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Editorial

From Conventional Dentistry to Precision Oral Medicine: The Emerging Role of Gene Therapy and Artificial Intelligence

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ABSTRACT

Gene therapy is emerging as a promising strategy for a range of dental and oral conditions, including periodontal disease, salivary gland dysfunction, bone/tooth regeneration, and oral cancer. However, its clinical translation has been constrained by challenges in target selection, delivery efficiency, safety and patient heterogeneity. At the same time, artificial intelligence (AI) is rapidly expanding its role in dentistry, particularly in image-based diagnosis, risk prediction, treatment planning and decision support. These two fields are increasingly complementary, and this overlap can reduce patient treatment time as well as overall costs per patient. AI can help identify therapeutic targets, stratify patients, optimize delivery systems, and monitor treatment response, thereby, strengthening the precision and translational potential of gene-based interventions. By integrating AI with gene therapy, dental medicine will move closer to a model of precision oral care that is more predictive, adaptive, and clinically impactful.

KEYWORDS: *Gene therapy; AI; oral disease; oral cancer; dentistry*

INTRODUCTION

Dentistry has traditionally focused on restorative, surgical, and antimicrobial approaches to manage oral diseases; however, many conditions remain difficult to treat because their underlying pathogenesis is driven by complex molecular pathways that cannot be fully corrected by conventional interventions. Periodontal disease, craniofacial bone defects, salivary gland dysfunction or oral malignancies represent examples where controlling symptoms or repairing structural damage does not necessarily address the biological drivers of disease. Gene therapy provides a paradigm shift by enabling direct modulation of disease-associated molecular pathways through gene replacement, gene silencing, genome editing, or immune regulation. Unlike conventional approaches that primarily treat the consequences of the disease, gene therapy has the potential to modify the biological mechanisms responsible for disease initiation and progression. Recent advances in AI and molecular therapeutics have created opportunities to redefine oral healthcare and dentistry [1]. Since COVID-19, development of gene-editing and RNA-based therapeutics has accelerated, including CRISR/Cas9-based strategies for rare diseases such as Hemophilia B and RNA therapeutics for common metabolic disorders such as hyperlipidemia—some of these approaches can produce sustained biological effects lasting months, thereby, improving disease outcome [2,3].

Gene therapy in dentistry

The success of nucleic acid-based therapeutics in medicine has accelerated interest in their application to oral healthcare. Among gene therapy strategies, RNA interference using small interfering RNA (siRNA) and gene addition/replacement approaches using viral vectors have demonstrated the most clinical advancement. Currently, siRNA therapeutics represent

one of the most successful non-viral gene therapy platforms, with multiple FDA-approved products targeting systemic diseases including patisiran, givosiran, lumisiran, inclisiran and vutrisiran, that demonstrate that transient but durable modulation of disease-related genes is clinically achievable, particularly when efficient delivery systems are available [4.5]. In contrast, CRISPR/Cas-based genome editing remains an emerging technology, with clinical applications expanding but still limited by challenges related to delivery, off-target effects and long-term safety considerations.

The oral cavity represents a particularly attractive target for gene therapy because of its accessibility, localized anatomy and ability to support site-specific delivery. Periodontal diseases are driven by chronic inflammation, immune dysregulation and tissue destruction, processes involving cytokines, inflammatory mediators and extracellular matrix degradation pathways. Conventional periodontal therapy can reduce bacterial burden and inflammation but cannot fully restore the molecular imbalance responsible for tissue destruction. Gene-based approaches targeting inflammatory pathways, osteogenic signaling, and tissue regeneration pathways may provide opportunities for more durable disease modification. For examples, delivery of osteogenic factors such as BMPs (bone morphogenetic proteins) has been investigated to enhance bone regeneration while nucleic acid-based approaches targeting inflammatory mediators such as interleukin pathways are being explored as potential strategies for controlling periodontal tissue damage as well as restoring salivary gland function after radiation injury [6,7].

Craniofacial regeneration represents another area where gene therapy may provide advantages over traditional treatment. Current approaches for alveolar bone loss and craniofacial defects rely heavily on grafting materials and regenerative scaffolds, which often have limitations related to supplies availability, integration, and predictable outcomes. Gene-enhanced tissue engineering approaches using viral vectors, nanoparticles, or extracellular vesicle-based systems may allow localized expression of regenerative signals and improve tissue formation. For example, exosomes can serve as carriers of genes and stem-cell mediated gene therapy can become useful to create exosomes to deliver CRISP/Cas9 to target cells that promote bone regeneration and healing[1,8,9]. Exosome-mediated delivery has gained considerable interest because of its biocompatibility and ability to transport functional RNA molecules, although challenges related to scalability, characterization and regulatory standardization remain[9].

Gene therapy in oral cancer

Oral cancer represents perhaps one of the most compelling applications for gene therapy because conventional treatments such as surgery, radiation, and chemotherapy are often associated with functional impairment, recurrence risk, and limited efficacy in advanced disease. Head and neck squamous cell carcinoma (HNSCC) is the eighth most common cancer, approximating 431,000 deaths annually which includes many malignancies in the oral cavity [10]. Gene therapy approaches for oral cancer aim to overcome these limitations by directly targeting tumor biology.

For HSNCC, gene therapy strategies under investigation include restoration of tumor suppressor genes, inhibition of oncogenic pathways, delivery of therapeutic microRNAs and immune-based gene modulation. In phase I/II clinical trial in China, p53 gene was delivered via recombinant adenovirus 5 vector to restore the tumor suppressor functions in HNSCC and currently, combination trials are ongoing [11] (ClinicalTrials.gov Identifier: NCT00003257, NCT02842125, NCT03544723). Furthermore, in 2025, the phase I dose escalation study was successfully concluded targeting AQP1 (Aquaporin-1) gene of parotid glands using AAV2 vector for grade 2/3 radiation-induced xerostomia (severe chronic dry mouth due to salivary hypofunction) caused as a result of HNSCC radiation [12] (ClinicalTrials.gov Identifier: NCT02446249, NCT04043104). Currently, the study has advanced to its Phase II efficacy study [13] (ClinicalTrials.gov Identifier: NCT06544798). Additionally, microRNAs (miRNAs are endogenous RNAs present responsible for temporarily silencing genes) are particularly attractive in HNSCC because they regulate multiple genes involved in cancer development, invasion and metastasis. Circulating miRNAs signatures in saliva and blood are being explored as minimally invasive biomarkers for early detection and prognosis [14.15]. Beyond diagnostics, miRNA replacement or inhibition therapy has been tested in *in vitro* and *in vivo* models and it may provide therapeutic opportunities by restoring normal gene regulation in HNSCC [16].

Despite these advances, drug delivery remains the biggest barrier to clinical translation in addition to immune response, manufacturing scalability, long term safety and regulatory challenges [17]. The oral tissues present unique anatomical and biological constraints, including saliva, microbial exposure, enzymatic degradation and variable tissue penetration; however, these challenges also create opportunities for localized delivery approaches that may reduce systemic toxicity and improve therapeutic precision.

AI for patient stratification and target discovery

Oral cancer and periodontal diseases are highly heterogenous, so gene therapy is unlikely to be equally effective for every patient. Because of this variability, there is a growing need for precision-medicine approaches that can identify which patients are most likely to benefit from gene-based interventions.

AI is already being used for image-based diagnosis and decision support, and these existing data streams can be used to stratify patients for gene therapy. In parallel, AI can assist in

target discovery by analyzing large datasets to identify disease-relevant pathways in oral cancer, periodontitis and regenerative dentistry [18]. Together, these applications allow AI to classify patients who are most likely to benefit from local gene delivery or regenerative gene therapy [19]. Beyond stratification, AI can strengthen diagnosis by detecting oral lesions, unusual masses and caries. It can also support post-treatment monitoring through imaging-based assessment, prediction of treatment response, and evaluation of tissue retention and off-target effects [20]. In this way, AI can improve clinical decision-making and provide valuable feedback for both clinicians and the pharmaceutical industry.

As the landscape of pharmaceutics and medical care is rapidly evolving, it is crucial that ethical and legal frameworks related to the use of AI in patient care is standardized. Poor data quality, algorithm bias and difficulty of validating AI models in real-world dental settings can have detrimental impact in patient care without careful supervision and remain a key challenge to using AI [17].

CONCLUSIONS

The future of gene therapy in dentistry lies in integrated, personalized platforms that combine molecular profiling, AI-driven analytics, biomarker-guided treatment selection, and advanced delivery systems. By targeting the molecular mechanisms underlying inflammation, tissue degeneration, and malignancy, gene-based approaches have the potential to overcome limitations of conventional therapies. Given the accessibility and unique characteristics of oral tissues, dentistry is well positioned to transition from primarily reparative disciple towards a preventative and regenerative model of precision oral medicine by leveraging AI.

CONFLICT OF INTEREST: The authors declare no conflict of interest.

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