells were placed in decellularized porcine molar tooth buds, successful regeneration of enamel and dentin structures occurred in living subjects.[88] Likewise, reseeding decellularized submandibular gland scaffolds with primary salivary gland cells has resulted in the creation of gland-like structures, which show improved cell survival and organization within the tissue.[89]

The Rise of Organoid Technology

Organoid technology has precipitated a paradigm shift in biomedical research, offering unprecedented fidelity in disease modeling, drug discovery, and regenerative medicine.[90] Defined as self-organizing, 3D *in vitro* constructs derived from PSCs or MSCs, organoids recapitulate the essential cytoarchitecture and functionality of native tissues.[91] Unlike traditional 2D monolayers, which often lose cellular polarity and specialized phenotype, organoids facilitate the emergence of complex, multicellular spatial arrangements.

Comparatively, while 3D bioprinting offers precise spatial control over cell deposition, organoids possess superior intrinsic self-assembly capabilities that better mimic developmental organogenesis.[92] For instance, recent studies indicate that oral mucosal organoids spontaneously generate mature, stratified epithelial layers containing distinct progenitor and differentiated cell populations, a feature often absent in synthetic scaffold-based models or standard 2D cultures.[93] This structural fidelity enables the precise interrogation of cellular mechanics, differentiation pathways, and disease etiology in a manner that remains physiologically distinct from alternative *in vitro* modalities.[92] Consequently, organoid platforms are increasingly pivotal in oncology for modeling intratumoral heterogeneity and patient-specific treatment responses, bridging the translational gap between bench-side discovery and clinical application.[90,94]

3D Cell Culture Modalities

Spheroid

A range of 3D culture techniques has been created to form cell aggregates, known as spheroids. These include hanging drops, spontaneous aggregation, and rotating culture vessels.[95] Such methods allow researchers to explore interactions between cells, their polarization, differentiation, and the characteristics of the ECM. However, they do not provide control over the size of spheroids, their predictability, or mechanical stimuli. Additionally, in larger aggregates, cell death often occurs at the center.[96] Spheroids are structurally simpler than organoids, which have more specific tissue structures and functional complexities. This difference makes spheroids better suited for high-throughput drug screening, particularly in toxicity assessments or targeted drug delivery, rather than functioning as models for organ-level functions.

Organoid

Cells are seeded into a hydrogel matrix resembling a basement membrane to developed an organoids.[97] Homogeneity, cell polarity, and cell connections are all improved in the organoid structures. The key drawbacks are the absence of mechanical stimulation, xenogeneic elements, and the scaffolds' unregulated disintegration.[98]

In contrast to spheres, organoids can simulate organ functions and multicellular interactions, facilitating the interaction between 2D cultures and living models. However, their reliance on animal-derived matrices (such as Matrigel) leads to batch variability and ethical concerns and is less common in scaffold-free sphere systems.[84]

3D microfluidic cell culture system

The microfluidic devices in question include microfluidic channels, spheroids, and organoids. *In vitro* models are more applicable to human physiological conditions. The cells are subjected to mechanical stress while being perfused with fluid-containing nutrients via the microfluidic channels. Multiple cellular layers may be cultured in coculture using this technique, making cell–cell interactions possible.[99–101] In most cases, photolithography is used to make the chip. Integrated microsensors can detect a wide range of physical, chemical, and electrical stimulus. Unfortunately, there is currently no standardization, and the chips are difficult to operate and build for cell culture.[97,102]

Even though spheres and organoids are often static cultures, microfluidic platforms introduce dynamic microenvironments such as shear stress and oxygen gradients, enhancing their importance in studying metastases or vascular tissues.[66,103,104] However, the lack of standardization and technical complexity limits their widespread use compared to uncomplicated sphere and organoid models.

Functional decellularized scaffolds

Research in solid organ transplantation has shown promising results in decellularizing and regenerating several organs, including the kidney, liver, and lungs.[105] Immune rejection is either eliminated or significantly diminished if all donor cellular components are removed.[106] Chemicals with an alkaline pH, acids, alcohols, detergents, and enzymes are among the decellularizing agents that have been used.[107] Collagen, glycosaminoglycans, laminin, and growth factors are some of the ECM components that aim to be preserved as cells are removed using this method.[108] For studying organ development and pathophysiology, it may be useful to create organ scaffolds that do not contain any cells but do have functioning vascular and interstitial compartments Table 2.[52]

OoC and organoid models

Organoid and OoC models are highly beneficial and are briefly summarized in Table 3. Recognizing the merits and limitations of these approaches in terms of cell origin, structural loyalty, genetic stability, and environmental control capabilities and throughput will provide more insights into both approaches and their applicable environments.[109–111] Moreover, such comparisons also reveal a future path to pursue an integration approach integrating organoid, OoC, 3D printing, and numerical simulation toward patient-specific disease-on-a-chip and human-on-a-chip.

Cellular Differentiation Pathways for Oral Mucosa Modeling

Defined signaling cues are essential to trigger stem cells toward oral mucosal lineages. Pathways such as BMP/TGF-β and WNT/β-catenin play pivotal roles in epithelial stratification, barrier formation, and immune cell differentiation. Notably, the differentiation of LCs in the oral mucosa is orchestrated through BMP7-mediated signaling via ALK3 and TGF-β1 via ALK5. These signals guide the migration and maturation of LC precursors from the bone marrow into the oral epithelium, a process that differs fundamentally from the development of self-renewing, radioresistant LCs in the epidermis.[112,113] The sequential activation of chemokine receptors (CCR2, CCR6), followed by the upregulation of epithelial markers such as E-cadherin and Langerin, illustrates the tightly regulated crosstalk between stromal and immune components within the mucosal niche.[114]

Advancing Personalized Medicine Through Oral Mucosal Organoids

PDOs have become groundbreaking instruments in the field of personalized medicine, acting as patient avatars that accurately mirror specific disease characteristics. These models allow for precise predictions regarding how patients will respond to medications, leading to targeted assessments that enhance treatment results while reducing side effects, as indicated in Figure 7.[51] For example, PDOs play a crucial role in individualized drug testing, permitting healthcare providers to evaluate a range of chemotherapy and targeted therapies to customize treatments for optimal effectiveness. They also help in refining treatments by identifying the best therapeutic options for each patient, which decreases the need for trial-and-error methods and enhances overall treatment success.[115]

In the studies of oral and maxillofacial tumors, organoid models have shown significant value for drug screening, developing new medications, and researching tumor biology. Important progress has been made in creating protocols for generating organoids from OSCC and epithelial tissues, as

Table 2. Three-Dimensional Cell Culture Modalities

Model	*Advantages*	*Disadvantages*	*Key applications*
Spheroid	• Studies cell–cell interactions, polarity, differentiation, and ECM properties. • Suitable for high-throughput drug screening, toxicity testing, and targeted drug delivery.[10]	• Lacks control, oversized, predictability, and mechanical stimulus. • Prone to central necrosis. • Simpler structure lacks tissue-specific complexity compared to organoids.[11]	High-throughput drug screening, toxicity testing, and targeted drug delivery.
Organoid	• Improved size homogeneity, cell polarity, and connections. • Simulates organ functions and multicellular interactions, bridging 2D cultures and living models.[47]	• Absence of mechanical stimulation, xenogeneic elements, and unregulated scaffold disintegration. • Reliance on animal-derived matrices (e.g., Matrigel) causes batch variability and ethical concerns.[89]	Modeling organ functions, multicellular interactions, disease mechanisms, and therapeutic responses.
3D microfluidic cell culture system	• More physiologically relevant. • Cells experience mechanical stress from fluid perfusion. • Enables coculture of multiple cell layers and cell–cell interactions. Integrated microsensors detect physical, chemical, and electrical stimulus. • Introduces dynamic microenvironments (shear stress, oxygen gradients) for studying metastases and vascular tissues.[2]	• Lack of standardization. • It is difficult to operate and construct. • Technical complexity limits widespread adoption.[47]	Studying metastases, vascular tissues, and drug screening under dynamic conditions.
Functional decellularized scaffolds	• Retains natural 3 D structure and biomechanical cues of whole organs. • Eliminates or significantly diminishes immune rejection.[4]	Challenges in recellularization and scalability for clinical application.[81]	Organ transplantation research and studying organ development and pathophysiology.
Organ-on-a-chip	• Highly beneficial for understanding cell origin, structural loyalty, genetic stability, environmental control, and throughput. • Facilitates integration with 3D printing and numerical simulation for patient-specific models.[16]	• Costly and technically complex, limiting widespread adoption. • They may not fully replicate systemic interactions found in whole organisms.[22]	Personalized medicine, drug discovery, and patient-specific disease modeling.

highlighted by Driehuis et al.[53] Additionally, organoids derived from circulating tumor cells have proven to be highly accurate in predicting the effectiveness of treatments for HNSCC, achieving a 93.75% success rate in forecasting responses to cisplatin, docetaxel, and 5-fluorouracil, thanks to a combination of organoid assessment and mathematical modeling.[116] Research conducted by Czerwonka et al. has also pointed out the promise of small-molecule Notch

Table 3. Complementary Strengths of Each Model, with OoC Favoring Reproducibility and OoCC Excelling in Physiological Relevance

Feature	*Organ-on-a-chip (OoC)*	*Organoid-on-a-chip (OoCC)*
Cell source	Predifferentiated cells (primary, lines)	Stem cells (iPSCs, ESCs) or biopsies
Culture method	Engineered microenvironments, perfusion	Self-assembly in hydrogels (e.g., Matrigel)
Structural fidelity	High for interfaces (e.g., barriers)	High for organ microarchitecture
Vascularization	Can integrate artificial vasculature	Typically lacks vascular networks
Applications	Drug screening, mechanobiology	Disease modeling, regenerative medicine
Throughput	High (multiwell systems)	Lower (batch variability)
Environmental control	Precise (flow, stress, gradients)	Limited (dependent on self-organization)

ESC, embryonic stem cell; iPSC, induced pluripotent stem cells.

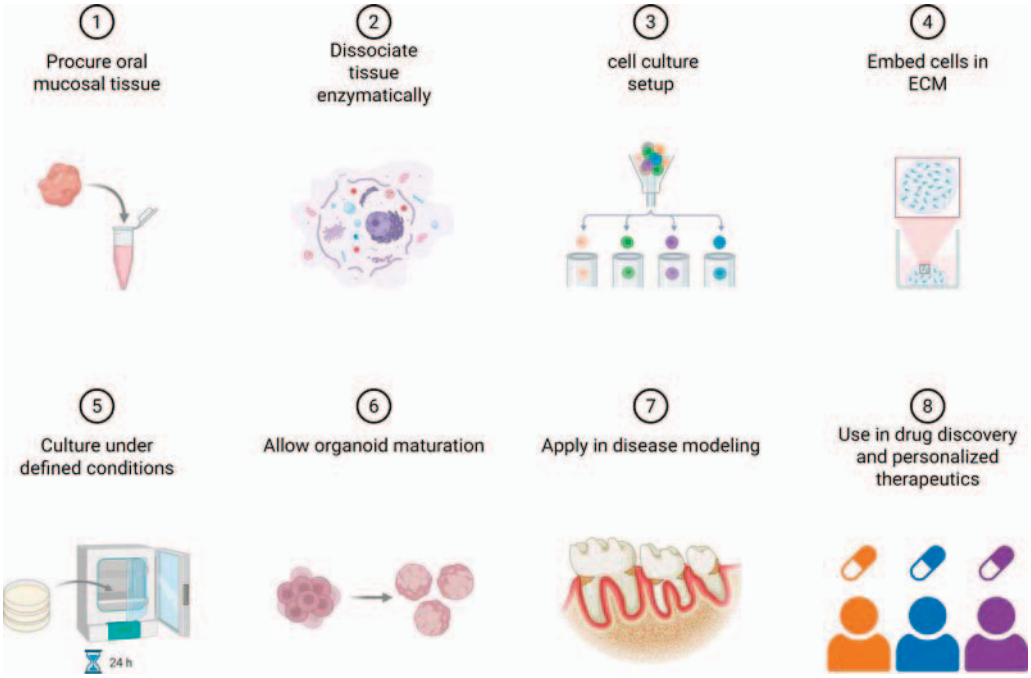

FIG. 7. Oral mucosal organoid construction: visual guide and workflow. This figure provides a stepwise schematic of the oral mucosal organoid generation process, encompassing tissue procurement, enzymatic dissociation, cell isolation, embedding within an extracellular matrix, and defined culture conditions that support organoid formation. The latter stages illustrate organoid maturation and its subsequent applications in disease modeling, drug discovery and screening, and personalized therapeutic approaches. This schematic is intended to serve as a practical reference for researchers developing and employing oral mucosal organoid platforms.

modulators, like RIN-1, as potential chemotherapy agents for HNSCC patients maintaining active Notch signaling pathways.[117] For instance, organoids from salivary gland cancer have allowed scientists to verify the activation of cancer-causing pathways and evaluate the effectiveness of genetically directed targeted treatments.[118] Furthermore, these organoids have exhibited varying responses to receptor tyrosine kinase inhibitors and standard chemotherapy drugs such as paclitaxel and erlotinib, emphasizing their importance in preclinical drug assessments. Oral mucosal organoids represent a new and promising area in personalized medicine, fostering advances in treatment approaches and improving patient care.

Clinical Applications of Organoids in Oral Mucosal Disorders

1. Disease modeling: Oral mucosal organoids are used to study the mechanisms of oral mucosal disorders, including inflammatory diseases and precancerous lesions.
2. Drug discovery and testing: These organoids provide a platform for personalized drug response testing and evaluating drug efficacy and safety.
3. Regenerative medicine: Oral mucosal organoids are applied in regenerative medicine, particularly in reconstructive surgery and tissue engineering.
4. Clinical decision-making: Tumor organoids derived from oral mucosa can help analyze tumor cell phenotype, tumorigenic potential, and response to therapies, aiding clinical decision-making.

For patients with OSCC, organoids derived from their tumors are instrumental in evaluating how effective chemotherapy and targeted medications might be. This tailored strategy is based on the genetic and molecular traits of the patient's tumor, which aids doctors in predicting treatment effectiveness more precisely. For example, research conducted by Driehuis and colleagues[6] showcased how oral mucosal organoids can be used to test responses to medications such as cisplatin and cetuximab, emphasizing their role in informing clinical choices. These results highlight how organoids can connect laboratory research with practical therapies (Fig. 8, and Fig. 9). Furthermore, when considering mucositis, a frequent consequence of chemotherapy and radiation, organoids serve as a valuable method for studying the condition and its mechanisms. Scientists can explore how the microorganisms in the mouth interact with epithelial cells by growing organoids with these microbes. Research by Reyes-Gebe et al. showed that certain microbial patterns correlate with a higher risk of mucositis in patients receiving treatment for HNSCC. This finding paves the way for developing specific strategies to prevent or reduce mucositis.[119]

Pros and Cons of Oral Mucosal Organoids

These organoids replicate the epithelial layer, connective tissue, and immune cells effectively, allowing for in-depth examination of tissue healing, regeneration, and cell behavior. Their similarity to the intricate structure of the oral mucosa makes them essential for studying how cells interact and how tissue behaves. Additionally, oral mucosal organoids can be cultured for extended periods, making them

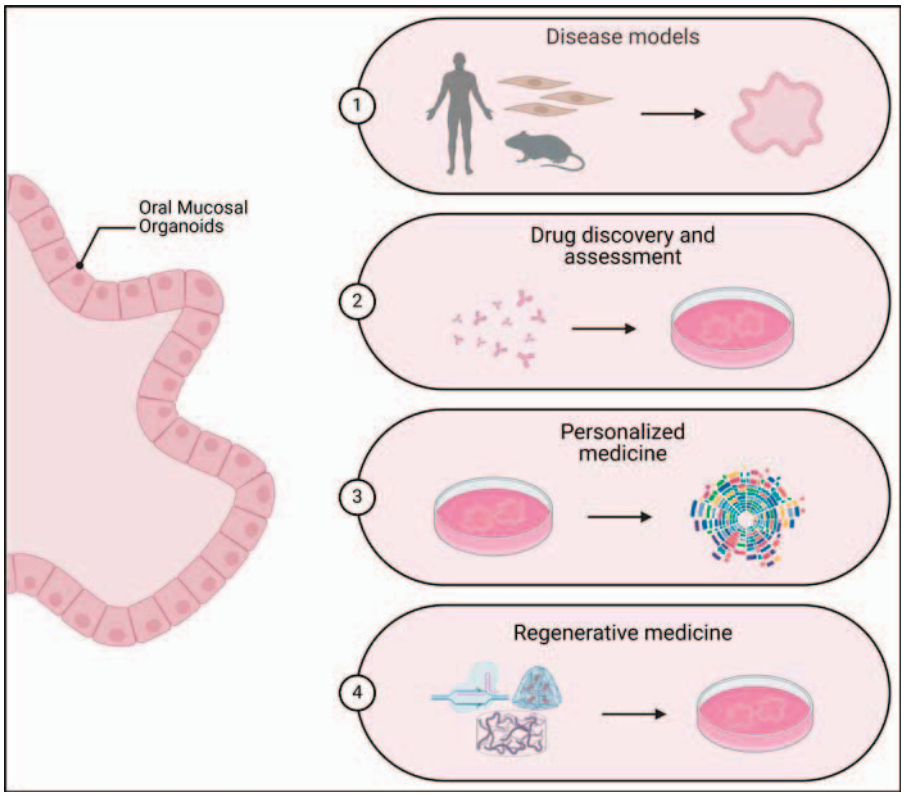

FIG. 8. Workflow illustrating the generation of oral mucosal organoids from patient-derived biopsy specimens. Created with BioRender.com.

particularly useful for researching long-lasting conditions like cancer and autoimmune diseases.[43,120] This ability to grow over time offers scientists a realistic model to explore disease development, biological reactions, and possible treatment options.

Issues with immunogenicity

When it comes to transplanting organoids, concerns regarding immunogenicity arise. First, the dense materials used in organoid structures, such as hydrogels and freeze-dried substances, might impact how immune cells, specifically T cells, infiltrate and complicate the use of autologous transplants.[121] Second, since organoids and immune cells need different factors for signaling and communication, there isn't a single cultivation medium that works for both.[122] Precise experiments are necessary before starting coculture to identify the best conditions that protect immune cells while allowing organoids to grow. Moreover, the presence of immune cells can restrict the growth of organoids. Another difficulty in organoid studies is creating an accurate immune environment that reflects the balance between organoids and immune responses.[116] Techniques to reduce immunogenicity are still being researched, but these may involve altering culture conditions or engineering organoids to produce cytokines that suppress the immune response. Nevertheless, PDOs that incorporate aspects of the immune system along with other connective tissue elements could help fulfill the potential of personalized medicine and targeted therapies.[123]

High costs and complex culture systems

Growing organoids from the oral mucosa requires a lot of money and complicated culture methods that make it hard to scale. A major obstacle is the need to simplify culture procedures, including synthetic matrices and sophisticated 3D culture systems. To lower costs and enable wider usage, automated manufacturing techniques, and high-throughput screening technologies are required.[123]

Technical limitations in characterization and screening

Regarding large-scale drug screening and disease modeling, 3D organoid structures aren't extremely useful because of their intricacy. Improving high-throughput applications and guaranteeing consistency require the creation of automated imaging and quantitative characterization methods.[124]

Ethical challenges in patient-derived organ research

The use of patient-derived organs raises significant ethical concerns that must be addressed to ensure responsible research practices.

1. Informed consent is essential, as donors, even those who donate themselves, must fully understand the potential long-term uses of their biological material, including creating patient-derived organs to screen for therapeutics or model diseases for a specific purpose. The HYBRIDA guidelines emphasize the need for dynamic consent frameworks, such as the TRUSTED (Research Utilization of Tissue Under Ethical, Transparent, and Safe Donation) protocol, which clarifies the scope of requests donors' consent to, and addresses uncertainties related to future research (HYBRIDA OGLs, Ch. 6). However, challenges remain in cases where withdrawing consent may conflict with the irreversible engineering of cells into patient-derived organs, necessitating unified policies at the international level.[125,126]

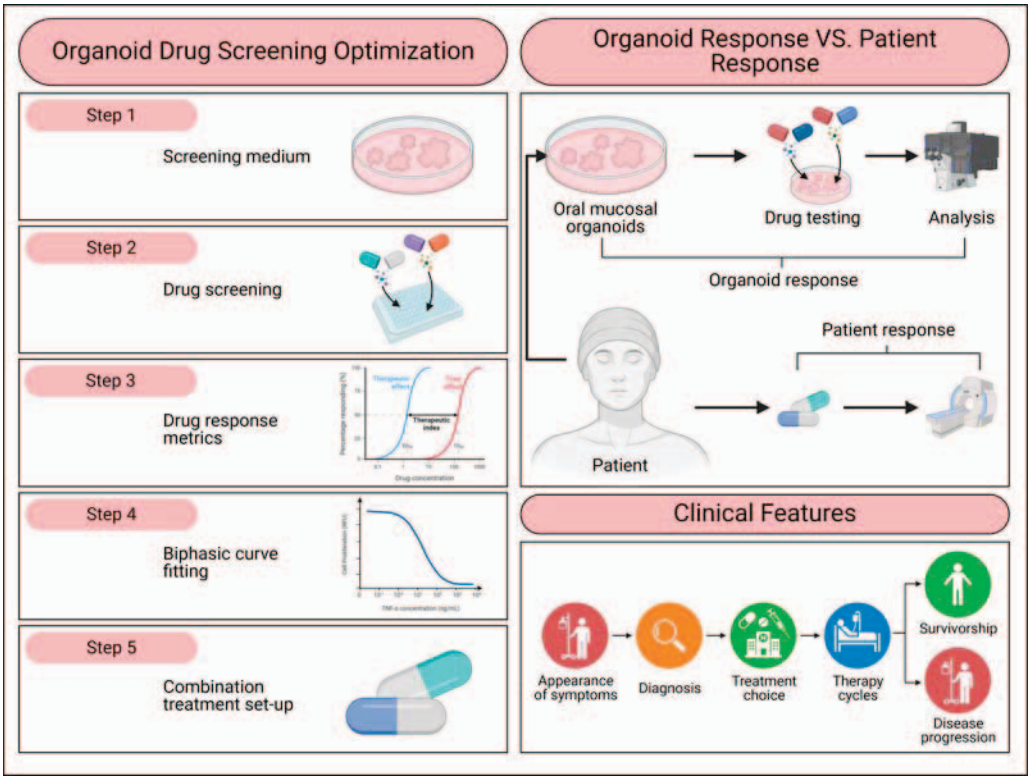

FIG. 9. Organoid-based modeling of mucositis and oral cancer for the development and evaluation of therapeutic strategies. Created with BioRender.com.

2. Commercialization complicates the issue of ethical justice, with only 12% of biobanks currently sharing profits with donors, putting vulnerable populations at risk. The HYBRIDA initiative advocates for governance consent models to ensure transparency and equitable benefit-sharing, particularly as research transitions to commercial applications.[127,128]
3. Dual-use risks, such as the potential for misusing organs for bioweapons development, require strict oversight and international cooperation to mitigate harm (Section 3.4, HYBRIDA D5.2).[126,129]
4. Maintaining public trust requires avoiding sensationalism, such as mislabeling organs as mini organs and exaggerated therapeutic promises, which can undermine trust in scientific integrity. These concerns underscore the need for robust ethical frameworks aligned with the international principles of transparency and integrity and the Nagoya Protocol to balance innovation, societal values, and donor rights.[125,127,130,131]

Future Directions and Conclusion

Organoid technology is set to transform research related to oral mucosal issues, especially regarding OSCC and similar diseases. The future involves creating organoid cocultures that include immune cells, which could greatly improve immunotherapy research by better mimicking the tumor microenvironment. Moreover, developing biobanks for OSCC organoids will support precision oncology initiatives, allowing researchers to create extensive libraries of HNSCC organoids. These innovations will deepen our understanding of the diversity within tumors and how they respond to drugs, aiding in the discovery of new biomarkers and treatment targets. Clinical trials that utilize organoid-based predictions for therapy are already in progress, showcasing a hopeful future for incorporating organoid models into everyday clinical care.

In conclusion, Organoids offer a powerful new method for researching and treating oral diseases, presenting notable benefits compared to conventional two-dimensional and animal testing methods. Their capability to accurately reflect the structure and complexity of human tissues enables more precise exploration of disease processes and treatment reactions. As the field develops, it will be essential to tackle challenges related to scalability, consistency, and their integration into healthcare practices. Advances in bioengineering, like OoC technologies and improved culture methods, will further increase the efficacy of organoids in tailored medicine and drug research. Ultimately, the ongoing progress of organoid technology has significant potential to enhance treatment approaches and patient results in oral health and other areas.

Acknowledgment

The authors extend their appreciation to the Deanship of Research and Graduate Studies at King Khalid University for funding this work through Large Research Project under grant number RGP.2/361/45.

Authors' Contributions

All authors contributed significantly to the conceptualization, drafting, revision, and final approval of the article.

Ethical Statement

Not applicable, as this is a review article with no human or animal data.

Declaration of Generative AI and AI-Assisted Technologies in the Article Preparation Process

During the preparation of this work, the authors used ChatGPT (OpenAI) to assist in designing the graphical abstract and outlining the review. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the published article. Figures were created using BioRender.

Data Availability Statement

No new data were created or analyzed in this study.

Author Disclosure Statement

The authors declare no competing interests.

Funding Information

No funding was received for this article.

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Received: July 31, 2025
Accepted: January 7, 2026
Online Publication Date: February 26, 2026