Odovtos-International Journal of Dental Sciences (Odovtos-Int. J. Dent. Sc.), Online First, 2025. ISSN: 2215-3411
https://doi.org/10.15517/ijds.2025.662

ODOVTOS
International Journal of Dental Sciences

UNIVERSIDAD DE COSTA RICA
FOd Facultad de Odontología

https://revistas.ucr.ac.cr/index.php/Odontos

LITERATURE REVIEW:

Optogenetics Era in Oral and Maxillofacial Field

La era de la optogenética en el ámbito oral y maxilofacial

Nehad M. Abd-elmonsif[1] https://orcid.org/0000-0003-0576-5099
Sherif Gamal[2] https://orcid.org/0000-0002-5266-8403

[1]Department of Oral Biology, Faculty of Oral and Dental Medicine, Future University in Egypt, Cairo, Egypt.
[2]Research Labs Supervisor, Faculty of pharmacy, Future University in Egypt, Cairo, Egypt.

Correspondence to: Nehad M. Abd-elmonsif - nehad.mostafa@fue.edu.eg

Received: 14-V-2025 Accepted: 28-V-2025

ABSTRACT: Optogenetics is an interdisciplinary field that blends genomics and optical technology to regulate gene expression and biological processes. It offers advantages such as precise control over timing and placement, low invasiveness, and excellent efficiency. This procedure is enabled by photosensory proteins that have been genetically engineered to change form when exposed to light. As a result, optogenetic technologies provide important insights into a variety of biological mechanisms, ranging from subcellular and cellular processes to brain circuitry and behavioural patterns. This review will discuss the evolution of optogenetics and recent advances in its application in oral and maxillofacial studies. We will also look at how optogenetics has affected preclinical studies. While the scope of optogenetic techniques grows, obstacles remain in their application to oral and dental research.

KEYWORDS: Optogenetics; Genes; Oral; Maxillofacial.

RESUMEN: La optogenética es un campo interdisciplinario que integra la genómica y la tecnología óptica para regular la expresión génica y diversos procesos biológicos. Esta técnica ofrece ventajas como el control preciso del momento y la localización de la activación, baja invasividad y una elevada eficiencia. El procedimiento se basa en proteínas fotosensibles que han sido modificadas genéticamente para cambiar su conformación al ser expuestas a la luz. Como resultado, las tecnologías optogenéticas han permitido avances significativos en la comprensión de múltiples mecanismos biológicos, que abarcan desde procesos subcelulares y celulares hasta circuitos neuronales y patrones conductuales. Esta revisión aborda la evolución de la optogenética y los avances recientes en su aplicación en estudios del sistema

estomatognático, específicamente en el ámbito oral y maxilofacial. Asimismo, se analiza el impacto de esta tecnología en investigaciones preclínicas. Aunque el alcance de las técnicas optogenéticas continúa ampliándose, persisten desafíos importantes para su implementación en el campo de la investigación odontológica y oral.

PALABRAS CLAVE: Optogenética; Genes; Cavidad oral; Maxilofacial.

INTRODUCTION

A rapidly developing field called optogenetics incorporates genetics and optical technologies to regulate and stimulate cells in biological tissues, animal peripheral nerves, and other physiological processes (1).

This technique has numerous major benefits, including remarkable timing precision, spatial accuracy, and the capacity to target specific locations with minimal invasiveness, all achieved by light-based stimulation (2). These features make optogenetics a viable tool for studying oral behaviours and bacterial activities. Optogenetic approaches recently gained popularity in both basic scientific research (3-5) and preliminary clinical trials (6, 7).

MAIN TEXT

HISTORY OF OPTOGENETICS

The discovery of opsins and the bacterial rhodopsin proteins (BR) they encode marked the beginning of optogenetics, and the technology depends on the sufficiency and specificity of opsin expression.Oesterhelt and Stoeckenius discovered BR, a purple-red retinol-containing molecule present in bacterial cell membranes that serves as a photoreceptor (8). Halorhodopsin (eNpHR), a protein that regulates chloride ion transport, was identified by Matsuno and Macerata in 1977. A discovering of channelrhodopsin (ChR), a protein abundantly produced in nerve cells that influences their physiological activity, was a big step forward in optogenetic technology. Today, ChR is regarded as an important instrument for light-based neuronal regulation (9).

When exposed to light, bacterial opsins give extraordinary spatiotemporal precision, allowing accurate regulation of molecular processes in cells and organisms. Microbial opsins are now divided into four categories: sensory rhodopsins (such as histidine kinase rhodopsins), ion pumps (such as eNpHR), proton pumps (such as archaerhodopsin-3 (Arch)), and ion channels (such as ChR) (10).

OPTOGENETICS' FUNDAMENTALS

Irradiation with specific light wavelengths can alter the structure of photosensitive channel proteins found in cell wall membranes. The voltage across the cell membrane changes when photosensitive channel proteins become activated, either activating or inhibiting neurones (11). In some cases, it is better to suppress neural signalling rather than activate it. Light activates the NpHR, a chloride pump, causing neurones to hyperpolarise and suppress spikes in response to yellow light. Light-activated proton pumps, such as Arch, are employed to hyperpolariseneurones and inhibit signalling. Various wavelengths of light activate different photosensitive channels (Figure 1), Hence, the selection of light-dependent channels is the main technological distinction of optogenetics science (12).

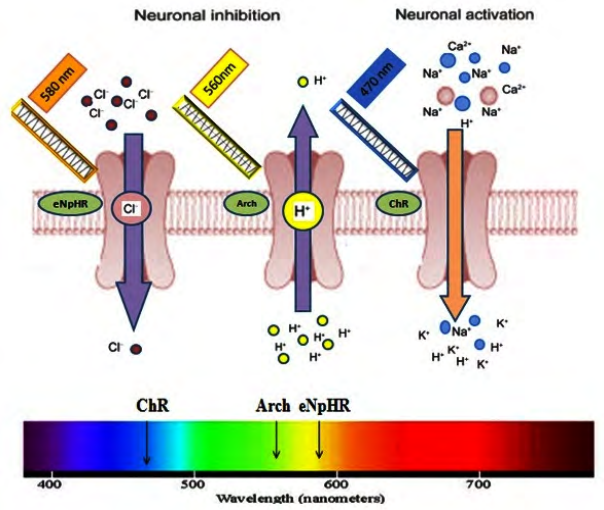

Figure 1. Various wavelengths of light activate different photosensitive channels.

AN OPTOGENETIC SWITCHING SYSTEM

Optogenetics is an innovative technique that allows for precise spatiotemporal modulation of gene expression to promote regeneration in specific cells. This is accomplished by light-induced transgenic expression approaches. One example of this system is a red/far-red light-controlled gene switch that has been tested *in vitro* with several mammalian cells. Subsequent *in vivo* tests with a chicken embryo model confirmed the ability to induce localised angiogenesis (13).

The "switch-on" optogenetic system: To regulate VEGF expression, the initial step is to transfect target cells, such as human umbilical vein endothelial cells (HUVECs). The cyanobacterium Spirulina's chromophore, phycocyanobilin B (PCB), isomerises when exposed to red light (around 660 nm). The intracellularly generated phytochromobilin (PhyB), which is associated with this chromophore, operates along with a split transcription factor consisting of the U1 and U2 subunits. The isomerisation of PhyB causes a conformational shift that activates the transcription factor.

This functioning PhyB-U1-U2 complex attaches to a specific operator region (CR) on the DNA strand via a distinct element (DE). The complex's attachment to the CR activates RNA polymerase II, which then initiates the gene of interest's (GOI) transcription among a response vector (RV). Genes such as human vascular endothelial growth factor (VEGF), which promotes angiogenesis and aids in wound healing, were used in these investigations. This optogenetic approach is appropriate for oral applications because VEGF in saliva has been demonstrated to promote healing following tooth extraction (13).

The "switch-off" system: When subjected to far-red light with wavelength740 nm, the PhyB-U1-U2 complex disintegrates, inhibiting GOI production in the RV (14). Initially, tissue targets were designed using optogenetic technology in a chicken chorio-allantoic membrane (CAM) experiment. In this study, Chinese hamster ovary cells (CHO-K1, ATCC CCL 61) were transfected with a red light-controlled system that uses human VEGF to trigger growth. The cells were then mixed with a PEG-based hydrogel and attached to the CAM. When exposed to 660-nm red light, chicken embryo CAMs exhibited considerably higher levels of VEGF-mediated angiogenesis than the control group, which remained in the off state (14).

An eye-catching feature of this technique is the capacity to control gene expression spatiotemporally utilising an optogenetic switch, which allows for the simultaneous regulation of numerous target genes within a single cell via on and off systems. This is accomplished by using various excitation wavelengths in a multichromatic method. Three optogenetic gene expression systems were applied to a single CHO-K1 cell in an initial demonstration study. The genes of interest (GOIs) were UVB-induced proangiogenic angiopoietin 1 (Ang1, 311 nm), red light-induced

production alkaline phosphatase (SEAP, 660 nm), which is required for forming of oral hard tissues like alveolar bone, and blue light-induced firefly luciferase (FLuc, 465 nm).Evidently, cells went through preconditioning in a UVB environment to reduce cytotoxicity (15).

RESEARCH ON OPTOGENETICS IN ORAL AND MAXILLOFACIAL FIELDS

In oral and craniofacial study evidence, light-sensitive channels have been successfully used to influence neurones, assisting in the investigation of the causes of various disorders and behaviours. Optogenetics has been applied to many regions in oral and maxillofacial studies throughout the pastdecade, including the following:

APPLYING OPTOGENETICS TO DIFFERENTIATE CELLS

Derived from migratory neural crest cells, human dental pulp stem cells (hDPSCs) are in fact ectoderm-derived mesenchymal stem cells capable of forming mineralised particles. Their capacity to differentiate has generated significant interest in therapy using stem cells and tissue engineering (17).

Recent study has demonstrated that hDPSCs have an immunophenotype comparable to bone marrow mesenchymal stem cells (BMSCs), making them interesting applicants for the development of human nerve cells (18).

Because hDPSCs are easily available and can be harvested from wisdomor third molars, their differentiation potential has generated significant interest. Optogenetics has been used to control neurogenic development in DPSCs. A previous investigation used a lentivirus encoding human ChR2 (hChR2) (H134R) to transfect hDPSCs, which were then exposed to blue light at 470 nm.Blue light activation of ChR2 caused depolarisation and morphological alterations in hDPSCs, converting the cell bodies from fusiform to neuron-like forms. Although what exactly happens is unknown, the results of this experiment indicate that differentiating hDPSCs could be a viable strategy for producing brain cells (4).

As a potential transplantation therapy for neurological disorders, this approach demands further investigation.

The transcription factor Lhx8, which is crucial for the growth and maturation of craniofacial components like bones and teeth, was examined by Huang and colleagues in a different study. A UV-inducible optogenetics device was used to inject Lhx8 into BMSCs. Lhx8 promotes cell proliferation, according to in vitro studies on hDPSCs, and its overexpression in hDPSCs reduced osteogenesis (19). UV-pulse-induced Lhx8 expression in BMSCs with polylactic-co-glycolic acid (PLGA) scaffolds dramatically improved bone production in vivo in a rat calvaria bone shortage model (20). These findings highlight the potential for optogenetic-driven restorative techniques in hard tissues, including the periodontium.

USING OPTOGENETICS TO CONTROL OROFACIAL MOVEMENT

Because of its precise regulatory capabilities, optogenetics has the potential to outperform traditional electrical stimulation methods for neurocontrol. Furthermore, Optogenetics are able to modify muscle cells to affect orofacial function.The facial nerve innervates most face muscles save the masticatory muscles and the levatorpalpebraesuperioris. In mice, facial neuropathy causes a decrease in whisker pad activity and movement. A recent study discovered that 24 hours after facial nerve transection, transgenic mice could produce significant denervation of the whisker pad muscles with optogenetic stimulation of the face nerves. Researchers used blue light

(460 nm, 8 mW) to depolarise facial neurones and directly excite muscle cells, therefore activating the optogenetic sensor ChR2.The sensitivity, amplitude, and speed of whisker pad muscle movements improved over time, and the muscles fatigued less after 48 hours of denervation (3). As a result, optogenetics is a more effective regulatory tool than traditional electrical stimulation for regulating cells and assisting muscle repair after nerve injury or motor neurone degeneration in many neuromuscular systems (21). Furthermore, optogenetics can generate orofacial movements by influencing neuronal activity in the brain. For this reason, red light has been studied since it can enter brain tissue more efficiently than blue light (21-22). In a study by Mercer Lindsay *et al*. (22), a novel ChR2 mutant, red-activatableChR (ReaChR), was utilised to investigate how activating neurones in the orofacial motor cortex influences movement. Given its ability to regulate orofacial motions, optogenetics has great promise for healing orofacial strained muscles and facial muscular paralysis.

CONTROLLING EATING AND DRINKING WITH OPTOGENETICS

Optogenetics has the benefit of directly manipulating certain parts of the brain, allowing researchers to isolate and study characteristics such as eating and drinking habits more precisely. The anterior peri-locus coeruleus regulates thirst and eating patterns, with glutamatergic neurones in this region acting as important convergence points for hunger and thirst signals. A subpopulation of excitatory neurones that emit prodynorphin in the anterior peri-locus coeruleus is engaged in the neurological mechanism. A recent study reinforced this by exposing the opsin ChR2 to blue light, which activated glutamatergic neurones in the anterior peri-locus coeruleus and resulted in decreased food intake.On the contrary, using 532 nm light (7-14 mW) to activate the optogenetic inhibitory channel protein archaerhodopsin (Arch) enhanced the intake of food, demonstrating the difference between excitatory and inhibitory stimulation on eating behaviour (23). Furthermore, optogenetic techniques have been employed to stimulate nociceptin/orphanin FQ neurones, resulting in an increase in conductivity of K+ and outward voltages when exposed to blue light at 470 nm.Irradiation activated ChR2, resulting in hyperpolarisation and decreased neuronal activity, showing that activating the hypothalamic arcuate nucleus enhances eating behaviour. In contrast, activating the ventral tegmental region had the opposite effect, lowering food intake (24).

MANAGING LICKING USING OPTOGENETICS

Licking behaviours include the coordinated expansion of the jaw and tongue accomplish specific targets. These motions necessitate precise and consistent muscle coordination, which somewhat is regulated by brainstem nuclei. According to optogenetics studies, stimulating individual neurones in specific brain regions can impact licking behaviour. By activating the light-sensitive channel ChR2, Esmaeili *et al.* (5) discovered that stimulating neurones in the tongue-jaw motor cortex with 473 nm blue light (mean power 8-10 mW) improved early licking. Unlike studies that concentrate on cell activation, another study triggered inhibitory neurones expressing ChR2 to deactivate one side of the primary tongue-jaw motor cortex, which led to increased ipsilateral promote licking and decreased spout licking on the other side (25).

Researchers also used optogenetically activating the lateral superior colliculus and indirect striatal projection neurones to track changes in licking movement. They found that while the contralateral lateral superior colliculus was stimulated, the ipsilateral lateral superior colliculus was inhibited by selective stimulation of light-sensitive proteins.

This study could shed light on the mechanisms underlying ipsiversive licking and suggests the presence of thalamic competition (26).

MAXILLOFACIAL PRECLINICAL RESEARCHES

MAXILLOFACIAL CELLULITIS

Maxillofacial cellulitis is an extremely serious infection that affects the tissues of the perimandibular fascial area. It is among the most hazardous illnesses that affect the craniofacial area. It has the ability to expand to the submandibular, submental, and sublingual compartments at the same time, increasing the risk of respiratory tract compromise or systemic poisoning in extreme cases (27). Pseudomonas aeruginosa, a well-known gram-negative bacteria, is the leading cause of maxillofacial cellulitis (28). Because of their chemical diffusion properties, small molecule inducers that alter bacterial pathogenicity might occasionally have unintended consequences (29). In contrast, light provides a non-invasive, non-toxic option with excellent spatiotemporal precision (30).

The use of optogenetics to control P. aeruginosa virulence has opened up new avenues for treating maxillofacial cellulitis (6). Cyclic adenosine monophosphate (cAMP) is a key secondary messenger in P. aeruginosa, regulating activities like carbon metabolism, type IV pili formation, and virulence (31). A bacterial photoactivatedadenylate cyclase (bPAC) gene was introduced into the bacteria in response to this knowledge. Light can alter intracellular cAMP levels by activating bPAC, which transforms adenosine triphosphate (ATP) into cAMP when exposed to blue light at 470 nm.After optogenetic stimulation of bPAC, cAMP levels surged by 6.6 times before reverting to baseline when the light was removed. This reversible alteration indicated that blue light can modulate bacterial motility and cytotoxicity (6).

Beyond that, targeting the Gac/Rsm pathway in *P. aeruginosa* improved treatment efficacy. GacS, a protein involved in the Gac/Rsmsignalling cascade, controls virulence factors. By introducing the YGS24 light-dependent fusion protein into *P. aeruginosa*, optogenetic techniques were used to recombine GacS and control the Gac/Rsm cascade. Using 470 nm blue light at 120 μW/cm², these light-dependent proteins can impact bacterial virulence, opening up new therapeutic prospects (30).

TRIGEMINAL NEURALGIA

Trigeminal neuralgia is a prevalent source of severe pain in the facial regions, and while there are several therapies available, they rarely provide long-term relief. A long-term treatment for atypical trigeminal neuralgia is currently lacking (32). One of the most difficult hurdles in creating new medicines is identifying the exact brain regions involved in the ailment, which is required to select prospective therapeutic targets. Recent research have combined optogenetics and behavioural measurements to investigate the brain areas important for regulating behaviour after trigeminal neuralgia (33). These strategies allow for the stimulation or reduction of trigeminal neuralgia by altering neurones in the pain transportation system. The "Ignition Theory" proposes that trigeminal neuralgia is caused by anomalies in the afferent neurones of the trigeminal root or ganglion (34).

Using blue light optogenetic triggers to reach peripheral sensory neurones in the trigeminal and dorsal root ganglions had been shown to cause chronic face pain and trigeminal nerve injury (35). Calcitonin gene-related peptide (CGRP), a neuropeptide found in trigeminal neuralgia, is believed to play an important role in disease development [36]. Researchers discovered that activating eNpHR with 593 nm yellow light boosted GABAergic inhibition

and lowered CGRP synthesis, hence alleviating trigeminal neuralgia symptoms. However, activating ChR2 with 473 nm blue light produced hypersensitivity, as is typical of the disease (7).

Moreover, studies demonstrated that α-CGRP treatment helped reduce pain after optogenetic stimulation of M1 in a rat model, suggesting that central modulation mechanisms are not dependent on peripheral pain control (37). In addition to these findings, In order to treat trigeminal neuralgia, some researchers have employed blue light at 470 nm for achieving circuit-specific neuromodulation in the primary motor cortex layer V. This approach offers benefits such as fewer side effects, better treatment outcomes, and precise control, making the concept of an "optical scalpel" a promising option. An important advantage of optogenetics is that it does not require invasive procedures like craniotomy, making it a safer alternative for patients (38).

LIMITATIONS OF OPTOGENETICS

Despite its capabilities, optogenetics is still underutilised in preclinical research and clinical practice due to a number of difficulties. These hurdles include hazards connected with genetic transfection, difficulties in establishing cell-specific expression, and intrinsic limits in optogenetic techniques itself. One major obstacle that restricts the therapeutic potential of optogenetics is the difficulties of penetration of light in the deeper layers of tissue. To solve this, the creation of excitation light that can penetrate deeper into tissues is a viable answer. Recent improvements in red-shifted actuators have enabled the use of longer near-infrared (NIR) wavelengths for stimulation, creating new opportunities for research. NIR-responsive proteins may see more use in the future, particularly in the oral and craniofacial areas, due to their benefits over traditional NIR light.These include minimised scattered light, decreased tissue absorption, and reduced autofluorescence (39). Although optogenetics has not yet been used to cure disorders in oral and maxillofacial research, it has the potential to address issues such dry sockets, xerostomia, burning mouth syndrome, and taste loss caused by COVID-19 (40). In the future, optogenetic approaches may also be used to regenerate craniomaxillofacial and periodontal tissues.

CONCLUSIONS

Because of its particular capabilities, optogenetics can shed light on oral and craniofacial operations and pathologies. While there have been tremendous advances in optogenetics and related technologies over the last decade, more study is required before these methods may be routinely used in therapeutic settings. Scientists are working to increase the effectiveness and safety of optogenetic techniques so that they can be used to treat a variety of clinical problems. Opogenetics, a promising and rising discipline, holds significant potential for stimulating tissue regeneration in the oral cavity.

ABBREVIATIONS LIST

Arch: archaerhodopsin-3.
ATP: Adenosine triphosphate.
BMSCs: Bone marrow mesenchymal stem cells
bPAC: Bacterial photoactivatedadenylate cyclase.
BR: Bacteriorhodopsin.
CAM: Chorio-allantoic membrane.
cAMP: Cyclic adenosine monophosphate.
CGRP: Calcitonin gene-related peptide.
CHO-K10: Chinese hamster ovary cells.
ChR: Channel rhodopsin.
CR: Certain operator region.
DE: Distinct element.
eNpHR: Mediates halorhodopsin's.
GOI: Gene of interest.
hDPSCs: Human dental pulp stem cells.
HUVEC: Primary endothelial cells of human umbilical veins.
NIR: Near infrared.
PCB: The chromophore phycocyanobilin B.
PhyB: Phytochromobilin.
PLGA: Polylactic-co-glycolic acid.
ReaChR: Red-activatableChR.
RV: Response vector.
VEGF: Vascular endothelial growth factor.

AUTHOR CONTRIBUTION STATEMENT

Design of the work: N.M.A.
Conception of the review: S.G.
Interpretation of data, drafting the review: N.M.A. and S.G.
Reviewing it critically for important intellectual content: N.M.A.
Final approval of the version to be published and agreement to be accountable for all aspects of the review in ensuring that questions related to the accuracy or integrity of any part of the review are appropriately investigated and resolved: N.M.A. and S.G.

CONFLICT OF INTERES

The authors had no conflict of interest to declare.

FINANCIAL DISCLOSURE

The authors declared that they have received no financial support.

ACKNOWLEDGEMENT

Not applicable.

REFERENCES

1. Cao Y., Pan S.W., Yan M.Y., et al. (2021). Flexible and stretchable polymer optical fibers for chronic brain and vagus nerve optogenetic stimulations in free-behaving animals. BMC Biol, 19: 252. https://doi.org/10.1186/s12915-021-01187-x
2. Moreno Morales N., Patel M.T., Stewart C.J., et al. (2021). Optogenetic tools for control of public goods in Saccharomyces cerevisiae. mSphere, 6 (4): e0058121.https://doi.org/10.1128/mSphere.00581-21
3. Vajtay T.J., Bandi A., Upadhyay A., et al. (2019). Optogenetic and transcriptomic interrogation of enhanced muscle function in the paralyzed mouse whisker pad. J Neurophysiol, 121 (4): 1491-1500. https://doi.org/10.1152/jn.00837.2018
4. Niyazi M., Zibaii M.I., Chavoshinezhad S., et al. (2020). Neurogenic differentiation of human dental pulp stem cells by optogenetics stimulation. J ChemNeuroanat, 109:101821.https://doi.org/10.1016/j.jchemneu.2020.101821
5. Esmaeili V., Tamura K., Muscinelli S.P., et al. (2021). Rapid suppression and sustained activation of distinct cortical regions for a

delayed sensory-triggered motor response. Neuron, 109 (13): 2183-2201. https://doi.org/10.1016/j.neuron.2021.05.005

6. Xia A.G., Qian M.J., Wang C.C., et al. (2021). Optogenetic modification of Pseudomonas aeruginosa enables controllabletwitching motility and host infection. ACS Synth Biol, 10 (3): 531-541.https://doi.org/10.1021/acssynbio.0c00559
7. Kc E., Islam J., Kim S., et al.(2022). Pain relief in a trigeminal neuralgia model via optogenetic inhibition on trigeminal ganglion itself with flexible optic fiber cannula. Front Cell Neurosci, 16: 880369. https://doi.org/10.3389/fncel.2022.880369
8. Oesterhelt D., Stoeckenius W. (1971). Rhodopsin-like protein from the purple membrane of Halobacteriumhalobium. Nat New Biol, 233 (39): 149-152. https://doi.org/10.1038/newbio233149a0
9. Matsuno-Yagi A., Mukohata Y. (1977). Two possible roles of bacteriorhodopsin; a comparative study of strains of Halo-bacterium halobium differing in pigmentation. BiochemBiophys Res Commun, 78 (1): 237-243.669
10. Chowdhury S., Yamanaka A. (2021). Fiberlessoptogenetics. In: Yawo H., Kandori H., Koizumi A., et al. (Eds.), Optogenetics: Light-Sensing Proteins and Their Applications in Neuroscience and Beyond, 2nd Ed. Springer, Singapore, p.407-416. https://doi.org/10.1007/978-981-15-8763-4_26
11. Reshetnikov V.V., Smolskaya S.V., Feoktistova S.G., et al. (2022). Optogenetic approaches in biotechnology and biomaterials. TrendsBiotechnol, 40 (7): 858-874. https://doi.org/10.1016/j.tibtech.2021.12.007
12. Fenno L., Yizhar O., Deisseroth K. (2011). The development and application of optogenetics. Annu Rev Neurosci, 34: 389-412. https://doi.org/10.1146/annurev-neuro-061010-113817
13. Radović K., Brković B., Roganović J., Ilić J., MilićLemić A., Jovanović B. (2022). Salivary VEGF and post-extraction wound healing in type 2 diabetic immediate denture wearers. ActaOdontol. Scand. 2022; 80: 9-14. doi: 10.1080/00016357.2021.1930149
14. Müller K., Engesser R., Metzger S., Schulz S., Kämpf M.M., Busacker M., Steinberg T., Tomakidi P., Ehrbar M., Nagy F. (2013). A. red/far-red light-responsive bi-stable toggle switch to control gene expression in mammalian cells. Nucleic Acids Res. 41: e77. doi: 10.1093/nar/gkt002
15. Müller K., Engesser R., Schulz S., Steinberg T., Tomakidi P., Weber C.C., Ulm R., Timmer J., Zurbriggen M.D., Weber W. (2013). Multi-chromatic control of mammalian gene expression and signaling. Nucleic Acids Res. 41: e124. https://doi.org/10.1093/nar/gkt340
16. Falkner A.L., Wei D.Y., Song A., et al. (2020). Hierarchical representations of aggression in a hypothalamic-midbrain circuit. Neuron, 106 (4): 637-648.e6. https://doi.org/10.1016/j.neuron.2020.02.014
17. Aly L. A. (2015). Stem cells: Sources, and regenerative therapies in dental research and practice. World journal of stem cells, 7 (7), 1047-1053. https://doi.org/10.4252/wjsc.v7.i7.1047
18. Bar J.K., Lis-Nawara A., Grelewski P.G. (2021). Dental pulp stem cell-derived secretome and its regenerative potential. Int J MolSci, 22 (21): 12018. https://doi.org/10.3390/ijms222112018
19. Kim J.-Y., Choung P.-H. (2020). USP1 inhibitor ML323 enhances osteogenic potential of human dental pulp stem cells. Biochem. Biophys. Res.Commun. 2020; 530: 418-424. https://doi.org/10.1016/j.bbrc.2020.05.095
20. Huang D., Li R., Ren J., Luo H., Wang W., Zhou C. (2021). Temporal induction of Lhx8 by optogenetic control system for

efficient bone regeneration. Stem Cell Res. Ther. 2021;12:339. https://doi.org/10.1186/s13287-021-02412-8

21. Benevides E.S., Sunshine M.D., Rana S., et al. (2022). Optogenetic activation of the diaphragm. Sci Rep, 12: 6503. https://doi.org/10.1038/s41598-022-10240-w
22. Mercer Lindsay N., Knutsen P.M., Lozada A.F., et al. (2019). Orofacial movements involve parallel corticobulbar projections from motor cortex to trigeminal premotor nuclei.Neuron, 104 (4): 765-780.e3. https://doi.org/10.1016/j.neuron.2019.08.032
23. Gong R., Xu S.J., Hermundstad A., et al.(2020). Hindbrain doublenegative feedback mediates palatability-guided food and water consumption. Cell, 182 (6): 1589-1605.e22. https://doi.org/10.1016/j.cell.2020.07.031
24. Hernandez J., Perez L., Soto R., et al.(2021). Nociceptin/orphanin FQ neurons in the arcuate nucleus and ventral tegmental area act via nociceptin opioid peptide receptor signaling to inhibit proopiomelanocortin and A10 dopamine neurons and thereby modulate ingestion of palatable food. PhysiolBehav, 228: 113183. https://doi.org/10.1016/j.physbeh.2020.113183
25. Mayrhofer J.M., El-Boustani S., Foustoukos G., et al. (2019). Distinct contributions of whisker sensory cortex and tonguejaw motor cortex in a goal-directed sensorimotor transformation. Neuron, 103 (6): 1034-1043.e5. https://doi.org/10.1016/j.neuron.2019.07.008
26. Lee J., Sabatini B.L. (2021). Striatal indirect pathway mediates exploration via collicular competition. Nature, 599 (7886): 645-649. https://doi.org/10.1038/s41586-021-04055-4
27. Sugai T., Nishie W., 2020. Odontogenic facial cellulitis. BMJ Case Rep, 13 (12): e239381. https://doi.org/10.1136/bcr-2020-239381
28. AlBassri T.K., AlShaibi S., Khan F., et al. (2020). A rare case of cellulitis after tetanus toxoid (TT) vaccination. J FamilyMed Prim Care, 9 (3): 1762-1764. https://doi.org/10.4103/jfmpc.jfmpc_1194_19
29. Morreale F.E., Kleine S., Leodolter J., et al. (2022). BacPROTACs mediate targeted protein degradation in bacteria. Cell, 185 (13): 2338-2353. e18. https://doi.org/10.1016/j.cell.2022.05.009
30. Lindner F., Diepold A. (2022). Optogenetics in bacteria –applications and opportunities. FEMS Microbiol Rev, 46 (2):fuab055. https://doi.org/10.1093/femsre/fuab055
31. Berry A., Han K., Trouillon J., et al. (2018). cAMP and Vfrcontrolexolysin expression and cytotoxicity of Pseudomonasaeruginosa taxonomic outliers. J Bacteriol, 200 (12): e00135-18. https://doi.org/10.1128/JB.00135-18
32. Ma Y.P., Hsu G., Zhang F.G. (2020). The applicability and efficacy of magnetic resonance-guided high intensity focused ultrasound system in the treatment of primary trigeminal neuralgia. Med Hypotheses, 139:109688. https://doi.org/10.1016/j.mehy.2020.109688
33. Chen L.Q., Lv X.J., Guo Q.H., et al. (2023). Asymmetric activation of microglia in the hippocampus drives anxiodepressive consequences of trigeminal neuralgia in rodents. BrJPharmacol, 180 (8): 1090-1113. https://doi.org/10.1111/bph.15994
34. Liu M.X., Li Y., Zhong J., et al. (2021). The effect of IL-6/Piezo2 on the trigeminal neuro-

pathic pain. Aging, 13 (10): 13615-13625. https://doi.org/10.18632/aging.202887

35. Hardt S., Fischer C., Vogel A., et al. (2019). Distal infraorbital nerve injury: a model for persistent facial pain in mice. PAIN, 160 (6): 1431-1447. https://doi.org/10.1097/j.pain.0000000000001518
36. Berger A.A., Winnick A., Carroll A.H., et al. (2022). Rimegepant for the treatment of migraine. Health Psychol Res, 10 (5): 38534. https://doi.org/10.52965/001c.38534
37. Islam J., Kc E., Kim S., et al. (2021). Stimulating GABAergic neurons in the nucleus accumbens core alters the trigeminal neuropathic pain responses in a rat model of infraorbital nerve injury. Int J MolSci, 22 (16): 8421. https://doi.org/10.3390/ijms22168421
38. Islam J., Kc E., Oh B.H., et al. (2020). Optogenetic stimulation of the motor cortex alleviates neuropathic pain in rats of infraorbital nerve injury with/without CGRP knockdown. J Headache Pain, 21:106. https://doi.org/10.1186/s10194-020-01174-7
39. Ntziachristos V. (2010). Going deeper than microscopy: the optical imaging frontier in biology. Nat Methods, 7 (8): 603-614. https://doi.org/10.1038/nmeth.1483
40. Abd-elmonsif N.M., Gamal S.(2023). Histological and molecular response of oral cavity tissues to Covid-19. MolBiol Rep 50, 7893-7899. https://doi.org/10.1007/s11033-023-08607-x