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Review

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Gene therapy: molecular foundations, therapeutic strategies, and emerging applications in dentistry and orthodontics

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ABSTRACT

Gene therapy has emerged as a transformative therapeutic strategy that addresses diseases at their genetic origin by replacing, repairing, silencing, or editing defective genes. Recent advances in gene-editing technologies, particularly CRISPR/Cas systems, together with improvements in viral and non-viral gene delivery platforms, have significantly enhanced the precision, safety, and clinical applicability of gene therapy. This review provides a comprehensive overview of the molecular foundations of gene therapy, including its historical evolution, classification, mechanisms of action, and gene delivery systems. Particular emphasis is placed on its emerging applications in dentistry and orthodontics, where gene therapy has demonstrated promising potential in periodontal and craniofacial regeneration, bone repair, salivary gland dysfunction, tooth regeneration, management of head and neck carcinomas, and modulation of orthodontic tooth movement through targeted regulation of the RANK-RANKL-OPG signalling pathway. The review also discusses the integration of gene therapy with tissue engineering and regenerative medicine to facilitate biologically driven and personalized treatment approaches. Current challenges, including delivery efficiency, safety concerns, immune responses, ethical considerations, and limited long-term clinical evidence, are critically evaluated. Despite these limitations, continued advances in vector technology, genome editing, and translational research are expected to accelerate the clinical implementation of gene therapy. Overall, gene therapy holds considerable promise for transforming future dental and orthodontic practice by enabling precision therapeutics, enhancing tissue regeneration, and improving long-term patient outcomes.

Keywords: Gene therapy, CRISPR/Cas9, viral vectors, non-viral vectors, regenerative dentistry, orthodontics

INTRODUCTION

All living organisms are composed of cells, the basic structural and functional units of life. Within the nucleus of each cell are chromosomes composed of deoxyribonucleic acid (DNA), the hereditary material that carries the genetic information required for normal growth, development, differentiation, and cellular function. Genes, the fundamental units of heredity, are specific DNA sequences that direct protein synthesis through transcription and translation, thereby regulating a wide range of biological processes. Alterations or mutations in these genes can disrupt normal cellular homeostasis, resulting in inherited or acquired disorders.[1-3]

Gene therapy has emerged as a transformative therapeutic strategy that addresses diseases at their genetic origin by replacing, repairing, silencing, or modifying defective genes rather than merely alleviating clinical symptoms.[1,4] Recent advances in gene-editing technologies, particularly the CRISPR/Cas system, together with improvements in viral and non-viral gene delivery platforms, have significantly enhanced the precision, efficiency, and safety of targeted genetic interventions, expanding their therapeutic potential across numerous medical specialties.[4-6]

Beyond systemic diseases, gene therapy has gained considerable attention in dentistry and orthodontics owing to its potential to promote tissue regeneration, modulate bone remodeling, enhance craniofacial development, and facilitate personalized treatment approaches. A deeper understanding of the genetic basis of dentofacial abnormalities, combined with emerging genome-editing technologies, has opened new possibilities for managing craniofacial disorders, accelerating orthodontic tooth movement, improving periodontal regeneration, and advancing precision orthodontics (**Figure 1, 2**).[2,3,7]

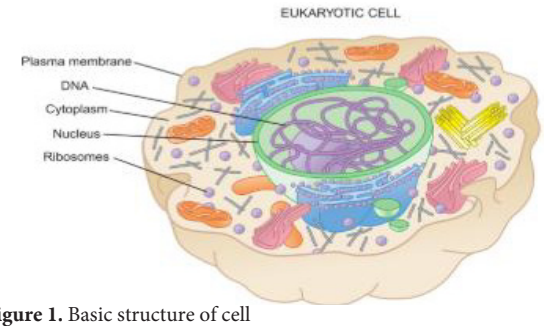

Figure 1. Basic structure of cell

Clark DP, Pazdernik NJ. Molecular Biology. 2nd ed. Elsevier; 2012.

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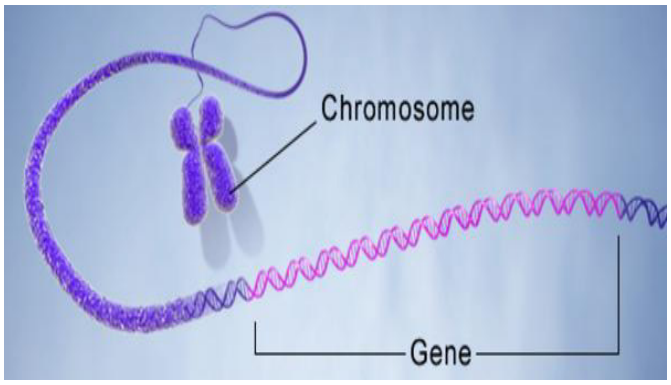

Figure 2. Gene and DNA

DNA: Deoxyribonucleic acid

Cummings S, Dobrea LF. Fundamentals of genetics and genomics in oncology nursing practice and navigation. *J Oncol Navig Surviv.* 2019;10(10):388-397.

MOLECULAR BASIS OF GENE THERAPY

Gene therapy involves the delivery of therapeutic DNA or RNA sequences into target cells or tissues to correct or modulate gene expression.[8-11] The therapeutic gene is introduced using vectors that facilitate cellular uptake and expression.[8,12] Once delivered, the gene may function by adding a normal gene copy, correcting a defective sequence, or silencing a harmful gene.[8]

The success of gene therapy depends on efficient gene delivery, sustained gene expression, minimal immunogenicity, and accurate targeting of specific tissues or cells.[8,12]

HISTORY OF GENE THERAPY

The concept of gene therapy originated in the mid-20th century with the understanding of DNA as the genetic blueprint of life.[13,14] The first approved clinical gene therapy trials in the 1990s targeted severe combined immunodeficiency (SCID)[15] Since then, advances in recombinant DNA technology, viral vector engineering, and gene-editing tools have accelerated research and clinical translation. Today, over a thousand clinical trials are underway worldwide, many focusing on cancer and genetic disorders.[16]

CLASSIFICATION OF GENE THERAPY

Based on Target Cells

Somatic gene therapy: Somatic gene therapy involves genetic modification of non-reproductive cells. The changes are not heritable and are confined to the treated individual. Most current clinical applications, including CAR-T cell therapy for leukaemia, fall under this category (**Figure 3**).[16]

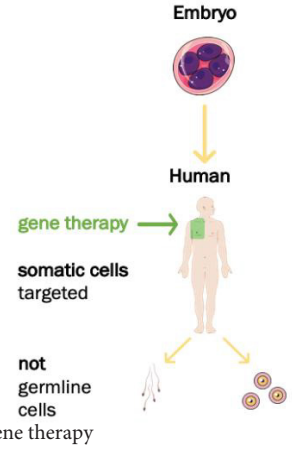

Figure 3. Somatic gene therapy

Frazier S. Embryo Gene Editing: Changing Life As We Know It. 2019.

Germline gene therapy: Germline gene therapy alters genes in sperm or egg cells, making changes heritable. Although it holds potential for preventing inherited diseases such as cystic fibrosis and sickle cell anaemia, it is ethically controversial and prohibited in humans in most countries (**Figure 4**).[11]

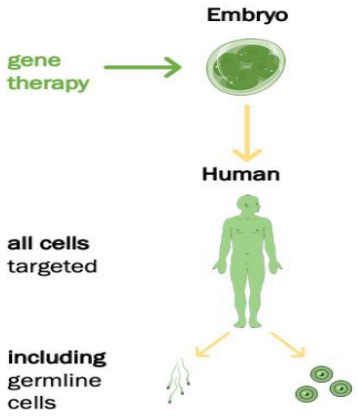

Figure 4. Germline gene therapy

Frazier S. Embryo Gene Editing: Changing Life As We Know It. 2019.

Based on Method of Gene Delivery

In vivo gene therapy: In vivo gene therapy involves direct introduction of the gene-vector complex into the patient's body. It is suitable for diseases affecting internal organs or widespread tissues. Common routes include intravenous, intramuscular, intrathecal, subretinal, and inhalation delivery (**Figure 5**).[8,12]

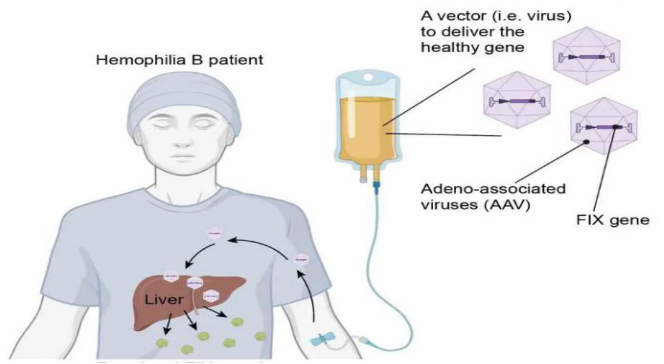

Figure 5. In vivo gene therapy

Rachael. Gene therapy: a promising biotechnology for the treatment of genetic diseases and cancers-basic introduction.

Ex vivo gene therapy: In this approach, patient cells are harvested, genetically modified outside the body, expanded in culture, and reintroduced. This method offers better control over gene transfer and is widely used in stem cell and immunotherapy applications (**Figure 6**).[16,17]

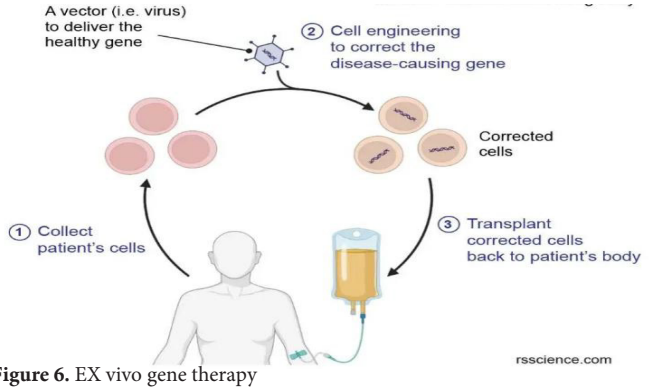

Figure 6. EX vivo gene therapy

Rachael. Gene therapy: a promising biotechnology for the treatment of genetic diseases and cancers-basic introduction.

Based on Therapeutic Approach

Gene augmentation therapy: Addition of a functional gene copy to compensate for a defective gene (Figure 7).[8]

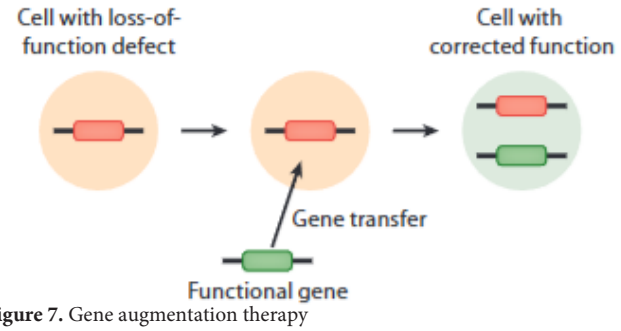

Figure 7. Gene augmentation therapy

Anguela XM, High KA. Entering the modern era of gene therapy. *Annu Rev Med.* 2019;70:273-288. doi:10.1146/annurev-med-012017-043332

Gene inhibition therapy: Silencing of harmful or overexpressed genes (Figure 8).[8]

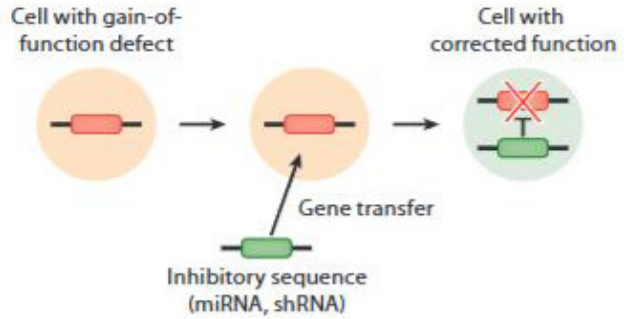

Figure 8. Gene inhibition therapy

miRNA: Micro ribonucleic acid, shRNA: Short hairpin ribonucleic acid

Anguela XM, High KA. Entering the modern era of gene therapy. *Annu Rev Med.* 2019;70:273-288. doi:10.1146/annurev-med-012017-043332

Gene editing therapy: Direct modification of DNA sequences for permanent correction.[12,18]

Suicide gene therapy: Introduction of genes that convert non-toxic prodrugs into toxic compounds within cancer cells.[12,18]

VECTORS AND GENE DELIVERY SYSTEMS

Viral Vectors

Modified viruses serve as efficient gene carriers due to their natural ability to enter cells. Common viral vectors include adenoviruses, retroviruses, lentiviruses, adeno-associated viruses (AAV), and herpes simplex viruses. These vectors are engineered to be replication-defective to enhance safety.[8,12]

Non-Viral Vectors

Non-viral vectors include liposomes, nanoparticles, electroporation, gene guns, microinjection, and calcium phosphate precipitation. Although safer and less immunogenic, they are generally less efficient than viral vectors.[8,19]

MECHANISMS OF GENE THERAPY

Gene therapy operates through three principal mechanisms:

Gene addition: Introduction of a functional gene to restore protein synthesis.[8,10]

Gene correction: Precise repair of mutated DNA sequences using gene-editing tools.[8,17]

Gene silencing: Suppression of harmful gene expression by targeting mRNA.[8,10]

APPLICATIONS OF GENE THERAPY IN DENTISTRY

Orofacial Pain

Gene therapy offers a novel approach to managing chronic orofacial pain by enabling continuous production of anti-nociceptive proteins. Viral or plasmid delivery near the spinal dorsal horn and herpes virus-mediated gene transfer to dorsal root ganglia have shown promising results (Figure 9 and Table).[12,20]

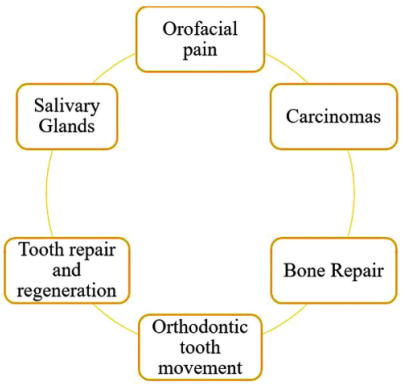

Figure 9. Application of gene therapy in dentistry

Karthika N, Bhat AR. Applications of gene therapy in dentistry: a review article. *J Health Allied SciNU.* 2023;13(4):445-452. doi:10.1055/s-0042-1759711

Table. Applications of gene therapy in dentistry and orthodontics

Application	Therapeutic strategy	Clinical benefit
Bone repair and regeneration	Delivery of osteogenic genes (BMP-2, BMP-4, BMP-7, PDGF)	Enhances osteogenesis, bone regeneration, and craniofacial reconstruction
Salivary gland dysfunction	AQP1 gene transfer	Restores salivary secretion in radiation-induced xerostomia
Tooth repair and regeneration	Gene-modified dental stem cells combined with tissue engineering	Regeneration of dentin, pulp, periodontal tissues, and biological tooth replacement
Orthodontic tooth movement	Modulation of the RANK-RANKL-OPG pathway and growth factor expression (VEGF, PDGF)	Accelerates tooth movement, improves anchorage control, and enhances periodontal healing
Root resorption	Regulation of osteoclast and odontoclast activity through RANK-RANKL-OPG signalling	Reduces orthodontically induced root resorption while maintaining effective tooth movement
Head and neck carcinoma	Tumour suppressor gene replacement, oncogene silencing, and suicide gene therapy	Targeted tumour destruction with reduced systemic toxicity
Orofacial pain	Viral or plasmid-mediated delivery of anti-nociceptive genes	Long-term management of chronic orofacial pain
Cleft lip and palate	BMP-mediated gene delivery for bone regeneration	Improves bone formation in craniofacial defects and supports reconstructive treatment

BMP: Bone morphogenetic protein, PDGF: Platelet-derived growth factor, AQP1: Aquaporin-1, RANK: Receptor activator of nuclear factor kappa B, RANKL: Receptor activator of nuclear factor kappa B ligand, OPG: Osteoprotegerin

Head and Neck Carcinomas

Squamous cell carcinoma of the head and neck is among the most common cancers globally. Gene therapy strategies include tumor suppressor gene replacement (p53), oncogene silencing, and suicide gene therapy. Localized gene delivery minimizes systemic toxicity and enhances therapeutic efficacy.[18,20]

Bone Repair and Regeneration

Gene therapy has emerged as a promising strategy for enhancing bone repair by delivering genes encoding osteogenic growth factors directly to target tissues. Genes encoding bone morphogenetic proteins (BMP-2, BMP-4, and BMP-7) and platelet-derived growth factor (PDGF) stimulate osteoblast differentiation, promote angiogenesis, and accelerate bone formation, thereby improving the quality and rate of osseous regeneration. When combined with stem cell-based tissue engineering approaches, gene delivery provides sustained local expression of regenerative molecules, overcoming the limitations associated with repeated protein administration. These strategies have shown encouraging potential for alveolar bone regeneration, craniofacial reconstruction, and periodontal tissue engineering, highlighting their future role in regenerative dentistry.[11,12,21]

Salivary Gland Dysfunction

Gene therapy using aquaporin-1 (AQP1) has shown success in restoring salivary flow in radiation-induced xerostomia. Salivary glands are ideal targets due to their encapsulated structure and protein secretion efficiency.[20]

Root Resorption

Orthodontically induced root resorption is associated with inflammatory mediators and senescent periodontal ligament cells expressing RANKL, which stimulate osteoclast and odontoclast activity. Targeted gene therapy aimed at modulating the RANK-RANKL-OPG signalling pathway may offer future strategies for minimizing root resorption while maintaining effective orthodontic tooth movement.[10,21]

Tooth Repair and Regeneration

Gene therapy combined with tissue engineering offers a biologically based approach for regenerating dental tissues rather than merely replacing lost structures. Genetically modified dental pulp stem cells and mesenchymal stem cells can enhance the regeneration of dentin, pulp, periodontal ligament, and alveolar bone through sustained expression of regenerative growth factors. These approaches may facilitate the development of bioengineered teeth and improve healing following dental trauma or disease. Although most evidence remains preclinical, continued advances in gene delivery systems are expected to accelerate the clinical translation of regenerative dental therapies.[11,12,21]

Cleft Lip and Palate

BMP-2 and BMP-7 gene delivery has shown improved bone regeneration in cleft defects. Although still experimental, prenatal gene therapy holds promise for preventing craniofacial anomalies.[21]

GENE THERAPY IN ORTHODONTICS

Orthodontic tooth movement involves controlled bone remodeling mediated by cytokines, chemokines, and growth factors. The RANK-RANKL-OPG pathway plays a pivotal role in osteoclast regulation.[10,21]

- RANKL gene delivery accelerates tooth movement.
- OPG gene delivery suppresses bone resorption and preserves anchorage.
- VEGF and PDGF gene overexpression enhances angiogenesis and periodontal healing.

Gene therapy enables spatial and temporal control of tooth movement, reducing treatment duration while avoiding systemic side effects.[10]

In addition to accelerating tooth movement, gene therapy has potential applications in anchorage preservation, periodontal regeneration, and prevention of orthodontically induced root resorption. Targeted modulation of the RANK-RANKL-OPG pathway may allow precise control of osteoclast activity, thereby facilitate desired tooth movement while minimize unwanted bone resorption. Furthermore, localized delivery of growth factors such as BMPs, PDGF, and VEGF may enhance alveolar bone remodelling, angiogenesis, and periodontal healing during orthodontic treatment. These emerging strategies highlight the potential of gene therapy to support more efficient, biologically guided, and patient-specific orthodontic care (**Figure 10**).[10,21]

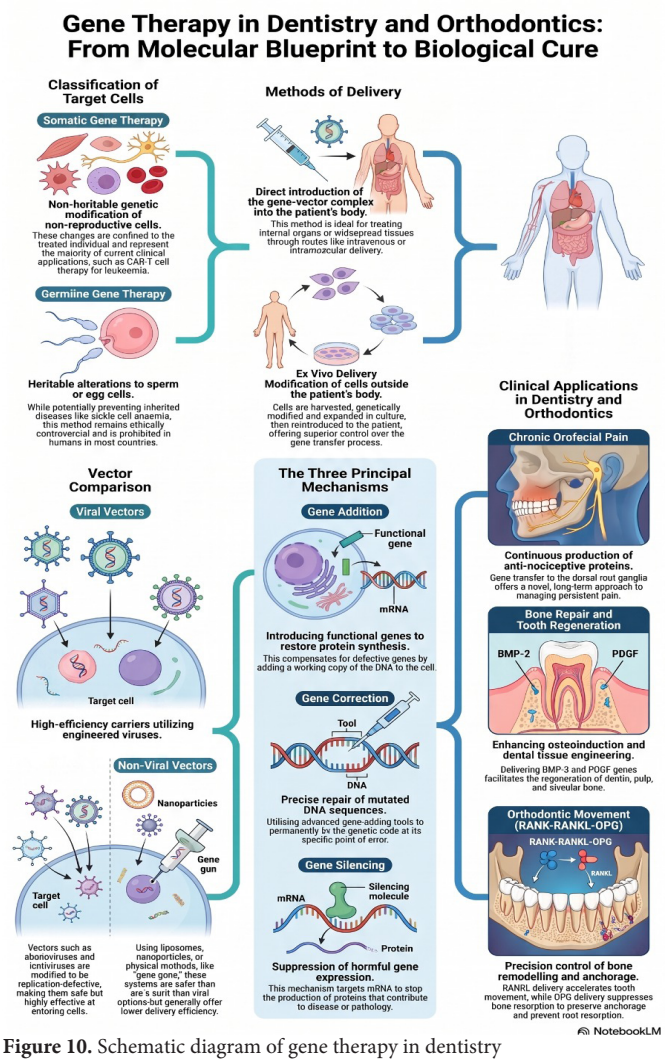

Figure 10. Schematic diagram of gene therapy in dentistry

FUTURE PERSPECTIVES

Future developments in gene therapy are expected to transform dental and orthodontic practice by integrating gene editing, tissue engineering, and regenerative medicine into routine clinical care. Advances in vector technology and targeted gene delivery may enable personalized treatment strategies for periodontal regeneration, craniofacial reconstruction, biological tooth repair, and controlled orthodontic tooth movement. As the safety and efficiency of gene delivery systems continue to improve, gene therapy has the potential to shift orthodontic treatment from purely mechanical approaches toward biologically guided therapies that optimize tissue remodeling and improve long-term treatment outcomes.[11,12,14,21]

Limitations

Despite its promise, gene therapy faces challenges including inefficient delivery, immune reactions, short-lived gene expression, insertional mutagenesis, high costs, ethical concerns, and limited long-term clinical data.

CONCLUSION

Gene therapy represents a transformative approach in modern medicine and dentistry by addressing diseases at their genetic basis. Continued advances in gene editing, vector technology, and tissue engineering are expected to accelerate its translation into routine clinical practice. In dentistry and orthodontics, gene therapy holds significant promise for periodontal and craniofacial regeneration, biological tooth repair, controlled orthodontic tooth movement, and personalized treatment strategies. Although challenges related to safety, delivery efficiency, long-term outcomes, and ethical considerations remain, ongoing research and well-designed clinical trials are likely to establish gene therapy as an integral component of future precision dental care.

ETHICAL DECLARATIONS

Peer Review Process

This review was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

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