Rovedar

JLAR

Journal of Lab Animal Research. 2025; 4(6): 67-77.

DOI: 10.58803/jlar.v4i6.91

http://jlar.rovedar.com/

ReviewArticle

CRISPR-Based Genome Editing in Oral and Maxillofacial Medicine: Bridging *in Vitro* and Animal Models to Clinical Translation

Farshad Shahkhah[1], Mehran Bahmani[2], Diana Abbasi[3], Faezeh Sadat Moazzeni[4], Amin Shahinzadeh[5], Fatemeh Keikha[6]*, and Marziyeh Saki[7]

[1] Department of Clinical Pathology, Faculty of Veterinary Medicine, Shahid Chamran University, Ahvaz, Iran
[2] Department of Basic Sciences, Faculty of Nursing and Midwifery, Kurdistan University of Medical Sciences, Sanandaj, Iran
[3] Doctor of Veterinary Medicine Student, Department of Clinical Sciences, Faculty of Veterinary Medicine, Tehran University, Tehran, Iran
[4] Doctor of Veterinary Medicine, Department of Clinical Sciences, Faculty of Veterinary Medicine, Shoushtar Branch, Islamic Azad University, Shoushtar, Iran
[5] Doctorate of Veterinary Medicine Student, Department of Clinical Sciences, Faculty of Veterinary Medicine, Shoushtar Branch, Islamic Azad University, Shoushtar, Iran
[6] Cellular and Molecular Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran
[7] Doctor of Veterinary Medicine, Shoushtar Branch, Islamic Azad University, Shoushtar, Iran

*** *Corresponding author:*** Fatemeh Keikha, Cellular and Molecular Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran. Email: keikha.fatemeh156@gmail.com

ARTICLE INFO

Article History:
Received: 02/11/2025
Revised: 29/11/2025
Accepted: 14/12/2025
Published: 30/12/2025

Keywords:
Animal model
CRISPR/Cas9
Gene editing
Oral disease
Maxillofacial medicine

ABSTRACT

The emergence of clustered regularly interspaced short palindromic repeats (CRISPR)/Cas genome-editing technology represents fundamental changes with significant implications for oral and maxillofacial medicine. The present study aimed to synthesize current evidence from fundamental *in vitro* studies, engineered animal models, and emerging clinical trials to critically evaluate the potential applications and challenges of this biotechnology. The current review explored the transformative effects of CRISPR-Cas9 in key issues, including developing animal models for oral cancer and hereditary syndromes, *ex vivo* cell engineering for immunotherapies such as Chimeric antigen receptor (CAR) T-cell (CAR-T cells) for head and neck cancers, regenerative strategies using CRISPR-enhanced induced pluripotent stem cells (iPSCs) for salivary gland and enamel repair, and rapid diagnostic platforms for oral pathogens. Although preclinical data from murine models and organoid systems offered considerable potential for target validation and mechanistic understanding, their adoption in clinical settings is constrained by significant limitations. These limitations included the lack of tissue-specific delivery vectors, including standard lipid nanoparticles or viral vectors, unresolved off-target effects, long-term safety concerns, and complex ethical and regulatory challenges. The most immediate clinical impact was anticipated in two key areas, including CRISPR-based diagnostic tools such as the SHERLOCK platform, used for identifying SARS-CoV-2 variants or drug-resistant tuberculosis, and *ex vivo* cellular therapies being tested in controlled trials for specific diseases. The current findings indicated that integrating CRISPR into personalized oral healthcare required coordinated efforts to overcome translational barriers, conduct thorough clinical validation, and develop standardized safety and efficacy criterion specific to dental and maxillofacial outcomes.

1. Introduction

Recent advancements in genetic engineering have significantly transformed diagnostic and therapeutic methods for a wide range of disorders, including oral and maxillofacial disorders in particular[1]. The circumstances affecting the oral and maxillofacial area pose a significant threat to public health worldwide. More than 3.5 billion people worldwide are affected by oral disorders, including untreated dental caries, severe periodontitis, and total tooth

Cite this paper as: Shahkhah F, Bahmani M, Abbasi D, Sadat Moazzeni F, Shahinzadeh A, Keikha F, and Saki M. CRISPR-Based Genome Editing in Oral and Maxillofacial Medicine: Bridging *in Vitro* and Animal Models to Clinical Translation. Journal of Lab Animal Research. 2025; 4(6): 67-77. DOI: 10.58803/jlar.v4i6.91

loss, which negatively affect the functioning of the orofacial region and patients' well-being[2]. Furthermore, the oral disorders are associated with an increased risk of systemic disease, underscoring the need to develop tailored treatment options[3]. The introduction of clustered regularly interspaced short palindromic repeats (CRISPR) technology, a highly selective and cost-effective gene-editing platform, stands out as a revolutionary innovation with significant promise for advancing medical practice[4-6].

CRISPR/Cas systems enable the correction of disease-associated genetic variations, the downregulation of harmful gene expression, and the refinement of diagnostic techniques[7], all made possible by their fundamental ability to perform precise genomic modifications. Thus, CRISPR/Cas systems have sparked significant interest across a variety of medical subspecialties, including oral pathology, maxillofacial surgery, and oral medicine[8]. A wide range of diseases is now being investigated for their potential translational applications. These ailments include hereditary craniofacial abnormalities, oral cancers, autoimmune pathologies, and microbial infections. Several of these conditions have been treated in the past with limited long-term success[9].

CRISPR technology's main advantage is the Cas9 endonuclease, guided by RNA, can precisely induce targeted DNA double-strand breaks[10]. These targeted breaks are then repaired by cellular mechanisms, such as homology-directed repair or non-homologous end joining[11,12]. This mechanism can result in precise gene correction or inactivation. However, some issues persist, including the possibility of off-target genomic modifications, accidental insertions or deletions, and inconsistent DNA repair fidelity[11]. Currently, these technological challenges, compounded by ongoing ethical arguments and regulatory concerns, are the primary impediments to the broad clinical use of the technology. In oral and maxillofacial medicine, the development of novel, patient-specific treatment methods remains a primary priority.

Beyond the direct therapeutic potential of CRISPR, it is a powerful tool for creating sophisticated animal models of oral cancer[13]. It is feasible to develop precise genetically engineered mouse models (GEMMs) that completely reproduce human disease-causing mutations by employing targeted knock-in or knock-out of specific genes, such as *TP53*, *NOTCH1*, and *CDKN2A*[14]. These models may be generated using targeted knock-in or knock-out techniques. Compared to the conventional xenograft systems, these CRISPR-engineered models provided improved preclinical insights by more accurately reproducing the native tumor microenvironment, natural carcinogenesis, and treatment response[15-18]. The aim of the current study was to critically examine the therapeutic and diagnostic potential of CRISPR/Cas for diverse oro-facial disorders by integrating basic findings and animal models, while also addressing the key translational challenges to its clinical application.

2. Fundamentals of Gene Editing in Medicine and Biomedical Studies

The CRISPR/Cas9 system has become the dominant technology in genome engineering due to its remarkable effectiveness, versatility, and relative simplicity[5]. There are several important benefits of CRISPR/Cas9 compared to the older gene-editing systems, such as zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs)[19]. One of these advantages is precisely targeting genomic regions with a single guide RNA molecule[19,20]. Additionally, the complexity of the process is decreased, which is another advantage[20]. The CRISPR/Cas9 system, originally discovered in *Streptococcus pyogenes*, has been primarily utilized in translational and clinical applications[21]. The CRISPR-Cas9 system operates through a guide RNA (gRNA), which directs the Cas9 endonuclease to a genomic region complementary to the target sequence, thereby generating a site-specific double-strand break[21,22]. This is accomplished by guiding the Cas9 system to the target area. The two main mechanisms responsible for repairing the lesions are error-prone non-homologous end joining (NHEJ), which often results in insertions or deletions, and high-fidelity homology-directed repair (HDR), which allows effective genetic correction when a donor DNA template is available[23-25].

CRISPR systems are categorized into six primary types (I–VI), characterized by unique structural and functional properties[26]. Among these, the Type II Cas9 enzyme remains the predominant tool in biomedical studies, mainly because of its flexible operations and steady activity pattern (Figure 1).

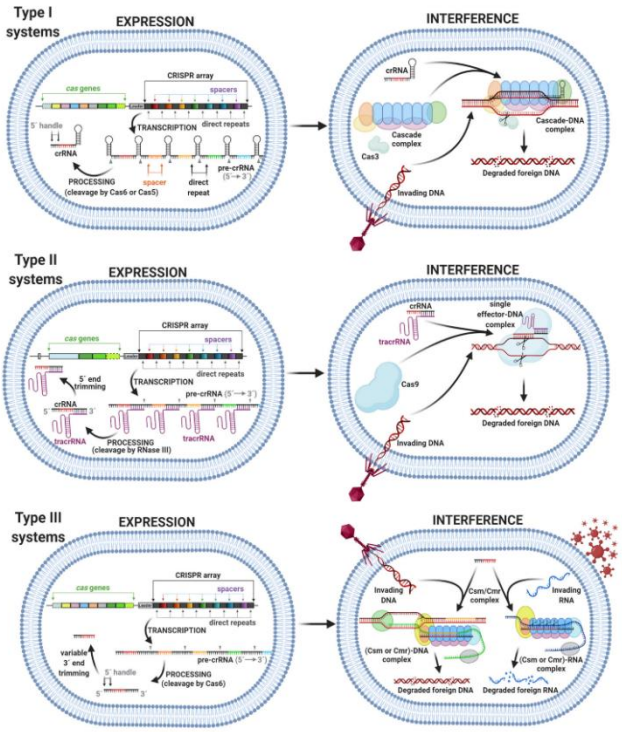
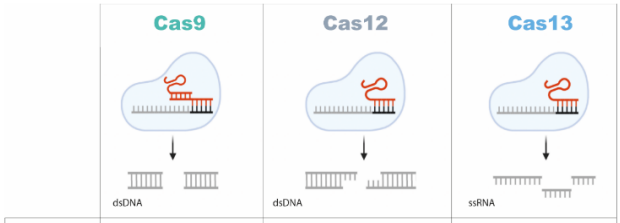


Figure 1. CRISPR expression and interference steps in type I, type II, and type III systems (Source: MDPI Copyright, 2021)[27].

Concurrently, alternative Cas effector proteins, including Cas12 (Type V) and Cas13 (Type VI), are gaining significant attention for their specialized applications in DNA and RNA modification, respectively[28-30] (Figure 2).



	Cas9	Cas12	Cas13
Target	DNA	DNA	RNA
Protospacer restrictions	PAM	PAM	PFS
Cut	Blunt-ended DSB	Sticky-ended DSB	Degraded RNA
Spacer size	16-20 nt	16-25 nt	25-35 nt
Characteristics	No collateral cleavage No secondary structure restrictions	Collateral cleavage No secondary structure restrictions	Collateral cleavage Secondary structure restrictions
Use	Gene editing Nucleic acid detection	Gene editing Nucleic acid detection	RNA knockdown Nucleic acid detection

Figure 2. Comparison of the properties of CRISPR/Cas9, /Cas12, and/Cas13 systems. PAM: Protospacer adjacent motif, PFS: Protospacer flanking site, DSB: Double-strand break (Source: MDPI Copyright, 2022)[27].

Due to the intricate nature of enzyme-specific mechanistic details, such as the functions of the *HNH* and *RuvC* nuclease domains[31], a simplified schematic overview of the CRISPR/Cas9 mechanism and its key domain activities was provided in Figure 3, with complementary details summarized in Table 1.

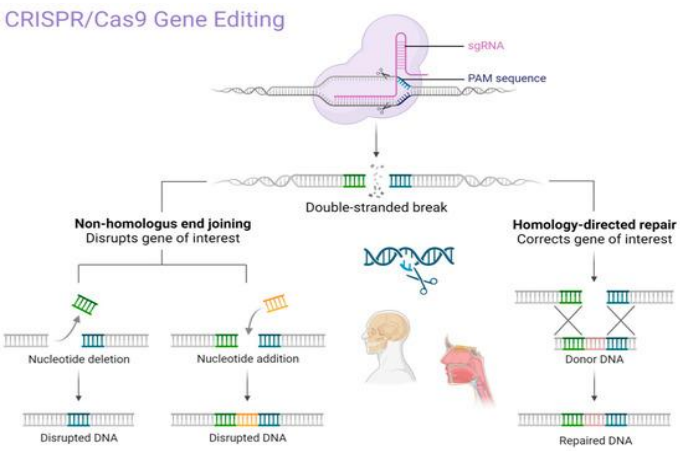


Figure 3. Schematic overview of the CRISPR/Cas9 mechanism gene editing technology (Source: MDPI Copyright, 2025)[32].

Table 1. Essential elements of therapeutic CRISPR-Cas9 editing

Component / Mechanism	Core function	Relevance in clinical and translational applications
Single-guide RNA (sgRNA)	Provides sequence specificity by guiding the Cas9 endonuclease to its complementary genomic target locus.	Governs the accuracy and specificity of the intervention, directly influencing target engagement and the risk of off-target effects.
Cas9 Endonuclease	Executes a double-strand break in the DNA duplex at the site specified by the sgRNA.	Serves as the molecular effector for genetic modifications, facilitating either disruptive (knock-out) or corrective (knock-in) editing.
Protospacer adjacent motif (PAM)	A short, conserved nucleotide sequence adjacent to the target site that is essential for Cas9 recognition and cleavage.	Defines the editable genomic space and is a critical parameter for gRNA design to minimize off-target activity.
Non-homologous end joining (NHEJ)	A dominant, error-prone cellular repair pathway for double-strand breaks, often resulting in small insertions or deletions (indels).	Exploited to disrupt gene function by frameshift mutations, applicable for silencing disease-causing alleles.
Homology-directed repair (HDR)	A high-fidelity repair pathway that uses an exogenous DNA template to edit the sequence at the break site precisely.	Enables precise gene correction or insertion, forming the basis for therapies aimed at rectifying specific pathogenic mutations.

3. Clinical Trials for CRISPR-Based Gene Editing Biological Therapies (GEBTs)

In clinical medicine, gene editing using CRISPR/Cas9 has the potential to be a substantial therapeutic tool for treating a wide range of diseases caused by genetic changes. Monogenic genetic illnesses, cancer immunotherapy, different inherited immunodeficiencies, and certain viral infections are also included in this category[33,34]. There is a growing number of clinical studies being conducted, and it is anticipated that the outcomes of these trials will guide the practical integration of therapeutics. A wide variety of diseases are being examined, including both systemic and hematological cancers. The cancers are often treated using cutting-edge methods, such as chimeric antigen receptor (CAR) T-cell therapy[35]. Diagnostic applications for diseases such as enterovirus and pulmonary TB, as well as tests for severe sepsis, are the primary focus of the ongoing clinical studies. Therapeutic gene editing was evaluated for sickle cell disease, HIV-1 infection via modified *CD34+* cells, HPV-related cervical intraepithelial neoplasia, transfusion-dependent thalassemia, renal cell carcinoma, nasopharyngeal carcinoma (with *PDL-1* knockout), advanced-stage solid tumors, Rett syndrome (and associated craniofacial manifestations), esophageal cancers, neurofibromatosis type 1 (which frequently presents with oral manifestations), Duchenne muscular dystrophy, retinal diseases, amyloidosis, and various metabolic, endocrine, and autoimmune disorders[35-44]. Table 2 provided a comprehensive compilation of present and projected clinical uses of CRISPR, with a particular focus on oral and maxillofacial medicine. Additionally, Table 2 outlined the roles that CRISPR plays in both the therapeutic and diagnostic domains.

Table 3 provided an overview of promising preclinical achievements in oral medicine. The results demonstrated effectiveness in a variety of domains, including the prevention of tumor development in mouse oral cancer models, the regeneration of enamel and bone tissue, and the targeted manipulation of the periodontal microbiota[36,38,40,45].

Table 2. Current and emerging CRISPR-Cas applications in oral and maxillofacial medicine

Condition/ Clinical domain	CRISPR-based therapeutic or diagnostic strategy	Current development stage	References
Oral squamous cell carcinoma (OSCC)	Disruption of oncogenes (e.g., *TP53*, *PD-1*) and development of engineered CAR-T cell immunotherapies	Advanced preclinical models and early-phase clinical trial initiatives	35
Heritable craniofacial disorders such as Amelogenesis/Dentinogenesis Imperfecta)	Precise gene correction strategies using CRISPR-Cas9 in patient-derived iPSCs and animal models	Proof-of-concept established in preclinical models	36,37
Chronic periodontitis	Targeting host inflammatory pathways and disrupting pathogenic biofilm formation	Exploratory stage, primarily in *in vitro* and animal model systems	38,39
Salivary Gland dysfunction and regeneration	Generation of patient-specific organoids and guided differentiation of iPSCs for tissue repair	Active preclinical investigation in disease modeling and regenerative approaches	40,41
Persistent oral viral infections such as HPV, HIV	Direct cleavage of integrated viral genomes and engineering of virus-resistant cells	Ongoing preclinical development with translational trials in planning phases	42,43
Rapid pathogen Detection (SARS-CoV-2, EBV in oral samples)	Deployment of CRISPR-based diagnostics such as SHERLOCK, DETECTR for point-of-care testing	Technology prototypes validated; clinical evaluation for regulatory approval in progress	44

Table 3. Preclinical CRISPR models: therapeutic outcomes and associated challenges

Experimental model / System	CRISPR Target	Primary Biological Outcome	References
Murine Oral Cancer Xenografts and GEMMs	Tumor-related genes (*TP53*, *CD44*, *HuR*, *PD-1*)	Significant tumor growth inhibition and increased sensitivity to conventional chemotherapy	45
Induced Pluripotent Stem Cell (iPSC)-Derived Ameloblast Lineages	Enamel matrix genes (*AMELX*, *ENAM*, *FAM83H*)	successful differentiation into ameloblast-like cells and partial biomimetic enamel matrix deposition	36
Salivary Gland Organoid Co-Culture Systems	Pluripotency and differentiation regulators (*SOX2*, *NANOG*, *AQP5*)	Enhanced epithelial cell proliferation and functional maturation in engineered salivary gland tissue	40
Periodontal Pathogen Model (*Porphyromonas gingivalis*)	Bacterial virulence factor (*cas3*)	Attenuation of pathogenicity, leading to reduced biofilm formation and host inflammatory response	38
Craniofacial Bone Defect Models (Mouse)	Osteogenic signaling pathways (*BMP*, *RUNX2*)	Accelerated bone mineralization and improved quality of new bone formation in critical-sized defects	45

4. Prospects for Gene-Editing Biotechnologies in Personalized Oral Medicine

In the field of oral medicine, the data available for the direct clinical use of CRISPR-Cas systems remains limited. The majority of available information consists of preliminary studies on diagnostics, disease screening, and therapeutic control[8,46,47]. When it comes to the management of viral infections, the treatment of head and neck malignancies, the control of periodontitis, and the facilitation of tissue regeneration, these early efforts are primarily focused on these areas. Although there is a vast theoretical space for the use of CRISPR-based gene-editing biological treatments (GEBTs) in this sector, the available evidence is inadequate to clearly forecast their precise future purposes or the timescale for their assimilation into routine clinical practice[48]. CRISPR technology, on the other hand, has the inherent capability for precise genomic intervention, suggesting that it could emerge as a viable therapeutic alternative for certain hereditary or autoimmune oral conditions[48].

In the field of oral and maxillofacial medicine, the potential applications of gene-editing biotechnologies encompass several promising pathways. For instance, the development of personalized screening protocols and gene-targeted therapies for head and neck cancers and immune-mediated pathologies, in particular hematologic malignancies such as lymphoma, leukemia, and multiple myeloma, as well as systemic conditions such as AIDS that manifest oral symptoms[49,50]. Additionally, CRISPR provided a platform for developing patient-specific therapeutics for cancers originating in the craniofacial complex, including new anticancer vaccines[51].

Another major possibility is the development of individualized treatments for genetic and developmental diseases that affect the structures of the craniofacial region[46]. In regenerative surgery, gene-edited xenotransplants have the potential to enhance biocompatibility and functional outcomes in complex reconstructions[52]. Furthermore, CRISPR/Cas9 has the potential to assist in converting somatic cells into induced pluripotent stem cells (iPSCs), which may then be used to create craniofacial tissue[5]. The use of CRISPR-based quick diagnostic platforms has the potential to improve the detection of oral infections. This techniqe can enable the accurate and timely identification of viral and bacterial agents responsible for infection[53].

5. Primary Head and Neck Cancers and Oral Manifestations of Systemic Malignancies

The development of therapeutic vaccinations is an example of a forward-looking use of CRISPR technology in oral oncology. CRISPR technology is particularly advantageous for treating cancers associated with human papillomavirus in the head and neck. The use of CRISPR technology is still in the early stages of investigation and lack substantial clinical validation, despite a solid conceptual base[54]. When used in a targeted manner, these vaccines have the potential to provide a refined therapeutic approach for certain oral neoplasms. Although current CRISPR-based gene editing biological treatments (GEBTs)

are largely used to treat hematopoietic diseases such as leukemia and multiple myeloma, their widespread implementation may help alleviate oral difficulties and reduce the unpleasant effects associated with traditional chemotherapy[54].

Focusing directly on the oncogenic drivers within head and neck tumors is currently being explored. CRISPR/Cas9 is a technology that can remove cancer stem cells defined by mutations in the *TP53* gene[55]. This technique gives a paradigm-shifting opportunity for gene therapy. As an additional application, the platform is being exploited to adjust the production of oncogenic microRNA and to overcome chemoresistance by altering genes such as *CD44*[56]. Furthermore, it has been established that decreasing urokinase plasminogen activator receptor (uPAR) levels using CRISPR can hinder tumor progression in model systems[35]. Most of the preclinical studies supported these methods, and several clinical studies are now underway to evaluate their therapeutic potential[35].

Additionally, CRISPR/Cas9 provided a synergistic technique that may enhance the effectiveness of traditional cancer therapies. The development of drug resistance is a significant challenge in the field of oncology[56]. This resistance is mediated by genes involved in drug efflux, DNA damage repair, apoptotic evasion, and pro-survival signaling. Targeting these resistance pathways with CRISPR has shown potential for re-sensitizing tumors to pharmacological treatments[57]. Thus, CRISPR/Cas9 cannot be overstated when it comes to head and neck squamous cell carcinoma (HNSCC), a rapidly progressing cancer that often results in adverse outcomes[13]. For instance, the RNA-binding protein *HuR*, encoded by *ELAVL1* and contributing to tumor growth and treatment resistance, has been successfully rendered inactive using CRISPR/Cas9. By coupling *HuR* deletion with the chemotherapeutic epirubicin, numerous cell death mechanisms, including apoptosis, necroptosis, and autophagy, were synergistically activated in SAS cell line models, resulting in increased cytotoxicity[45]. These results were supported by earlier studies demonstrating that the combination of nanoparticle-delivered, *HuR*-targeted CRISPR components with epirubicin improved therapeutic efficacy while preserving a high safety profile in mouse models[58-61] (Figure 4).

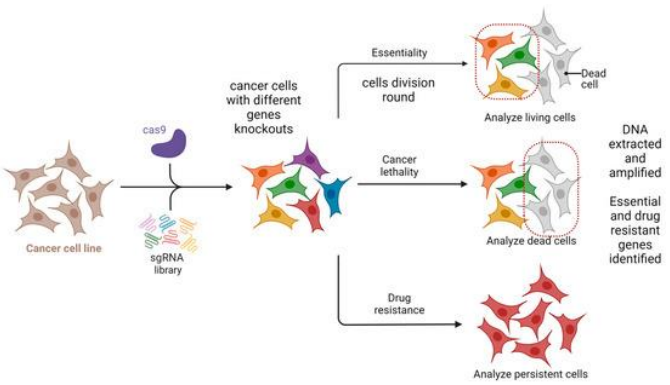


Figure 4. CRISPR-based screening for essentiality and drug resistance (Source: MDPI Copyright, 2025)[32].

6. CRISPR-Engineered Xenotransplantation for Oral and Maxillofacial Reconstruction

New advancements in gene-editing technologies, notably in translational models utilizing pigs and humans, have brought to light the promise of CRISPR-Cas systems in xenotransplantatio[62-65]. According to the findings of a preliminary study, certain genetic alterations can reduce the immunological barriers between species, thereby improving the biocompatibility of animal-derived tissues for human implantation[66-68]. The main concept of the preliminary studies was to use CRISPR to reduce essential xenogeneic immune reactions, thereby making it easier for transplant acceptance to occur despite considerable genetic differences. The reconstruction of craniofacial skeletal defects following trauma or tumor ablation, complex composite tissue flap transfers, salivary gland replacement, and the utilization of bioengineered xenogeneic bone matrices for alveolar or facial ridge augmentation are all examples of potential applications in maxillofacial surgery[67]. The development of technologies for elective and quality-of-life treatments in maxillofacial surgery is expected to progress slower. Thus, the majority of emphasis in the most recent studies in xenotransplantation has been on addressing significant organ shortages in situations that pose a threat to life.

7. CRISPR/Cas9 Applications in Organoid Models and Tissue Engineering for Oral Diseases

Excision by surgical means, prosthetic implantation, or autologous grafts are the primary methods that are used in the majority of modern therapeutic approaches for maxillofacial and oral diseases[69]. Often, these methods are insufficient to fully restore the body's natural beauty and physiological function. Organoid technology has thus emerged as a critical area in regenerative medicine, with particular emphasis on pluripotent stem cells and customized biomaterial scaffolds, in particular collagen-based biopolymers and poly(lactic-co-glycolic acid) hydrogels[70]. The formation of three-dimensional organoid structures is significantly influenced by external morphogenic stimuli that direct stem cell differentiation toward specific lineages[15,16]. CRISPR/Cas9 systems can precisely initiate this process by activating or suppressing critical genetic variations. This technique enables the orchestration of cellular differentiation and the formation of induced pluripotent stem cells[71-74]. Ono et al.[40] explored the potential of salivary gland cells to regenerate using iPSCs. When embryonic submandibular gland cells and mouse-induced pluripotent stem cells were co-cultured, a synergistic effect was observed, significantly enhancing mutual differentiation[75,76]. Morphological changes toward more complex structures resembling bone marrow were observed and served as proof, and they were compared with monoculture controls[76]. Furthermore, molecular studies indicated that more complex, bone marrow-like structures were associated with reduced expression of pluripotency genes. (*Sox2*, *c-Myc*, *Nanog*) and the overexpression of

differentiation markers (*Klf4*, *Aqp5*), thereby increasing the capacity of salivary gland cells to regenerate[75]. Induced pluripotent stem cells generated using CRISPR/Cas9 have the potential to significantly expand therapeutic options for salivary gland diseases, according to these results[72].

Moreover, a previous study by Arakaki et al.[77] indicated that iPSC co-culture for enamel regeneration was beneficial. Co-culturing mouse-iPSC with dental epithelial cells promoted differentiation into ameloblast-like cells, which are necessary for enamel matrix production[77]. It is important to note that the generated cells, although exhibiting a stromal-like shape, lacked the distinctive molecular markers of mature ameloblasts (such as amelogenin) and epithelial cells (such as *p63* and *cytokeratin 14*)[77]. Despite regenerated tissues having structural similarity to their native counterparts, molecular differences may persist. There is a lack of direct evidence on the use of CRISPR/Cas9 for the regeneration of maxillofacial tissue. Reprogramming somatic cells into patient-specific (iPSCs and correcting harmful mutations in hereditary oral disorders are only two examples of how this technique provided significant potential to advance regenerative medicine.

8. CRISPR/Cas as a Transformative Tool for Animal and Laboratory Modeling of Oral and Maxillofacial Diseases

The development of CRISPR/Cas genome-editing technology has profoundly transformed the modeling of oral and maxillofacial diseases, allowing for a level of genetic precision previously unattainable[8]. With CRISPR, it is now possible to construct intricate genetically modified animal models and sophisticated *in vitro* systems that reliably reproduce human disease genotypes and phenotypes[78,79]. CRISPR/Cas techniqe is particularly significant for a sector that comprises a wide variety of challenging conditions, including oral squamous cell carcinoma (OSCC), hereditary craniofacial syndromes, and autoimmune oral maladies[80].

The production of realistic genetically engineered mouse models, which are often referred to as GEMMs, is one of the most essential applications. Using CRISPR, produced knock-in and knock-out models that incorporate specific human-relevant mutations efficiently[81]. For instance, to explore the initiation, progression, and metastasis of ovarian squamous cell carcinoma within an immunocompetent native environment, it is feasible to construct mouse models with combinatorial mutations in key driver genes such as *TP53*, *NOTCH1*, and *CDKN2A*[82]. This approach provided the opportunity to investigate the progression of oral squamous cell carcinoma beyond the initial stage. By introducing orthologous mutations into the mouse genome, CRISPR plays a crucial role in modeling monogenic craniofacial defects, such as cleidocranial dysplasia[83]. Also, CRISPR-engineered models represented a major improvement over established xenografts. Unlike xenografts, which may form in immunocompromised hosts, GEMMs can drive carcinogenesis within an intact immune system and within genuine tissue stroma[84]. This contrasts with xenografts, which can develop in immunocompromised hosts. However, it is now feasible to conduct physiologically relevant investigations, such as studies on tumor-microenvironment interactions, angiogenesis, immune evasion, and spontaneous metastatic dissemination. As a result, therapeutic testing, in particular for immunotherapies, generates more predictive information and supports translational studies.

Furthermore, the CRISPR/Cas technology serves as the basis for the next generation of sophisticated laboratory models, which go beyond complete organisms. To conduct conclusive causal investigations of particular mutations on cellular behavior, drug resistance, and invasive potential, isogenic cell line pairs can be created that vary only in a single CRISPR-modified gene[85,86]. In addition, CRISPR is crucial for generating iPSCs from patients. Genetically modified induced pluripotent stem cells (iPSCs) have the potential to differentiate into sophisticated, three-dimensional organoids of oral tissues, such as dental epithelium or salivary glands[32]. Such disease-in-a-dish models are useful platforms for individualized drug screening and for dissecting the molecular cascades of genetic diseases in a human cellular setting[32]. CRISPR-based functional genomic screenings using comprehensive guide RNA libraries are now being implemented in oral cancer cell lines as a complementary approach to these established techniques[5]. In the process of methodically identifying genes that are important for cell survival, tumor development, or treatment response, new therapeutic targets and resistance mechanisms were identified. Consequently, the CRISPR/Cas technology is the foundation for contemporary experimental pathology in oral medicine. The acceleration of deconvolving disease processes and the development of targeted therapeutics is achieved by providing models that are resilient, precise, and physiologically appropriate. These models range from modified animals to human organoids grown from induced pluripotent stem cells. Additionally, the combination of CRISPR-based models with single-cell omics and advanced imaging is paving the way for a new era of personalized, predictive investigation in oral and maxillofacial health.

9. Conclusion

CRISPR-based treatments are not yet ready to be integrated into standard oral and maxillofacial care, because the evidence base remains fragmented and inconsistent. The primary clinical uses of CRISPR are expected to be in diagnostics based on CRISPR and in *ex vivo* cellular therapies, both implemented through strict, protocol-based methods frameworks. Conversely, *in vivo* therapeutic genome editing should remain under rigorous examination through clinical investigations. CRISPR/Cas technique requires standardizing safety evaluations for off-target effects, defining clinically relevant functional goals for oral-facial outcomes, and developing cost-efficient manufacturing processes to enable equitable access. Key limitations included a lack of targeted delivery mechanisms for oral tissues, a scarcity of evidence on long-term safety and efficacy, and the absence of preclinical models that

accurately capture the multidimensional nature of clinical diseases. The rapid deployment of healthcare solutions is further hampered by persistent ethical dilemmas, significant financial constraints, and continually evolving regulatory frameworks. Although CRISPR technology has potential applications in diagnostics, regenerative medicine, and oral cavity cancer, these areas remain largely exploratory and experimental for now. Three critical prerequisites must be met before considering integration into routine care including of generating robust clinical data, addressing the technique's core limitations, and conducting a realistic assessment of its practical viability.

Declarations

Competing interests

The authors declared that they have no competing interests.

Authors' contributions

All authors contributed to the study's conceptualization and methodology. Fatemeh Keikha conceived and designed the study, and Marziyeh Saki drafted the manuscript. Farshad Shahkhah, Mehran Bahmani, Diana Abbasi, Faezeh Sadat Moazzeni, and Amin Shahinzadeh performed data collection and revised the manuscript. All authors read and approved the final edition of the manuscript before publication in the present journal.

Ethical considerations

All the authors confirmed that ethical concerns, such as plagiarism, permission to publish, research misconduct, data fabrication or falsification, duplicate submissions, and redundant publication, have been thoroughly reviewed. No AI-assisted technologies were used in the generation of this manuscript.

Funding

No external funding was received for the present study.

Availability of data and materials

All datasets are available upon request from the corresponding author.

References

1. Kadir AS, Asaduzzaman M, Kundu J, Rahman MA, Rabbany MG, Shemanto MU, et al. Integrating genetic insights and artificial intelligence for enhanced oral and maxillofacial cancer care. Artificial intelligence (AI) in cell and genetic engineering. 2025. p. 107-124. DOI: 10.1007/978-1-0716-4690-8_7
2. World health organization (WHO). Global oral health status report: Towards universal health coverage for oral health by 2030. Executive summary. Geneva: World Health Organization; 2022. Available at: https://www.who.int/publications/i/item/9789240061484
3. Jin L, Lamster I, Greenspan J, Pitts N, Scully C, and Warnakulasuriya S. Global burden of oral diseases: Emerging concepts, management and interplay with systemic health. Oral Dis. 2016; 22(7): 609-619. DOI: 10.1111/odi.12428
4. Lahari S, Sneha Y, Sathwika C, Tharun M, and Rao TR. Innovations and implementations of clustered regularly interspaced short palindromic repeats in next-generation diagnostic tools: A review of current and emerging techniques. J Clin Sci. 2025; 22(1): 36-41. DOI: 10.4103/jcls.jcls_108_24
5. Lotfalizadeh N, Sadr S, Simab PA, Hajjafari A, Borji H, and Bayat Z. CRISPR/Cas9-mediated genome editing: In vivo review. J Lab Anim Res. 2022; 1(1): 47-51. DOI: 10.58803/jlar.v1i1.13
6. Sadr S, Simab PA, and Borji H. CRISPR-Cas9 as a potential cancer therapy agent: An update. Res Biotechnol Environ Sci. 2023; 2(1): 12-17. DOI: 10.58803/RBES.2023.2.1.02
7. Kim HS, Kweon J, and Kim Y. Recent advances in CRISPR-based functional genomics for the study of disease-associated genetic variants. Exp Mol Med. 2024; 56(4): 861-869. DOI: 10.1038/s12276-024-01212-3
8. Marimuthu A, Subramani RP, Deepika G, and Alagianambi AA. Gene therapy and CRISPR/Cas technology in dentistry: A review. Gene Ther. 2024; 12(1): 269553279. DOI: 10.5005/djas-11014-0033
9. Yu N, Yang J, Mishina Y, and Giannobile W. Genome editing: A new horizon for oral and craniofacial research. J Dent Res. 2019; 98(1): 36-45. DOI: 10.1177/0022034518805978
10. Doetschman T, and Georgieva T. Gene editing with CRISPR/Cas9 RNA-directed nuclease. Circ Res. 2017; 120(5): 876-894. DOI: 10.1161/CIRCRESAHA.116.309727
11. Doudna JA, and Charpentier E. The new frontier of genome engineering with CRISPR-Cas9. Science. 2014; 346(6213): 1258096. DOI: 10.1126/science.1258096
12. Wang JY, and Doudna JA. CRISPR technology: A decade of genome editing is only the beginning. Science. 2023; 379(6629): eadd8643. DOI: 10.1126/science.add8643
13. Chai AWY, Yee PS, Price S, Yee SM, Lee HM, Tiong VK, et al. Genome-wide CRISPR screens of oral squamous cell carcinoma reveal fitness genes in the Hippo pathway. Elife. 2020; 9: e57761. DOI: 10.7554/eLife.57761
14. Bahmani M. Nano-carrier-based delivery of CRISPR-Cas9 for oncolytic gene therapy: Insights from xenograft models. J Lab Anim Res. 2025; 4(2): 12-21. DOI: 10.58803/jlar.v4i2.66
15. Al-Kabani A, Huda B, Haddad J, Yousuf M, Bhurka F, Ajaz F, et al. Exploring experimental models of colorectal cancer: A critical appraisal from 2D cell systems to organoids, humanized mouse avatars, organ-on-chip, CRISPR engineering, and AI-driven platforms-challenges and opportunities for translational precision oncology. Cancers. 2025; 17(13): 2163. DOI: 10.3390/cancers17132163
16. Zhu Z, Shen J, Ho PCL, Hu Y, Ma Z, and Wang L. Transforming cancer treatment: Integrating patient-derived organoids and CRISPR screening for precision medicine. Front Pharmacol. 2025; 16: 1563198. DOI: 10.3389/fphar.2025.1563198
17. Chira S, Nutu A, Isacescu E, Bica C, Pop L, Ciocan C, et al. Genome editing approaches with CRISPR/Cas9 for cancer treatment: Critical appraisal of preclinical and clinical utility, challenges, and future research. Cells. 2022; 11(18): 2781. DOI: 10.3390/cells11182781
18. Feng X, Li Z, Liu Y, Chen D, and Zhou Z. CRISPR/Cas9 technology for advancements in cancer immunotherapy: From uncovering regulatory mechanisms to therapeutic applications. Exp Hematol Oncol. 2024; 13(1): 102. DOI: 10.1186/s40164-024-00570-y
19. Wani AK, Akhtar N, Singh R, Prakash A, Raza SHA, Cavalu S, et al. Genome centric engineering using ZFNs, TALENs and CRISPR-Cas9 systems for trait improvement and disease control in Animals. Vet Res Commun. 2023; 47(1): 1-16. DOI: 10.1007/s11259-022-09967-8
20. Shamshirgaran Y, Liu J, Sumer H, Verma PJ, and Taheri-Ghahfarokhi A. Tools for efficient genome editing; ZFN, TALEN, and CRISPR. Applications Genome Mod Edit. 2022. p. 29-46. DOI: 10.1007/978-1-0716-2301-5_2
21. Saffari Natanzi A, Poudineh M, Karimi E, Khaledi A, and Haddad Kashani H. Innovative approaches to combat antibiotic resistance: Integrating CRISPR/Cas9 and nanoparticles against biofilm-driven infections. BMC Med. 2025; 23(1): 486. DOI: 10.1186/s12916-025-04323-4
22. Marraffini LA. The CRISPR-Cas system of Streptococcus pyogenes: Function and applications. In: Ferretti JJ, Stevens DL, and Fischetti VA, editors. *Streptococcus pyogenes*: Basic biology to clinical manifestations. Oklahoma City: University of Oklahoma Health

Sciences Center; 2016. Available at: https://www.ncbi.nlm.nih.gov/books/NBK343995/
23. Haider S, and Mussolino C. Fine-tuning homology-directed repair (HDR) for precision genome editing: Current strategies and future directions. Int J Mol Sci. 2025; 26(9): 4067. DOI: 10.3390/ijms26094067
24. Yang H, Ren S, Yu S, Pan H, Li T, Ge S, et al. Methods favoring homology-directed repair choice in response to CRISPR/Cas9 induced-double strand breaks. Int J Mol Sci. 2020; 21(18): 6461. DOI: 10.3390/ijms21186461
25. Shams F, Bayat H, Mohammadian O, Mahboudi S, Vahidnezhad H, Soosanabadi M, et al. Advance trends in targeting homology-directed repair for accurate gene editing: An inclusive review of small molecules and modified CRISPR-Cas9 systems. Bioimpacts. 2022; 12(4): 371-391. DOI: 10.34172/bi.2022.23871
26. Makarova KS, and Koonin EV. Annotation and classification of CRISPR-Cas systems. CRISPR: Methods and protocols. 2015. p. 47-75. DOI: 10.1007/978-1-4939-2687-9_4
27. Nidhi S, Anand U, Oleksak P, Tripathi P, Lal JA, Thomas G, et al. Novel CRISPR-Cas Systems: An updated review of the current achievements, applications, and future research perspectives. Int J Mol Sci. 2021; 22(7): 3327. DOI: 10.3390/ijms22073327
28. Bharathkumar N, Sunil A, Meera P, Aksah S, Kannan M, Saravanan KM, et al. CRISPR/Cas-based modifications for therapeutic applications: A review. Mol Biotechnol. 2022; 64(4): 355-372. DOI: 10.1007/s12033-021-00422-8
29. Tong B, Dong H, Cui Y, Jiang P, Jin Z, and Zhang D. The versatile type V CRISPR effectors and their application prospects. Front Cell Dev Biol. 2021; 8: 622103. DOI: 10.3389/fcell.2020.622103
30. Hillary VE, and Ceasar SA. A review on the mechanism and applications of CRISPR/Cas9/Cas12/Cas13/Cas14 proteins utilized for genome engineering. Mol Biotechnol. 2023; 65(3): 311-325. DOI: 10.1007/s12033-022-00567-0
31. Babu K, Kathiresan V, Kumari P, Newsom S, Parameshwaran HP, Chen X, et al. Coordinated actions of Cas9 HNH and RuvC nuclease domains are regulated by the bridge helix and the target DNA sequence. Biochemistry. 2021; 60(49): 3783-3800. DOI: 10.1021/acs.biochem.1c00354
32. Dziedzic A, Kubina R, Skonieczna M, Madej M, Fiegler-Rudol J, Abid M, et al. CRISPR genome editing in personalized therapy for oral and maxillofacial diseases: A scoping review. Biomedicines. 2025; 13(11): 2745. DOI: 10.3390/biomedicines13112745
33. Wu SS, Li QC, Yin CQ, Xue W, and Song CQ. Advances in CRISPR/Cas-based gene therapy in human genetic diseases. Theranostics. 2020; 10(10): 4374-4382. DOI: 10.7150/thno.43360
34. Papasavva P, Kleanthous M, and Lederer CW. Rare opportunities: CRISPR/Cas-based therapy development for rare genetic diseases. Mol Diagn Ther. 2019; 23(2): 201-222. DOI: 10.1007/s40291-019-00392-3
35. Allemailem KS, Alsahli MA, Almatroudi A, Alrumaihi F, Alkhaleefah FK, Rahmani AH, et al. Current updates of CRISPR/Cas9-mediated genome editing and targeting within tumor cells: An innovative strategy of cancer management. Cancer Commun. 2022; 42(12): 1257-1287. DOI: 10.1002/cac2.12366
36. Eid A, and Mahfouz MM. Genome editing: The road of CRISPR/Cas9 from bench to clinic. Exp Mol Med. 2016; 48(10): e265. DOI: 10.1038/emm.2016.111
37. Kolanu ND. CRISPR-Cas9 gene editing: Curing genetic diseases by inherited epigenetic modifications. Glob Med Genet. 2024; 11(1): 113-122. DOI: 10.1055/s-0044-1785234
38. Cho S, Shin J, and Cho B-K. Applications of CRISPR/Cas system to bacterial metabolic engineering. Int J Mol Sci. 2018; 19(4): 1089. DOI: 10.3390/ijms19041089
39. Solbiati J, Duran-Pinedo A, Godoy Rocha F, Gibson III FC, and Frias-Lopez J. Virulence of the pathogen Porphyromonas gingivalis is controlled by the CRISPR-Cas protein Cas3. mSystems. 2020; 5(5): e00852-20. DOI: 10.1128/mSystems.00852-20
40. Ono H, Obana A, Usami Y, Sakai M, Nohara K, Egusa H, et al. Regenerating salivary glands in the microenvironment of induced pluripotent stem cells. Biomed Res Int. 2015; 293570. DOI: 10.1155/2015/293570
41. Yamano S, Inoue K, and Taguchi Y. Application of gene therapy to oral diseases. Pharmaceutics. 2025; 17(7): 859. DOI: 10.3390/pharmaceutics17070859
42. Mahas A, and Mahfouz M. Engineering virus resistance via CRISPR-Cas systems. Curr Opin Virol. 2018; 32: 1-8. DOI: 10.1016/j.coviro.2018.06.002
43. Tripathi S, Khatri P, Fatima Z, Pandey RP, and Hameed S. A landscape of CRISPR/Cas technique for emerging viral disease diagnostics and therapeutics: Progress and prospects. Pathogens. 2022; 12(1): 56. DOI: 10.3390/pathogens12010056
44. Son H. Harnessing CRISPR/Cas systems for DNA and RNA detection: Principles, techniques, and challenges. Biosensors. 2024; 14(10): 460. DOI: 10.3390/bios14100460
45. Zhang H, Qin C, An C, Zheng X, Wen S, Chen W, et al. Application of the CRISPR/Cas9-based gene editing technique in basic research, diagnosis, and therapy of cancer. Mol Cancer. 2021; 20(1): 126. DOI: 10.1186/s12943-021-01431-6
46. Barbour A, Glogauer J, Grinfeld L, Ostadsharif Memar R, Fine N, Tenenbaum H, et al. The role of CRISPR-Cas in advancing precision periodontics. J Periodontal Res. 2021; 56(3): 454-461. DOI: 10.1111/jre.12846
47. Padaru M, Shetty P, Kini A, and Bhat R. CRISPR/Cas-mediated targeted gene editing of *Streptococcus mutans*: A promising approach for precision dentistry for the prevention and management of caries. World Acad Sci J. 2025; 7(4): 61. DOI: 10.3892/wasj.2025.349
48. Niazi SK. The Dawn of *in vivo* gene editing era: A revolution in the making. Biologics. 2023; 3(4): 253-295. DOI: 10.3390/biologics3040014
49. Chavez-Granados PA, Manisekaran R, Acosta-Torres LS, and Garcia-Contreras R. CRISPR/Cas gene-editing technology and its advances in dentistry. Biochimie. 2022; 194: 96-107. DOI: 10.1016/j.biochi.2021.12.012
50. Niklander SE, and Hunter KD. A protocol to produce genetically edited primary oral keratinocytes using the CRISPR-Cas9 system. Oral biology: Molecular techniques and applications. New York, US: Springer; 2022. p. 217-229. DOI: 10.1007/978-1-0716-2780-8_14
51. Kedlaya MN, Puzhankara L, Prasad R, and Raj A. Periodontal disease pathogens, pathogenesis, and therapeutics: The CRISPR-Cas effect. CRISPR J. 2023; 6(2): 90-98. DOI: 10.1089/crispr.2022.0094
52. Gong T, Tang B, Zhou X, Zeng J, Lu M, Guo X, et al. Genome editing in Streptococcus mutans through self-targeting CRISPR arrays. Mol Oral Microbiol. 2018; 33(6): 440-449. DOI: 10.1111/omi.12247
53. Todor H, Silvis MR, Osadnik H, and Gross CA. Bacterial CRISPR screens for gene function. Curr Opin Microbiol. 2021; 59: 102-109. DOI: 10.1016/j.mib.2020.11.005
54. Hsu MN, Chang YH, Truong VA, Lai PL, Nguyen TKN, and Hu YC. CRISPR technologies for stem cell engineering and regenerative medicine. Biotechnol Adv. 2019; 37(8): 107447. DOI: 10.1016/j.biotechadv.2019.107447
55. Sowmya S, Augustine D, Mushtaq S, Baeshen HA, Ashi H, Hassan RN, et al. Revitalizing oral cancer research: CRISPR-Cas9 technology the promise of genetic editing. Front Oncol. 2024; 14: 1383062. DOI: 10.3389/fonc.2024.1383062
56. Liu Z, Shi M, Ren Y, Xu H, Weng S, Ning W, et al. Recent advances and applications of CRISPR-Cas9 in cancer immunotherapy. Mol Cancer. 2023; 22(1): 35. DOI: 10.1186/s12943-023-01738-6
57. Vaghari-Tabari M, Hassanpour P, Sadeghsoltani F, Malakoti F, Alemi F, Qujeq D, et al. CRISPR/Cas9 gene editing: A new approach for overcoming drug resistance in cancer. Cell Mol Biol Lett. 2022; 27(1): 49. DOI: 10.1186/s11658-022-00348-2
58. Amen RA, Hassan YM, Essmat RA, Ahmed RH, Azab MM, Shehata NR, et al. Harnessing the Microbiome: CRISPR-based gene editing and antimicrobial peptides in combating antibiotic resistance and cancer. Probiotics Antimicrob Proteins. 2025. DOI: 10.1007/s12602-025-10573-8
59. Kim HK, Cheong H, Kim MY, and Jin HE. Therapeutic targeting in ovarian cancer: Nano-enhanced CRISPR/Cas9 gene editing and drug combination therapy. Int J Nanomedicine. 2025; 20: 3907-3931. DOI: 10.2147/IJN.S507688
60. Wang CS, Chang CH, Tzeng TY, Lin AMY, and Lo YL. Gene-editing by CRISPR-Cas9 in combination with anthracycline therapy via tumor microenvironment-switchable, EGFR-targeted, and nucleus-directed nanoparticles for head and neck cancer suppression. Nanoscale Horiz. 2021; 6(9): 729-743. DOI: 10.1039/D1NH00254F
61. Hii ARK, Qi X, and Wu Z. Advanced strategies for CRISPR/Cas9 delivery and applications in gene editing, therapy, and cancer detection using nanoparticles and nanocarriers. J Mater Chem B. 2024; 12(6): 1467-1489. DOI: 10.1039/D3TB01850D

62. Nie D, Guo T, Yue M, Li W, Zong X, Zhu Y, et al. Research progress on nanoparticles-based CRISPR/Cas9 system for targeted therapy of tumors. Biomolecules. 2022; 12(9): 1239. DOI: 10.3390/biom12091239
63. Ryczek N, Hryhorowicz M, Zeyland J, Lipiński D, and Słomski R. CRISPR/Cas technology in pig-to-human xenotransplantation research. Int J Mol Sci. 2021; 22(6): 3196. DOI: 10.3390/ijms22063196
64. Hryhorowicz M, Lipiński D, Hryhorowicz S, Nowak-Terpiłowska A, Ryczek N, and Zeyland J. Application of genetically engineered pigs in biomedical research. Genes. 2020; 11(6): 670. DOI: 10.3390/genes11060670
65. Hryhorowicz M, Zeyland J, Słomski R, and Lipiński D. Genetically modified pigs as organ donors for xenotransplantation. Mol Biotechnol. 2017; 59(9): 435-444. DOI: 10.1007/s12033-017-0024-9
66. Sharma D, and Subramaniam KG. A remarkable journey of porcine to human xenotransplantation. Indian J Transplant. 2024; 18(2): 109-115. DOI: 10.4103/ijot.ijot_49_22
67. Niemann H, and Petersen B. The production of multi-transgenic pigs: Update and perspectives for xenotransplantation. Transgenic Res. 2016; 25(3): 361-374. DOI: 10.1007/s11248-016-9934-8
68. Stewart ZA. Xenotransplantation: The contribution of CRISPR/cas9 gene editing technology. Curr Transplant Rep. 2022; 9(4): 268-275. DOI: 10.1007/s40472-022-00380-3
69. Peterson L, Yacoub MH, Ayares D, Yamada K, Eisenson D, Griffith BP, et al. Physiological basis for xenotransplantation from genetically modified pigs to humans. Physiol Rev. 2024; 104(3): 1409-1459. DOI: 10.1152/physrev.00041.2023
70. Nicolae CL, Pîrvulescu DC, Niculescu AG, Epistatu D, Mihaiescu DE, Antohi AM, et al. An up-to-date review of materials science advances in bone grafting for oral and maxillofacial pathology. Materials. 2024; 17(19): 4782. DOI: 10.3390/ma17194782
71. Alfayez E. Current trends and innovations in oral and maxillofacial reconstruction. Med Sci Monit. 2025; 31: e947152. DOI: 10.12659/MSM.947152
72. Han JL, and Entcheva E. Gene modulation with CRISPR-based tools in human iPSC-cardiomyocytes. Stem Cell Rev Rep. 2023; 19(4): 886-905. DOI: 10.1007/s12015-023-10506-4
73. De Masi C, Spitalieri P, Murdocca M, Novelli G, and Sangiuolo F. Application of CRISPR/Cas9 to human-induced pluripotent stem cells: From gene editing to drug discovery. Hum Genomics. 2020; 14(1): 25. DOI: 10.1186/s40246-020-00276-2
74. Stojkovic M, Han D, Jeong M, Stojkovic P, and Stankovic KM. Human induced pluripotent stem cells and CRISPR/Cas-mediated targeted genome editing: Platforms to tackle sensorineural hearing loss. Stem Cells. 2021; 39(6): 673-696. DOI: 10.1002/stem.3353
75. Ben Jehuda R, Shemer Y, and Binah O. Genome editing in induced pluripotent stem cells using CRISPR/Cas9. Stem Cell Rev Rep. 2018; 14(3): 323-336. DOI: 10.1007/s12015-018-9811-3
76. Zhou H, Ye P, Xiong W, Duan X, Jing S, He Y, et al. Genome-scale CRISPR-Cas9 screening in stem cells: Theories, applications and challenges. Stem Cell Res Ther. 2024; 15(1): 218. DOI: 10.1186/s13287-024-03831-z
77. Zhang Y, Sastre D, and Wang F. CRISPR/Cas9 genome editing: A promising tool for therapeutic applications of induced pluripotent stem cells. Curr Stem Cell Res Ther. 2018; 13(4): 243-251. DOI: 10.2174/1574888X13666180214124800
78. Arakaki M, Ishikawa M, Nakamura T, Iwamoto T, Yamada A, Fukumoto E, et al. Role of epithelial-stem cell interactions during dental cell differentiation. J Biol Chem. 2012; 287(13): 10590-10601. DOI: 10.1074/jbc.M111.285874
79. Nasrallah A, Sulpice E, Kobaisi F, Gidrol X, and Rachidi W. CRISPR-Cas9 technology for the creation of biological avatars capable of modeling and treating pathologies: From Discovery to the latest improvements. Cells. 2022; 11(22): 3615. DOI: 10.3390/cells11223615
80. Ali F, Hameed A, Rehman A, Sarfraz S, Rajput NA, and Atiq M. CRISPR system discovery, history, and future perspective. OMICs-based techniques for global food security. 2024. p. 159-170. DOI: 10.1002/9781394209156.ch8
81. Elumalai P, and Ezhilarasan D. Emerging applications of CRISPR/Cas9 gene editing technology in reversing drug resistance in oral squamous cell carcinoma. Oral Oncol. 2022; 134: 106100. DOI: 10.1016/j.oraloncology.2022.106100
82. Lima A, and Maddalo D. SEMMs: Somatically engineered mouse models. A new tool for in vivo disease modeling for basic and translational research. Front Oncol. 2021; 11: 667189. DOI: 10.3389/fonc.2021.667189
83. Kordbacheh F, and Farah CS. Molecular pathways and druggable targets in head and neck squamous cell carcinoma. Cancers. 2021; 13(14): 3453. DOI: 10.3390/cancers13143453
84. Dragomirescu AO, Băluţa AM, Albu ŞD, Tănase M, Merişescu MM, Albu CC, et al. Genetic architectures and molecular interventions in craniofacial development: paving the way for advanced diagnostic and therapeutic frontiers. Rom J Oral Rehabil. 2025; 17(1): 149-161. DOI: 10.62610/RJOR.2025.1.17.16
85. Papapetrou EP. Patient-derived induced pluripotent stem cells in cancer research and precision oncology. Nat Med. 2016; 22(12): 1392-1401. DOI: 10.1038/nm.4238
86. Yadav N, Narang J, Chhillar AK, and Rana JS. CRISPR: A new paradigm of theranostics. Nanomedicine. 2021; 33: 102350. DOI: 10.1016/j.nano.2020.102350