



Review Article

From Biology to Bio-devices: RANKL-Functionalized Dissolving Microneedles for Controlled Orthodontic Tooth Movement

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Orthodontic tooth movement (OTM) is fundamentally governed by alveolar bone remodeling mediated through the RANK-RANKL-OPG signaling axis. Contemporary acceleration strategies, including surgical and pharmacologic approaches, are limited by invasiveness, lack of site specificity, and patient compliance issues. Microneedle-based delivery systems have emerged as minimally invasive platforms capable of precise, localized biomolecule administration across mucosal barriers. This narrative review synthesizes current evidence on RANKL biology in orthodontics and microneedle drug-delivery technology and proposes a conceptual framework for RANKL-functionalized dissolving microneedle patches to achieve controlled, site-specific acceleration of tooth movement. Potential mechanisms, design considerations, clinical applications, advantages, and safety concerns are critically analyzed. Although still theoretical, this bio-device paradigm represents a promising step toward precision, biologically driven orthodontics and warrants focused translational research.

Introduction

The contemporary orthodontic landscape is increasingly driven by the demand for reduced treatment duration without compromising biological safety or treatment quality. Prolonged orthodontic therapy is associated with higher risks of enamel decalcification, external apical root resorption, and reduced patient compliance, thereby motivating the search for efficient and biologically sound acceleration strategies [1,2]. Orthodontic tooth movement (OTM) is fundamentally a biologically mediated process that depends on the coordinated remodeling of the periodontal ligament (PDL) and surrounding alveolar bone in response to mechanical loading [3]. The application of orthodontic force initiates a cascade of cellular and molecular events that culminate in bone resorption on the pressure side and bone apposition on the tension side [4,5]. These events are tightly regulated by inflammatory mediators, cytokines, and mechanotransduction pathways within the periodontal microenvironment [6].

Among the molecular regulators of OTM, the receptor activator of nuclear factor-kappa B (RANK), its ligand RANKL, and osteoprotegerin (OPG) constitute the principal signaling triad govern-

ing osteoclast differentiation and activity [7]. RANKL expressed by osteoblasts and periodontal ligament cells binds to RANK receptors on osteoclast precursors, promoting osteoclastogenesis and subsequent bone resorption [8]. Conversely, OPG functions as a soluble decoy receptor that competitively inhibits RANKL-RANK interaction, thereby reducing osteoclastic activity and slowing tooth movement [9]. The dynamic balance between RANKL and OPG is therefore considered a critical determinant of the rate and efficiency of orthodontic tooth movement [10].

In an effort to shorten treatment time, various acceleration strategies have been investigated, broadly categorized into surgical, pharmacologic, and physical approaches. Surgical interventions such as corticotomy, periodontally accelerated osteogenic orthodontics (PAOO), and micro-osteoperforations have demonstrated the ability to induce a regional acceleratory phenomenon and enhance tooth movement [11-13]. However, their invasive nature, postoperative morbidity, and variable patient acceptance limit widespread clinical adoption. Pharmacologic modulation using agents such as prostaglandins and vitamin D metabolites has also been explored to enhance osteoclastic activity and accelerate tooth movement [14,15]. Although promising in experimen-

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tal settings, these approaches raise concerns regarding systemic exposure, dose control, and lack of site specificity. Physical stimulation modalities, including vibrational therapy, have shown inconsistent clinical outcomes and remain controversial [16].

Given these limitations, contemporary orthodontic research has shifted toward biologically targeted and minimally invasive approaches capable of modulating bone remodeling at a localized level. Advances in osteoimmunology and molecular orthodontics have reinforced the concept that controlled manipulation of the RANK-RANKL-OPG axis could provide a rational pathway for accelerating tooth movement [17-19]. Nevertheless, a clinically practical delivery system that enables precise, site-specific biomolecule administration within the oral environment is still lacking. Microneedle-based drug delivery systems have recently emerged as minimally invasive platforms capable of bypassing epithelial barriers and delivering bioactive molecules directly into target tissues with minimal discomfort [20-22]. Originally developed for transdermal applications, dissolving microneedle arrays demonstrate favorable safety profiles, controlled release kinetics, and potential for self-administration [23-25]. Early investigations in dentistry further suggest their feasibility for intraoral therapeutic delivery and soft-tissue modulation [26].

The convergence of molecular orthodontics and microneedle engineering presents an opportunity to bridge fundamental bone biology with localized therapeutic delivery. Although both fields have evolved independently, their integration has received limited attention within orthodontics, leaving an important translational opportunity largely unexplored. Therefore, this review aims to integrate current understanding of RANKL-mediated bone remodeling with advances in microneedle technology and to propose a conceptual bio-device framework for controlled orthodontic tooth movement.

Literature Search Strategy

A narrative literature search was conducted to identify relevant studies pertaining to orthodontic biology, osteoimmunology, biomaterials, and microneedle-based drug delivery systems. Electronic databases including PubMed, Scopus, Web of Science, and Google Scholar were searched for articles published in English up to January 2026. Search terms and combinations included “orthodontic tooth movement,” “RANKL,” “RANK-RANKL-OPG axis,” “osteoclastogenesis,” “microneedles,” “dissolving microneedles,” “oral drug delivery,” “biomaterials,” and “intraoral therapeutic systems.”

Priority was given to systematic reviews, original research articles, translational studies, and recent investigations relevant to molecular orthodontics and microneedle engineering. Additional references were identified through manual screening of the bibliographies of selected publications. Owing to the narrative and conceptual nature of the review, formal risk-of-bias assessment and meta-analytic methods were not performed. The collected evidence was synthesized to develop a translational framework for RANKL-functionalized dissolving microneedle systems in orthodontics.

Biology of Orthodontic Tooth Movement

Phases of orthodontic tooth movement

Orthodontic tooth movement occurs through biologically coordinated phases initiated by sustained mechanical loading [27]. The initial phase involves rapid displacement within the periodontal ligament due to viscoelastic deformation and fluid redistribution and does not represent true bone remodeling [28,29]. This is followed by a lag phase characterized by periodontal ligament hyalinization and temporary slowing of movement while osteoclast recruitment and undermining bone resorption are initiated [30-32]. Subsequently, the post-lag phase is marked by coordinated pressure-side bone resorption and tension-side bone formation, enabling continuous tooth movement [33,34]. Overall, orthodontic tooth movement is now recognized as a controlled inflammatory remodeling process rather than a purely mechanical phenomenon [35].

Cellular events in orthodontic tooth movement

Orthodontic force initiates a complex cellular response involving periodontal ligament cells, osteoclast precursors, osteoblasts, endothelial cells, and immune mediators [36]. Mechanical strain activates mechanotransduction pathways that stimulate the release of cytokines, prostaglandins, and growth factors, thereby regulating bone remodeling [37-38]. On the pressure side, osteoclast precursors are recruited and differentiate into multinucleated osteoclasts responsible for alveolar bone resorption [39]. In contrast, osteoblastic activity predominates on the tension side, where new bone formation preserves periodontal support and tooth stability during movement [27]. The balance between these cellular processes determines the rate and biologic safety of orthodontic treatment. In addition, inflammatory mediators such as interleukins, tumor necrosis factor- α , and prostaglandin E, amplify osteoclastogenesis and contribute to periodontal remodeling [28-29].

RANK-RANKL-OPG axis

Among the various molecular pathways involved in orthodontic tooth movement, the RANK-RANKL-OPG axis is considered the master regulator of osteoclast differentiation and function [30]. RANKL, primarily expressed by osteoblasts and periodontal ligament cells under mechanical stress, binds to RANK receptors on osteoclast precursors and initiates intracellular signaling that promotes osteoclast maturation [31].

Osteoprotegerin acts as a soluble decoy receptor that competitively binds RANKL and prevents its interaction with RANK, thereby inhibiting osteoclastogenesis [32]. The relative expression levels of RANKL and OPG within the periodontal microenvironment therefore determine the net bone resorptive activity during orthodontic tooth movement [33]. Experimental studies have demonstrated that increased RANKL expression correlates with accelerated tooth movement, whereas elevated OPG levels are associated with reduced osteoclastic activity and slower movement [34].

Recent molecular investigations further confirm that modulation of the RANKL/OPG ratio under compressive orthodontic forces directly influences the rate of alveolar bone remodeling [35]. Additionally, immune-mediated pathways and intracellular signaling mechanisms have been shown to amplify RANKL-induced osteoclast differentiation, highlighting the central role of osteoimmunology in orthodontic biomechanics [36]. Collectively, these findings establish the RANK-RANKL-OPG axis as a biologically rational and highly promising target for site-specific acceleration of orthodontic tooth movement. However, the clinical translation of this concept remains limited by the absence of a minimally invasive and precisely controllable delivery platform capable of localized biomolecule administration within the oral environment.

Current Approaches to Accelerate Orthodontic Tooth Movement

Surgical methods

Surgical approaches have been employed to accelerate orthodontic tooth movement by enhancing localized bone remodeling [10]. Corticotomy-assisted orthodontics and periodontally accelerated osteogenic orthodontics (PAOO) utilize the regional acceleratory phenomenon, resulting in transient osteopenia and increased bone turnover [11]. Although these techniques can reduce treatment duration, their invasive nature and associated postoperative morbidity limit routine acceptance [12]. Microosteoperforation (MOP) has emerged as a minimally invasive alternative aimed at inducing localized inflammatory responses and increasing osteoclastic activity [13]. While some studies have reported enhanced tooth movement following MOP, systematic reviews indicate that the extent and predictability of acceleration remain inconsistent [10,12].

Pharmacologic modulation

Pharmacologic approaches seek to accelerate orthodontic tooth movement by modulating osteoclast activity and bone metabolism. Prostaglandin E, (PGE,) has been shown to enhance bone resorption and increase the rate of tooth movement in experimental studies [14]. Like-

wise, vitamin D metabolites can stimulate osteoclast differentiation and bone turnover following local administration [13]. Despite these favorable biologic effects, clinical application remains limited because of difficulties in maintaining optimal local concentrations, concerns regarding systemic exposure and dose-dependent adverse effects, and the lack of precise spatial control within the periodontal environment [39]. Consequently, predictable and site-specific biologic modulation remains unavailable, highlighting the need for targeted intraoral drug-delivery systems.

Physical stimulation methods

Noninvasive physical modalities have been investigated as adjuncts to accelerate orthodontic tooth movement. Mechanical vibration may influence bone remodeling through mechanotransductive activation of periodontal ligament cells, but clinical outcomes remain inconsistent and protocol-dependent [38,39]. Other approaches, including low-level laser therapy and therapeutic ultrasound, show variable evidence and lack standardized clinical guidelines [39]. A comparative overview of acceleration strategies and their biologic relevance is presented in table 1.

Despite the availability of surgical, pharmacologic, and physical acceleration strategies, a predictable and site-specific biologic modulation approach remains unavailable [40,41.] Increasing emphasis has therefore been placed on integrating biomechanics with targeted molecular regulation to improve treatment efficiency. In this regard, microneedle-based delivery systems represent a minimally invasive platform capable of localized biomolecule administration within the oral environment.

Microneedle Technology in Oro-Dental Applications

Types of microneedles

Microneedle systems are minimally invasive micro-projection arrays designed to penetrate biological barriers and enable localized drug delivery

with minimal discomfort [22]. Based on structural design and drug-loading strategy, microneedles are broadly classified into solid, coated, hollow, and dissolving types [23]. Solid microneedles primarily create microchannels to enhance subsequent drug diffusion, whereas coated microneedles carry surface-bound therapeutics for rapid release following insertion [24]. Hollow microneedles permit active infusion of liquid formulations but require more complex fabrication and handling [25].

Among these, dissolving microneedles have gained particular attention for intraoral applications because they are fabricated from biodegradable polymers that encapsulate the therapeutic payload and dissolve completely after insertion [26]. This design eliminates the risk of needle fracture or retention and allows controlled release of bioactive molecules within target tissues [27]. Recent biomedical advances further demonstrate that microneedle geometry, density, and polymer composition can be precisely engineered to tailor penetration depth and release kinetics [28,29].

Advantages for oral and orthodontic use

The oral cavity presents unique challenges for localized drug delivery due to constant salivary flow, mechanical disturbance, and rapid mucosal clearance [36]. Microneedle platforms offer several advantages that directly address these limitations by physically bypassing the epithelial barrier and depositing therapeutic agents within the underlying connective tissue [22].

One of the most significant benefits of microneedles is their minimally invasive and nearly painless mode of action, which improves patient acceptance compared with conventional injections [23]. In addition, these systems enable site-specific drug deposition, thereby reducing systemic exposure and enhancing therapeutic efficiency [24]. Their capacity for controlled and sustained release further supports their suitability for biologically driven orthodontic interventions that require precise modulation of bone remodeling pathways [25].

Accumulating evidence from oral drug-delivery research supports

Table 1: Comparative Overview of Orthodontic Acceleration Modalities and Their Relevance to Biologic Modulation

Modality	Primary Mechanism	Invasiveness	Site Specificity	Level of Clinical Evidence	Key Limitations	Relevance to RANKL Axis
Corticotomy / PAOO	Regional Acceleratory Phenomenon (RAP); transient osteopenia and increased bone turnover	High (surgical flap, bone injury)	Moderate (regional effect)	Moderate to high (clinical studies, systematic reviews)	Postoperative morbidity, patient reluctance, cost, technique sensitivity	Indirect upregulation of RANKL via surgical inflammation
Micro-osteoperforation (MOP)	Local inflammatory stimulation and osteoclast recruitment	Mild to moderate (minimally invasive perforations)	Moderate (localized but not tooth-specific)	Moderate (variable clinical outcomes)	Inconsistent acceleration magnitude, limited predictability	Transient increase in RANKL expression secondary to micro-injury
Prostaglandins (PGE ₂)	Direct stimulation of osteoclastogenesis and bone resorption	Low (injection-based)	Low (diffusion beyond target site)	Experimental and limited clinical data	Dose control issues, systemic exposure risk, root resorption concerns	Direct enhancement of osteoclastic activity downstream of RANKL
Vitamin D Metabolites	Stimulation of osteoclast differentiation and bone turnover	Low (local injection)	Low to moderate	Primarily experimental	Short duration of effect, unclear optimal dosing	Modulates RANKL/OPG balance indirectly
Vibrational Therapy	Mechanotransductive stimulation of bone remodeling	Noninvasive	Low (systemic skeletal response)	Mixed and heterogeneous evidence	Compliance-dependent, inconsistent results	Indirect and variable influence on RANKL expression
Low-Level Laser Therapy (LLLT)	Photobiomodulation influencing cellular metabolism	Noninvasive	Moderate (localized irradiation)	Variable clinical evidence	Parameter variability, lack of standardization	May modulate inflammatory mediators affecting RANKL expression
Therapeutic Ultrasound	Mechanical stimulation of bone remodeling	Noninvasive	Low to moderate	Limited clinical validation	Equipment dependency, variable response	Indirect osteogenic modulation
Proposed RANKL-Functionalized Microneedle Patch	Direct localized RANKL delivery enhancing osteoclastogenesis	Minimally invasive (micro-penetration)	High (tooth-specific targeting)	Conceptual; requires preclinical and clinical validation	Dose-response uncertainty, safety consideration, regulatory pathway	Direct modulation of RANK–RANKL–OPG axis with spatial confinement

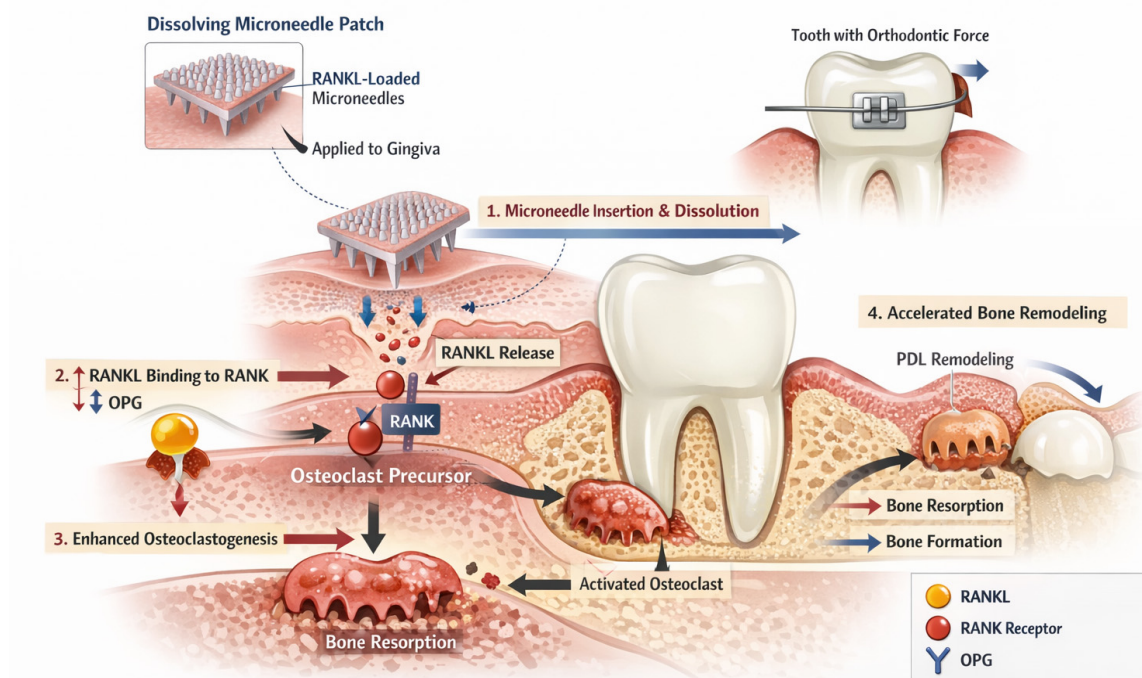


Figure 1: Proposed Mechanism of RANKL-Functionalized Dissolving Microneedle Patch for Accelerated Orthodontic Tooth Movement

the value of localized therapeutic systems capable of maintaining effective concentrations at the site of action, thereby improving treatment specificity and reducing systemic exposure [37]. This principle aligns closely with the requirements for controlled modulation of the RANK-RANKL-OPG axis during orthodontic tooth movement.

Current dental and orthodontic applications

Emerging dental literature demonstrates the feasibility of microneedle-based approaches for several intraoral applications. Microneedle systems have been investigated for enhanced local anesthesia delivery, offering faster onset and improved patient comfort compared with conventional techniques [30]. They have also shown potential in biomarker sampling from gingival crevicular fluid, enabling minimally invasive monitoring of periodontal and orthodontic treatment responses [31].

In periodontology, microneedling approaches alone or combined with biologic adjuncts such as injectable platelet-rich fibrin or hyaluronic acid have demonstrated improvements in gingival thickness and soft-tissue phenotype [32]. These findings support the biocompatibility of microneedle-mediated micro-injury within oral tissues and provide indirect evidence for their potential translational use in orthodontic biologic modulation.

Beyond soft-tissue applications, localized delivery of antimicrobial and remineralizing agents highlights the broader therapeutic versatility of microneedle systems and suggests potential roles in the prevention of enamel demineralization associated with fixed appliance therapy [30]. Although direct orthodontic implementations remain limited, the accumulating evidence from periodontal and drug-delivery research indicates that microneedles are technically feasible and biologically well tolerated in the oral environment.

Although microneedle technology has demonstrated promising applications in dentistry and localized drug delivery, its use for targeted modulation of osteoclastogenesis during orthodontic tooth movement remains largely unexplored. Given their ability to provide site-specific and minimally invasive biomolecule delivery, dissolving microneedles represent a promising platform for localized RANKL administration.

Accordingly, the following section presents a conceptual framework for integrating RANKL-functionalized microneedle patches into precision orthodontic therapy.

Conceptual Framework: RANKL-Functionalized Dissolving Microneedle Patch

The convergence of molecular orthodontics and micro-device engineering creates an opportunity to develop biologically precise and minimally invasive acceleration strategies. Given the central role of the RANK-RANKL-OPG axis in regulating osteoclastogenesis during orthodontic tooth movement, a delivery platform capable of localized RANKL modulation may provide controlled enhancement of alveolar bone remodeling [1,3]. Building on advances in microneedle technology and intraoral drug delivery, a RANKL-functionalized dissolving microneedle patch is proposed as a conceptual bio-device for site-specific orthodontic acceleration [22,37].

Proposed biological mechanism

The proposed mechanism involves a stepwise sequence beginning with placement of a dissolving microneedle patch on the attached gingiva adjacent to the target tooth. Upon gentle digital pressure, the microneedles penetrate the oral epithelium and create microconduits for localized biomolecule deposition [23]. The polymeric microneedle matrix then undergoes controlled dissolution within the superficial connective tissue, enabling sustained release of recombinant RANKL in proximity to the periodontal ligament [26]. Localized elevation of RANKL concentration is expected to enhance binding to RANK receptors on osteoclast precursors, thereby promoting osteoclast differentiation and activation [7,16]. This targeted increase in osteoclastic activity may accelerate pressure-side bone resorption while maintaining spatial confinement of the biologic effect [18]. If appropriately titrated, the process could facilitate more efficient orthodontic tooth movement without the need for invasive surgical adjuncts. A central feature of this framework is the emphasis on controlled and reversible biologic modulation rather than

indiscriminate enhancement of bone turnover, thereby preserving the physiologic balance between treatment efficiency and tissue safety. By adjusting dose, frequency, and microneedle geometry, the clinician may theoretically fine-tune the magnitude of orthodontic acceleration. The stepwise mechanism of action is summarized in figure 1.

Proposed device design

Successful implementation of the proposed bio-device depends on rational selection of biomaterials and optimization of microneedle architecture. Dissolving microneedles fabricated from biocompatible poly-

Figure 2. Translational Roadmap for RANKL-Functionalized Dissolving Microneedle Patch in Orthodontic Tooth Movement

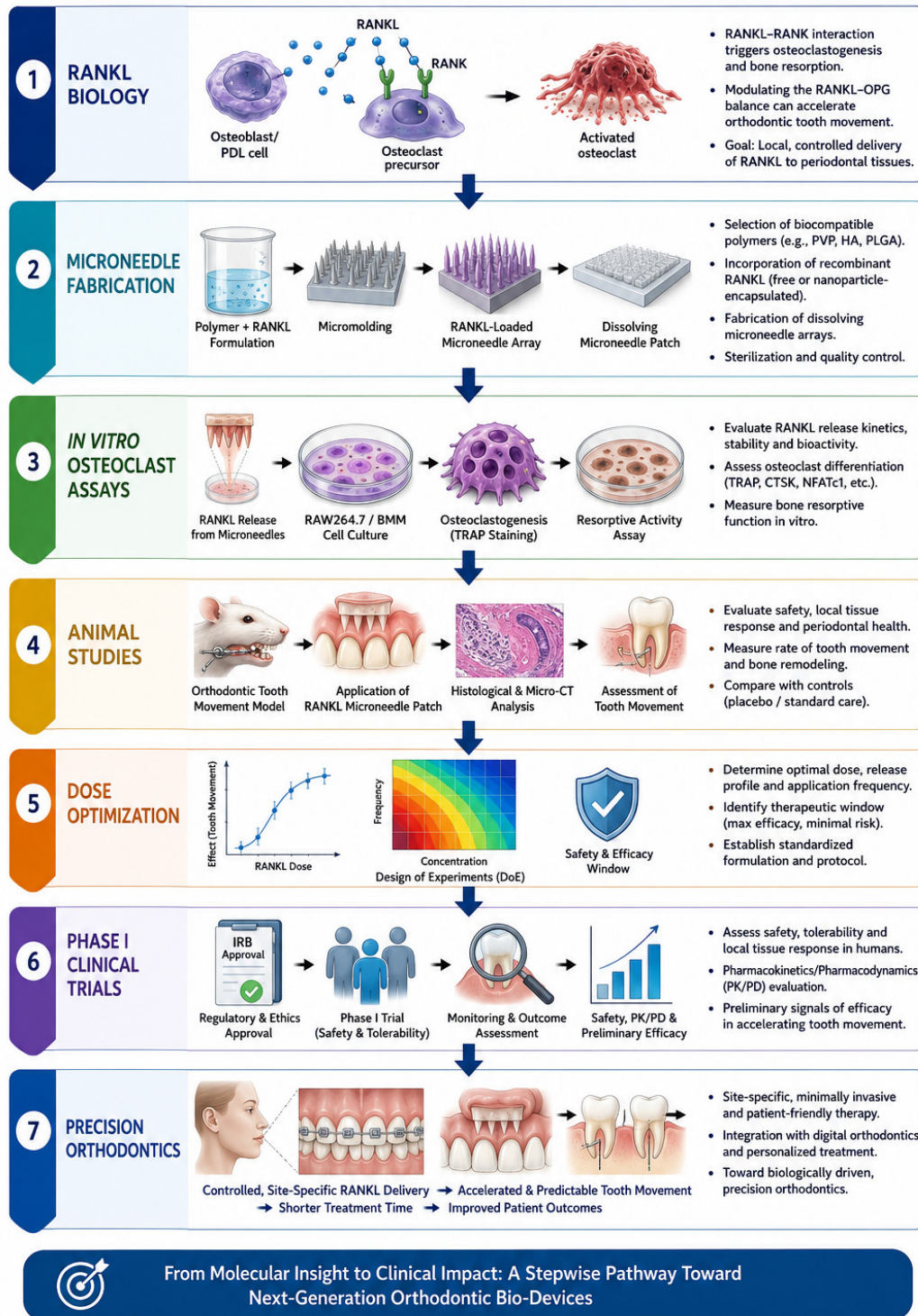


Figure 2: Translational Roadmap for Development of a RANKL-Functionalized Dissolving Microneedle Patch for Precision Orthodontics

Table 2: Proposed Design Parameters for RANKL-Functionalized Dissolving Microneedle Patch

Parameter	Proposed Specification	Biological Rationale	Engineering Consideration	Safety Implication
Microneedle Length	300-800 μm	Penetrates oral epithelium while avoiding deep tissue trauma	Must balance penetration efficiency with mechanical stability	Excessive length may increase tissue injury or discomfort
Needle Density	100-400 needles/ cm^2 (optimized per tooth region)	Ensures adequate localized RANKL distribution	Uniform fabrication required to prevent uneven drug delivery	High density may increase inflammatory response
Insertion Force	0.05-0.5 N per needle	Provides sufficient tissue penetration with minimal discomfort	Influenced by polymer stiffness and microneedle geometry	Excessive force may increase pain and tissue trauma
Polymer Matrix	Hyaluronic acid / PVP / PLGA (biodegradable)	Biocompatible and resorbable materials suitable for oral mucosa	Requires adequate mechanical strength and predictable dissolution characteristics	Inadequate degradation may cause residue retention
Drug Payload	Recombinant RANKL (10-500 μg per patch)	Direct enhancement of osteoclastogenesis via RANK activation	Stability of protein during fabrication and storage is critical	Overexposure may increase risk of root resorption and excessive bone loss
Encapsulation Strategy	Nanoparticle-assisted or matrix-embedded release	Enables controlled and sustained RANKL exposure	Requires reproducible loading efficiency	Burst release may induce excessive osteoclastic activity
Release Kinetics	Controlled low-to-moderate sustained release; dissolution time 2-20 min	Maintains localized shift in RANKL/OPG balance	Polymer composition must regulate dissolution rate	Prolonged exposure may induce unintended bone loss
Application Frequency	Periodic (to be determined by dose-response studies)	Supports staged biologic modulation	Requires protocol standardization	Excessive repetition may increase cumulative biologic risk
Backing Layer	Bioadhesive intraoral patch support	Maintains positional stability in the moist oral environment	Must resist salivary washout and mechanical disturbance	Poor retention may compromise dose precision
Sterility and Manufacturing	Good Manufacturing Practice (GMP)-compliant fabrication	Ensures biologic safety and reproducibility	Strict quality control required	Contamination risk must be minimized
Regulatory Classification	Combination product (medical device + biologic agent)	Integrates mechanical and molecular therapy	Requires coordinated regulatory pathway	Extensive preclinical and clinical validation necessary

mers such as hyaluronic acid (HA), polyvinylpyrrolidone (PVP), and poly (lactic-co-glycolic acid) (PLGA) are attractive candidates for intraoral application because of their favorable safety profiles, mechanical properties, and biodegradability [27]. The therapeutic payload would consist of recombinant RANKL, potentially nanoparticle-encapsulated to permit controlled and sustained release [28].

Hyaluronic acid is a naturally occurring hydrophilic polysaccharide widely used in biomedical applications owing to its excellent biocompatibility and mucoadhesive properties. Its predominantly amorphous structure facilitates rapid hydration and dissolution, making it suitable for immediate drug release. However, HA exhibits relatively limited mechanical strength and undergoes enzymatic degradation in the oral cavity through the action of hyaluronidases present in saliva and surrounding tissues.

Polyvinylpyrrolidone is a synthetic amorphous polymer characterized by high aqueous solubility, good film-forming ability, and favorable mechanical properties. PVP-based microneedles demonstrate rapid dissolution and adequate fracture resistance, enabling efficient delivery of encapsulated biomolecules. These characteristics make PVP particularly attractive for applications requiring rapid release and minimal residue retention.

Poly (lactic-co-glycolic acid) is a biodegradable copolymer possessing greater mechanical strength and slower degradation kinetics than hydrophilic polymers. Depending on the lactic acid-to-glycolic acid ratio and degree of crystallinity, PLGA can provide sustained release profiles and improved stabilization of protein therapeutics. Degradation occurs primarily through hydrolysis of ester bonds, producing lactic acid and glycolic acid, which are subsequently metabolized through physiological pathways.

Microneedle geometry and array configuration are critical determinants of device performance. Lengths of approximately 300-800 μm are generally sufficient to penetrate the oral epithelium while minimizing tissue trauma, whereas optimized needle density influences localized distribution of the therapeutic payload [29]. Mechanical integrity must be sufficient to withstand insertion forces encountered during intraoral application while ensuring complete dissolution after delivery.

Release kinetics and dosing considerations

Controlled release and dose titration will be critical to maintain localized modulation while minimizing adverse effects. Further preclinical studies are required to define optimal kinetics and reapplication intervals. Key engineering and biologic considerations are summarized in table 2.

Engineering parameters derived from existing microneedle studies

Although the proposed RANKL-functionalized microneedle system remains conceptual, several engineering parameters can be inferred from existing microneedle literature. Previous investigations have demonstrated that needle lengths ranging from 300 to 800 μm are generally adequate for penetration of oral and cutaneous tissues while minimizing pain and tissue trauma [22-24]. Typical insertion forces reported for dissolving microneedles range from 0.05 to 0.5 N per needle, depending on polymer composition and microneedle geometry [25].

Drug loading capacities are influenced by matrix composition and fabrication methods and have been reported to range from approximately 10 to 500 μg of therapeutic agent per patch [27]. Dissolution times commonly vary between 2 and 20 minutes, with hydrophilic polymers such as hyaluronic acid and polyvinylpyrrolidone exhibiting rapid dissolution characteristics, whereas PLGA-based systems may provide more prolonged release profiles [26-28]. Needle densities of approximately 100-400 needles/ cm^2 have been employed to achieve uniform payload distribution while maintaining mechanical integrity [29].

These values provide a preliminary engineering framework for future development of RANKL-functionalized dissolving microneedles. Nevertheless, optimization of insertion force, payload concentration, release kinetics, and application frequency will require dedicated *in vitro* and *in vivo* investigations before clinical translation.

Potential Orthodontic Applications

The proposed RANKL-functionalized dissolving microneedle patch represents a shift from mechanically driven adjuncts toward precision biologic orthodontics. By enabling localized and controllable modulation of osteoclast activity, this conceptual bio-device may offer several po-

tential applications within contemporary orthodontic practice, particularly in clinical scenarios where treatment duration or biologic resistance to tooth movement presents a challenge. Although the framework remains theoretical and requires rigorous preclinical and clinical validation, its site-specific nature provides a basis for exploring biologically guided acceleration strategies across a range of orthodontic treatment situations [1,18].

Acceleration of canine retraction

Canine retraction following premolar extraction remains one of the most time-consuming phases in fixed appliance therapy. The rate-limiting step in this stage is pressure-side bone resorption adjacent to the canine root. [3] Targeted upregulation of RANKL in this region could theoretically enhance osteoclast recruitment and reduce the lag phase, thereby improving the efficiency of space closure [16].

Because the microneedle patch allows site-specific delivery, it may provide a more controlled alternative to surgical adjuncts such as microosteoperforations, which induce a broader regional inflammatory response [11]. If validated, this approach could offer clinicians a repeatable and minimally invasive method to accelerate canine distalization.

En-masse retraction

In cases requiring en-masse anterior retraction, biologic resistance from the cortical plate and surrounding alveolar bone often limits the rate of tooth movement. Controlled local delivery of RANKL adjacent to the anterior segment may enhance coordinated osteoclastic activity across multiple teeth, potentially improving the efficiency of sliding mechanics [19].

The patch-based format also allows staged or sequential application, which may help maintain anchorage balance and avoid uncontrolled acceleration. Such precision could be particularly advantageous in extraction cases requiring careful torque and anchorage control.

Anchorage modulation

Selective modulation of bone remodeling raises the possibility of differential anchorage control. By applying the microneedle patch strategically around teeth intended for movement, clinicians may theoretically enhance tooth displacement while preserving anchorage units [15].

This approach reflects the emerging paradigm of biologically guided orthodontics, in which tissue response becomes an additional determinant of tooth movement alongside conventional biomechanical force systems. If proven effective, this approach could complement temporary anchorage devices and reduce reliance on extraoral anchorage in selected cases.

Adult orthodontics and biologically resistant tooth movement

Adult patients often exhibit slower orthodontic tooth movement due to reduced cellular turnover and denser alveolar bone, increasing overall treatment duration [39]. As demand for adult orthodontic therapy rises, minimally invasive biologic acceleration strategies become increasingly relevant. A dissolving microneedle-based RANKL delivery system may offer advantages in adults by providing localized stimulation without the morbidity associated with corticotomy or PAOO [12]. This approach may be particularly useful in biologically resistant situations such as impacted canines, bodily molar movement, or movement through dense cortical bone where enhanced osteoclastogenesis could improve biomechanical efficiency. [8,17] The controlled and repeatable nature of microneedle application may also permit stage-specific biologic modulation, advancing orthodontic care toward a precision-based therapeutic model.

Adjunct to aligner therapy

With the expanding use of clear aligner systems, the need for biologic adjuncts that can enhance tooth movement without invasive procedures has become more pronounced. The thin, patch-based design of dissolving microneedles may be compatible with aligner therapy, allowing intermittent application without significant disruption of appliance wear

[22]. If future studies confirm safety and efficacy, integration of microneedle-mediated biologic modulation with digital orthodontic workflows could represent an important step toward personalized and accelerated aligner treatment.

Despite the potential applications described above, the proposed system remains conceptual. Comprehensive preclinical studies, dose optimization, and carefully designed clinical trials will be essential before routine orthodontic implementation can be considered.

Advantages Over Existing Acceleration Modalities

By combining targeted molecular regulation with minimally invasive delivery, the proposed system has the potential to address several limitations associated with existing orthodontic acceleration techniques and represents a shift toward precision biologic orthodontics. By combining targeted molecular modulation with minimally invasive delivery, it aligns with emerging precision-based orthodontic strategies [15,19].

Minimally invasive approach

Surgical methods such as corticotomy and PAOO are effective but invasive and associated with morbidity [11,12]. In contrast, dissolving microneedles penetrate only the superficial mucosa and are generally well tolerated [23]. This reduced invasiveness may enhance patient acceptance, particularly in adults.

Site-specific biologic modulation

Pharmacologic approaches often lack spatial precision and may result in systemic exposure [14]. Microneedle platforms enable localized delivery adjacent to the target tooth, improving specificity and limiting off-target effects [22,37]. Such confinement of RANKL activity represents a conceptual advantage over regional surgical stimulation.

Controlled and repeatable delivery

Surgical and mechanical adjuncts frequently yield variable biologic responses [39]. Microneedle systems can be engineered for reproducible dosing, controlled penetration depth, and tunable release kinetics [25,27]. Scheduled application may allow phase-specific biologic modulation based on individual treatment needs.

Simplified clinical application

Microneedle patches may be applied chairside with minimal instrumentation compared to surgical procedures [22]. With appropriate validation, supervised application protocols could potentially reduce chair time while maintaining procedural control.

Patient acceptance

Surgical adjuncts are often associated with discomfort and procedural anxiety [12]. Because microneedle systems are minimally invasive, they may offer improved patient acceptance relative to traditional acceleration techniques [23].

Collectively, microneedle-mediated RANKL delivery has the potential to overcome several limitations associated with existing acceleration modalities, including invasiveness, lack of targeting, and biologic variability. Nevertheless, these advantages remain theoretical and require systematic validation through preclinical and clinical investigations.

Biological Risks and Safety Considerations

Although the proposed microneedle-based RANKL delivery system may enhance orthodontic treatment efficiency, successful clinical translation will depend on maintaining a balance between accelerated tooth movement and preservation of periodontal and root integrity. Because the strategy intentionally promotes osteoclastogenesis within the periodontal environment, careful assessment of potential adverse tissue responses remains essential before clinical implementation [15,17].

Risk of external apical root resorption

External apical root resorption (EARR) remains one of the most significant biologic complications associated with accelerated orthodontic tooth movement. Increased osteoclastic activity within the periodontal environment may inadvertently stimulate odontoclastic resorption of the root surface [15]. Experimental evidence indicates that excessive or poorly controlled inflammatory signaling can heighten the risk of root resorption during orthodontic treatment [17]. Localized RANKL delivery, if not carefully titrated, could theoretically amplify this risk by intensifying clastic activity near the root surface. Therefore, dose optimization and spatial confinement of RANKL activity will be critical parameters in future investigations.

Excessive osteoclast activation and bone loss

Although targeted osteoclast stimulation is desirable for accelerating tooth movement, uncontrolled upregulation of the RANK-RANKL pathway may lead to undesirable alveolar bone loss [18]. The balance between RANKL and OPG is physiologically tightly regulated, and artificial perturbation of this equilibrium must be approached cautiously.

Sustained or high-dose exposure to recombinant RANKL could potentially induce transient osteopenia beyond the intended treatment site [19]. This highlights the importance of controlled-release formulations, limited application frequency, and careful patient selection in any future clinical protocol.

Periodontal tissue considerations

The oral mucosa and periodontal tissues present a dynamic biologic environment that may respond variably to repeated microneedle application. Although periodontal microneedling studies have generally reported favorable soft-tissue healing and biocompatibility [32], the effects of repeated intraoral microneedle-mediated biologic delivery during active orthodontic treatment remain insufficiently studied. Potential concerns include localized inflammation, transient gingival irritation, and patient-specific variability in tissue response. Long-term histologic studies will therefore be necessary to confirm periodontal safety.

Immunogenicity of recombinant RANKL

The use of recombinant biologic molecules introduces the possibility of immunogenic reactions, particularly with repeated administration [28]. Although localized delivery may reduce systemic exposure, immune sensitization cannot be entirely excluded. Careful molecular design, purification standards, and preclinical immunogenicity testing will be essential prior to human application.

Dose-response uncertainty

One of the major translational challenges in biologically mediated orthodontic acceleration is defining the optimal therapeutic window. Insufficient RANKL exposure may fail to produce meaningful acceleration, whereas excessive dosing could increase the risk of adverse effects [18]. At present, the dose-response relationship for localized RANKL delivery in the orthodontic context remains inadequately characterized. Future studies must establish safe concentration ranges, duration of effect, and appropriate reapplication intervals.

Regulatory and translational considerations

From a regulatory perspective, the proposed system represents a combination product involving both a medical device and a biologic agent. Such platforms typically require rigorous preclinical validation, including biocompatibility testing, toxicology assessment, and controlled clinical trials [22]. Manufacturing consistency, sterility assurance, and quality control of the microneedle matrix will also be critical for regulatory approval. Additionally, long-term safety surveillance would be necessary to monitor for delayed adverse effects following repeated intraoral application.

Overall, successful clinical translation of microneedle-mediated RANKL delivery will depend on comprehensive safety evaluation. Particular emphasis should be placed on root resorption risk, periodontal

tissue integrity, immunologic safety, and optimization of dose-response relationships to ensure that treatment acceleration does not compromise long-term tissue health.

Future Research Directions

Translation of the proposed RANKL-functionalized dissolving microneedle system into clinical orthodontics will require a staged, evidence-driven research pathway. Initial preclinical studies should establish dose-response relationships, spatial confinement of osteoclast activation, and histologic effects on the periodontal ligament, alveolar bone, and root surface [17,18]. Optimization of microneedle engineering including needle geometry, polymer composition, mechanical strength, and dissolution kinetics will be essential to ensure reliable mucosal penetration and predictable intraoral drug release [25-28].

Parallel development of advanced delivery strategies, such as nanoparticle-encapsulated RANKL and stimuli-responsive or biosensor-integrated microneedle platforms, may further improve dosing precision and biologic control [27,29]. Following successful preclinical validation, early-phase human trials preferably split-mouth randomized designs should evaluate safety, tolerability, and preliminary efficacy in accelerating specific orthodontic movements [19].

Subsequent large-scale clinical studies must assess long-term outcomes, including root resorption risk, periodontal health, stability of tooth movement, and patient-reported experience [15]. The eventual clinical viability of this technology will depend not only on biologic efficacy but also on regulatory considerations, manufacturing reproducibility, economic feasibility, and acceptance by clinicians and patients. Multidisciplinary collaboration between orthodontists, biomaterial scientists, and biomedical engineers will be critical to advance this concept from experimental framework to clinically viable precision orthodontic therapy.

In addition to biologic validation, future investigations should address polymer optimization, protein stabilization strategies, manufacturing reproducibility, sterilization protocols, and scalability of production. Emerging technologies such as nanoparticle-assisted delivery, stimuli-responsive polymers, and biosensor-integrated microneedle systems may further enhance dosing precision and therapeutic control. Such developments could facilitate the transition from proof-of-concept studies to clinically applicable precision bio-devices for orthodontic therapy.

Conclusion

Orthodontic tooth movement is fundamentally regulated by the RANK-RANKL-OPG axis, making targeted modulation of osteoclastogenesis an attractive strategy for controlled acceleration. Existing surgical, pharmacologic, and physical approaches provide partial benefits but remain limited by invasiveness, lack of site specificity, and inconsistent biologic control. Microneedle-based delivery systems offer a minimally invasive platform capable of localized and programmable biomolecule administration within the oral environment. The proposed RANKL-functionalized dissolving microneedle patch represents a novel conceptual bridge between molecular orthodontics and precision bio-device engineering. By enabling site-specific enhancement of bone resorption, this strategy has the potential to improve the efficiency and predictability of orthodontic tooth movement. However, the concept remains theoretical and requires rigorous preclinical validation, dose optimization, and carefully designed clinical trials to establish safety and efficacy. With continued advances in biomaterials engineering, protein delivery systems, and osteoimmunology, microneedle-mediated biologic modulation represents a promising avenue for the development of precision orthodontic therapies. Realization of this concept will require multidisciplinary collaboration among orthodontists, biomaterial scientists, biomedical engineers, and regulatory experts to ensure safe and effective clinical translation.

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