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SPECIAL ISSUE: Oral Regenerative Medicine

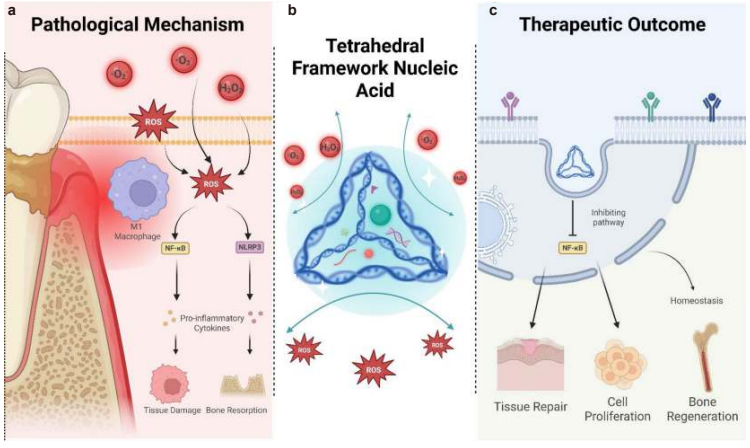
ROS-scavenging tetrahedral framework nucleic acids: reprogramming the pathological microenvironment for oral tissue regeneration

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ABSTRACT: The structural deterioration observed in maxillofacial skeletal conditions and associated mucosal tissues is fundamentally governed by a vicious cycle of sustained immunological activation and severe oxidative stress. Consequently, this continuous reactive oxygen species (ROS) accumulation directly fuels the etiology of debilitating diseases, notably bisphosphonate-related osteonecrosis of the jaw (BRONJ), oral submucous fibrosis (OSF), and periodontitis. Conventional therapeutic regimens often exhibit compromised localized efficacy or induce severe systemic adverse effects. To surmount these delivery impediments, tetrahedral framework nucleic acids (tFNAs) have emerged as versatile three-dimensional DNA nanostructure platforms. Characterized by high structural rigidity, intrinsic radical-scavenging bioactivity, rapid cellular internalization, and precise programmability, tFNAs enable the targeted co-delivery of regulatory oligonucleotides, small-molecule antioxidants, and bioactive peptides. This review evaluates how ROS modulate downstream oxidative stress and inflammatory networks to drive tissue destruction and bone metabolic imbalances. Furthermore, we examine structural optimization strategies, including the integration of tFNAs into hydrogel matrices, the incorporation of pH-responsive lysosomal escape elements, and the conjugation of targeting surface ligands. Preclinical evidence demonstrates that functionalized tFNAs networks effectively disrupt the self-amplifying oxidative stress-inflammation cascade, remodeling hostile microenvironments to promote structural tissue regeneration. To conclude, this review delineates major clinical translation hurdles, including industrial scale-up and pharmacokinetic elimination profiles. These considerations establish a conceptual baseline for engineering future targeted oxidative therapies.



KEYWORDS: tetrahedral framework nucleic acids, ROS scavenging, oral diseases, nanotherapeutics

1 Introduction

As an essential biological safeguard, the inflammatory response is activated upon exposure to detrimental factors like microbial invasion or cellular injury. Ultimately, this complex biological cascade strives to restore systemic homeostasis. Under physiological conditions, it eradicates localized infections, confines injury spread, and orchestrates tissue healing. However, when overactivated or unresolved, the inflammatory cascade shifts pathologically into an auto-destructive process. This prolonged state causes progressive tissue damage, clinically characterized by erythema, edema, calor, dolor, and loss of function[1,2]. While acute inflammation involves transient microvascular responses, a failure in resolution establishes chronic inflammation. Driven by persistent cellular dysfunction, metabolic stress, or immune abnormalities, chronic inflammation features pathological tissue remodeling and progressive fibrosis, culminating in organ dysfunction[3,4]. Accumulating evidence highlights this cascade as a pivotal pathogenic link bridging oral

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diseases such as periodontitis, maxillofacial bone pathologies including medication-related osteonecrosis of the jaw, and systemic skeletal disorders such as rheumatoid arthritis and osteoporosis. Furthermore, systemic low-grade inflammation drives widespread conditions like cardiovascular disease and type 2 diabetes mellitus, highlighting the profound interconnectivity between the oral cavity, skeletal structures, and systemic inflammatory networks[5–8].

Serving as pivotal signaling intermediates within these biological circuits, reactive oxygen species (ROS) are broadly classified into two categories. This diverse chemical family encompasses radical molecules, such as hydroxyl radicals (•OH) and superoxide anions (O_2•$^-$), alongside non-radical oxidants like singlet oxygen ($^1O_2$) and hydrogen peroxide (H_2O_2)[9]. ROS exert highly critically dose-dependent, dichotomous effects. At physiological concentrations, they act as indispensable secondary messengers by reversibly oxidizing target proteins, thereby modulating cell proliferation, differentiation, and immune defense. On the other hand, if the buildup of ROS surpasses the scavenging capacity of cellular antioxidant systems, profound oxidative stress ensues. Consequently, vital cellular macromolecules, such as DNA arrays, structural proteins, and lipid membranes, suffer permanent biochemical damage. Ultimately, this molecular deterioration promotes premature aging or necrotic cell death, acting as a fundamental mechanism underlying the etiology of numerous pathological conditions[10,11]. Crucially, a bidirectional feedback loop exists between inflammatory cascades and intracellular ROS. Physiologically, controlled ROS generation initiates host defense via the nuclear factor-kappa B (NF-κB) and nucleotide-binding oligomerization domain-like (NOD-like) receptor family pyrin domain-containing 3 (NLRP3) inflammasome pathways, while simultaneously activating the nuclear factor erythroid 2-related factor 2 (Nrf2) negative feedback axis to restrict hyper-inflammation. When these thresholds are breached, excessive ROS hyperactivate these cascades, amplifying the response. Simultaneously, stimulated inflammatory cells secrete massive amounts of ROS, which fundamentally degrade the adjacent structural scaffolding. By perpetuating this positive feedback cycle, these oxidative molecules critically drive the clinical worsening of various severe conditions, such as rheumatoid arthritis and periodontal disease[12–16].

Given this interdependency, targeted ROS clearance represents a promising therapeutic frontier. Current ROS-scavenging biomaterials predominantly fall into two categories. The first encompasses natural antioxidants particularly plant-derived polyphenols like curcumin and tannic acid, which neutralize free radicals, chelate transition metals, and actively upregulate the cytoprotective Nrf2/antioxidant response element (ARE) signaling axis[17,18]. The second category involves functional nucleic acid therapeutics, such as miRNAs and siRNAs. These molecules regulate oxidative stress by promoting antioxidant gene expression or silencing pro-inflammatory pathways.The second features functional nucleic acid therapeutics, such as miRNAs and siRNAs, designed to modulate the cellular oxidative stress network by driving endogenous antioxidant gene expression or silencing upstream pro-inflammatory pathways[19,20]. Compared with conventional pharmacotherapies, these ROS-scavenging strategies offer highly advantageous mechanisms. Traditional regimens rely heavily on non-steroidal anti-inflammatory drugs (NSAIDs) and synthetic glucocorticoids. While NSAIDs alleviate symptoms by inhibiting cyclooxygenase (COX) enzymes, chronic administration is inextricably linked to gastrointestinal mucosal ulceration, elevated cardiovascular risks, and hepatorenal toxicity[21]. Moreover, prolonged systemic usage of glucocorticoids inevitably induces profound metabolic disturbances including severe hyperglycemia, secondary osteoporosis, and extensive immunosuppression[22]. Consequently, targeted ROS-scavenging formulations bypass these severe systemic toxicities, achieving safer, highly localized inflammatory modulation. Despite their clinical promise, conventional ROS scavengers are hindered by poor tissue targeting, rapid physiological clearance, and exceedingly low systemic bioavailability[23].

To overcome these profound delivery barriers, advanced nanoscale delivery platforms have attracted intensive research interest. However, existing vehicles possess inherent limitations. Specifically, synthetic polymeric nanoparticles risk long-term tissue accumulation due to delayed degradation kinetics[24]; liposomal carriers frequently suffer from poor structural stability and rapid reticuloendothelial clearance[25-27]; and inorganic metallic nanoparticles face prevailing concerns regarding chronic systemic heavy metal toxicity[28]. In this highly challenging landscape, tetrahedral framework nucleic acids (tFNAs) have emerged as a uniquely advantageous nanocarrier platform, addressing many limitation of existing delivery vehicles. Unlike the heterogeneous size distribution and stochastic drug encapsulation typical of liposomes and polymeric nanoparticles, tFNAs offer absolute structural uniformity and precise spatial programmability. The structure of tFNAs is created through the self-assembly of DNA into a defined geometric framework. Specifically, the architectural foundation of tFNAs relies on the autonomous geometric folding of synthetic genetic material these entities are composed of four single-stranded DNA sequences programmed to form a stable pyramid shape. They form highly uniform, structurally rigid tetrahedrons with precisely controllable nanoscale dimensions spanning 10 –15 nm and unparalleled spatial programmability[29,30]. The integration of tFNAs into anti-inflammatory therapeutics offers multiple distinct advantages. First, the structural framework possesses intrinsic ROS-scavenging properties, which directly decreases cellular anti-inflammatory effects by downregulating hyperactive NF-κB hyperactivation and cytokine networks[29,31]. Second, its compact nanoscale geometry, combined with well-defined structural rigidity, endows the platform with exceptional cellular uptake kinetics and deep tissue penetration capabilities[32,33]. Third, the unique geometric corners and hollow interior inherent to this tetrahedral framework facilitate exact, multiplexed functionalization. This allows researchers to easily attach therapeutic agents, homing receptors, or genetic payloads, enabling the delivery of multiple therapeutic components at once[34-37]. Finally, because tFNAs are constructed entirely from natural nucleotides, they exhibit absolute biocompatibility, predictable enzymatic biodegradability, and an exemplary biosafety profile[30,38]. Based on these combined attributes, functionalized tFNA delivery complexes have been successfully deployed in preclinical models of periodontitis, osteoporotic bone defects, and other inflammatory disorders, demonstrating profound efficacy in remodeling hostile oxidative microenvironments and driving functional tissue regeneration[39,40]. As an advanced, highly efficient delivery vehicle, tFNAs transport localized ROS scavengers to act synergistically with the host tissue bed, significantly elevating overall therapeutic outcomes and providing a highly versatile platform for clinical translation and stomatological medicine.

Therefore, the current manuscript seeks to critically analyze how

ROS govern the initiation and exacerbation of prominent craniomaxillofacial disorders. Specifically, we focus on mucosal and osseous afflictions like apical lesions, marginal periodontal destruction, and submucosal fibrotic changes. Furthermore, this article explores the mechanistic bridges connecting these localized oxidative processes to broader systemic complications, notably highlighting joint degeneration, intestinal inflammation, skeletal fragility, and cardiac dysfunction. We focus explicitly on how ROS specifically mediate downstream oxidative stress and inflammatory cascades to drive progressive tissue destruction and bone metabolic imbalances. Furthermore, this manuscript critically analyzes contemporary engineering approaches alongside clinical translation progress concerning the application of tetrahedral DNA vehicles. Our primary focus lies in how these specific structures can maximize site-specific oxidative radical scavenging. Ultimately, this detailed exploration establishes a solid conceptual framework to inspire future advanced redox-modulating pharmacological agents (Fig. 1a-c).

2 Biological characteristics and signaling regulatory networks of ROS

ROS dictate cellular fate in the oral cavity, where physiological levels orchestrate mucosal repair while pathological overproduction induces severe oxidative stress. Across major stomatological diseases, including periodontitis and maxillofacial osteonecrosis, excessive ROS hyperactivate core inflammatory networks, such as NF-κB, Mitogen-Activated Protein Kinase (MAPK) and disease-specific metabolic pathways to drive progressive tissue destruction. Compounding this intracellular damage, the harsh oral microenvironment features fluctuating acidity, salivary flushing, and dense pathogenic biofilms that severely degrade localized antioxidant buffering and restrict exogenous drug penetration. Consequently, persistent oxidative stress serves as the fundamental pathological driver of oral diseases, necessitating advanced delivery platforms to overcome these formidable microenvironmental clearance barriers (Fig. 2a-c).

2.1 Biological characteristics of ROS

As previously established, ROS are intermediate metabolites containing reactive oxygen atoms. Biochemically, scientists categorize this diverse oxidative family into two principal subsets. One classification involves highly reactive radical molecules, explicitly $O_2\bullet^-$ and •OH. The other classification contains non-radical reactive counterparts, predominantly $^1O_2$ and H_2O_2[11,41,42]. The kinetic profiles of these oxidative intermediates vary significantly, evidenced by superoxide dismutase swiftly converting the $O_2\bullet^-$ anion into H_2O_2[43,44]. Thanks to its stability, H_2O_2 freely passes through lipid bilayers, serving as a crucial messenger for communication between cells.[10,45,46] However, due to its fleeting existence, the •OH species inflicts devastating, non-targeted biochemical alterations upon critical biological polymers[47]. Finally, separate reactive entities, notably $^1O_2$ combined with alkoxy radicals, are chiefly responsible for executing pathogen clearance and initiating lipid degradation[48-51]. The stability of ROS is closely tied to the local microenvironment; for example, acidic conditions combined with free metal ions catalyze Fenton and Haber-Weiss reactions, generating large quantities of •OH[52–56].

The generation of ROS within cells originates from external environmental triggers alongside internal physiological processes. Internally, these oxidative molecules are primarily produced through premature electron escape along the mitochondrial respiratory pathway, coupled with the enzymatic functions of NADPH oxidases (NOX)[57,58]. Exogenous induction occurs through exposure to ionizing radiation, ultraviolet light, environmental toxins, and specific chemotherapeutic agents[60-63]. During normal biological homeostasis, low-level ROS serves essentially as crucial intracellular signaling molecules. They regulate essential signaling cascades, including MAPK/extracellular signal-regulated kinase (ERK) and NF-κB, to mediate cell cycle progression and tissue

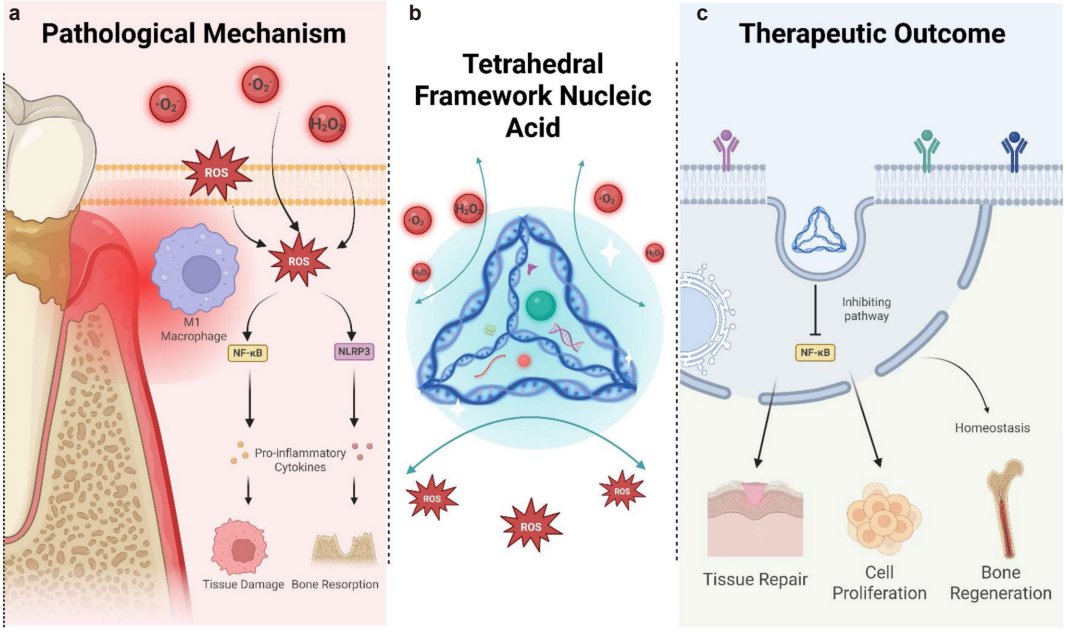


Figure 1 An overall summary of this review. (a) Oral pathogens trigger macrophage ROS overproduction; (b) Rigid, biocompatible tFNAs act as an active radical-scavenging platform and a versatile nanocarrier for multi-drug co-delivery; (c) Intracellular delivery of tFNAs suppresses hyperactivated inflammatory signaling, driving soft-tissue repair and bone regeneration. Created by BioRender.com.

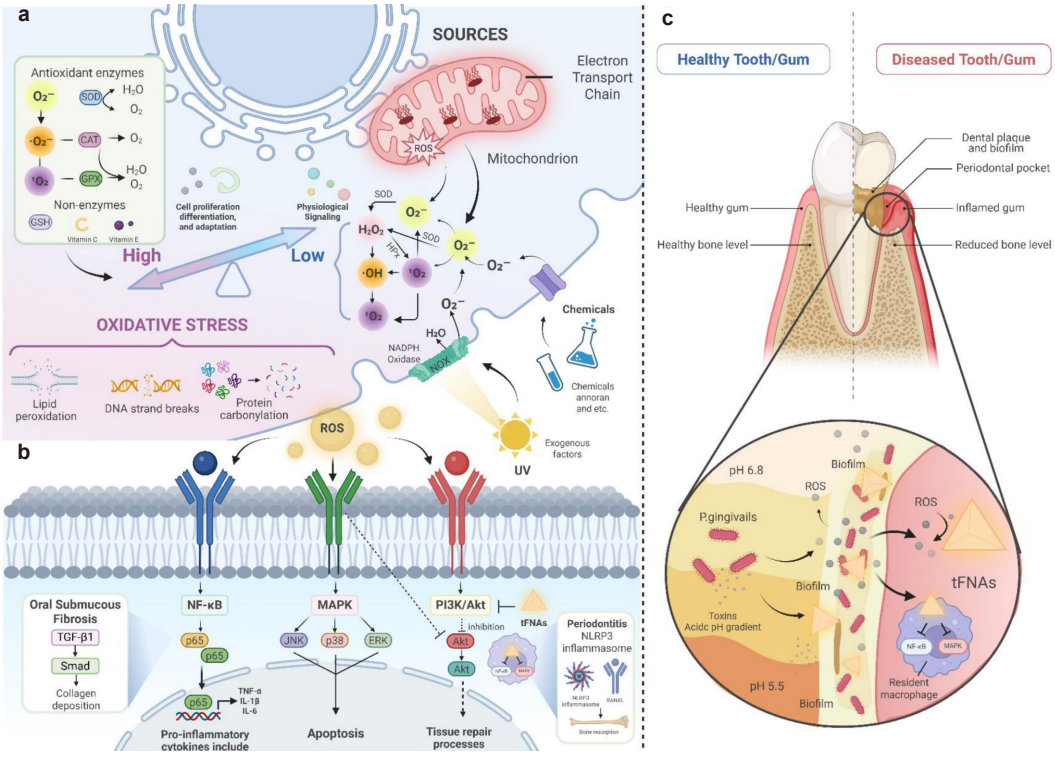


Figure 2 Schematic illustration of the biological characteristics, signal regulation networks, and microenvironmental factors of ROS in oral diseases, alongside the therapeutic mechanism of tFNAs. (a) Endogenous and exogenous sources of ROS balanced against cellular antioxidant systems; (b) Pathological oxidative stress triggers downstream fibrotic, pro-inflammatory, apoptotic, and repair signaling cascades; (c) The hostile periodontitis pocket microenvironment marked by pathogenic biofilms, fluctuating acidity, and structural tFNA-mediated therapeutic intervention. Created by BioRender.com.

regeneration[1,64,65]. Furthermore, controlled ROS production is required for mitochondrial mitophagy and phagocyte-mediated pathogen clearance[59,65-67], while also maintaining the baseline expression of cytoprotective genes via transcription factors like Nrf2[68,69].

However, a state of profound oxidative stress is triggered if the generation of ROS overwhelms the innate scavenging abilities of intracellular antioxidant networks[70]. This pathological accumulation causes direct damage to biomacromolecules, leading to protein carbonylation, lipid peroxidation, and DNA mutagenesis, such as the formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG) adducts[71-73]. Indirectly, sustained ROS levels activate inflammatory transcription factors including Activator Protein 1 (AP-1) and NF-κB[64]. This activation induces the secretion of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), which subsequently promote cellular apoptosis and necrosis[74-77]. Consequently, a positive feedback loop is established where mitochondrial damage causes further ROS leakage. Such disrupted oxidation-reduction equilibrium acts as a universal underlying mechanism propelling numerous persistent clinical diseases. Specifically, this systemic imbalance heavily contributes to the progression of neural degeneration, heart-related pathologies, severe metabolic dysfunctions, and diverse oncological formations[74,78-81].

To effectively neutralize the cellular damage induced by ROS, biological systems deploy a robust internal redox network. This vital protective machinery intrinsically relies on specialized catalytic proteins operating in tandem with various small-molecule radical-quenching compounds[82,83]. The enzymatic defense includes superoxide dismutase (SOD) for $O_2^{\bullet-}$ disproportionation[84], catalase (CAT) for H_2O_2 decomposition[85], and the glutathione peroxidase (GPX) and peroxiredoxin (Prx) families for reducing organic peroxides[86,87]. These molecules intercept free radicals and terminate lipid peroxidation chain reactions. Together, these spatially compartmentalized networks maintain cellular redox homeostasis, ensuring a physiological balance between signal transduction and cytoprotection.

2.2 Regulatory networks of ROS in oral diseases

ROS serve as central upstream pathological signals in stomatological and maxillofacial pathologies, including mucosal inflammatory disorders, progressive fibrotic syndromes, osteolytic skeletal lesions, and perioral cutaneous defects. These molecules modulate downstream signaling networks centered on three primary cellular axes, which comprise persistent pro-inflammatory transcription, metabolic dysregulation, and accelerated apoptotic cell death[70,88-91].

2.2.1 Common regulatory mechanisms

Across various oral diseases, pathological ROS accumulation activates three signaling pathways, namely the canonical NF-κB cascade, the MAPK network (comprising ERK, c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (p38)), and the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) survival axis[92-94]. Within this shared molecular framework, the canonical NF-κB pathway mediates the local inflammatory response[95], the MAPK network governs secondary pro-inflammatory amplification and stress-induced apoptosis[96], and the PI3K/Akt axis regulates cell survival, matrix synthesis, and tissue repair kinetics[97]. Together,

these interconnected pathways establish the mechanistic foundation through which ROS mediate localized oral tissue destruction[98].

Mechanistically, elevated ROS levels promote the degradation of cytosolic Inhibitor of nuclear factor kappa-B (IκB) inhibitors, facilitating the nuclear translocation of the NF-κB p65 subunit. This translocation upregulates the transcription of pro-inflammatory cytokines, primarily TNF-α, IL-1β, and IL-6, leading to sustained leukocyte infiltration. This transcriptional mechanism contributes to the pathogenesis of chronic periodontitis, oral submucous fibrosis (OSF), bisphosphonate-related osteonecrosis of the jaw (BRONJ), radiation-induced osteonecrosis of the jaw (RION), the tumor-promoting inflammatory microenvironment of oral squamous cell carcinoma (OSCC), and non-healing mucosal wounds[93,99]. Concurrently, sustained oxidative stress activates the pro-apoptotic JNK and p38 MAPK cascades[100]. This shifts the balance of the Bcl-2 protein family by upregulating pro-apoptotic effectors, such as Bax and cleaved Caspase-3, while downregulating anti-apoptotic proteins, including Bcl-2 and Bcl-xL. This imbalance induces apoptosis across various vital cell populations, including gingival fibroblasts, epithelial cells, and osteoblasts, thereby impairing localized regenerative capacity.Furthermore, while transient, physiological ROS levels activate the PI3K/Akt network to support cell survival, proliferation, and osteogenic differentiation, pathological ROS accumulation suppresses this pathway. This inhibition increases cellular apoptosis and impairs periodontal regeneration, alveolar bone remodeling, and mucosal wound closure[101-103]. Consequently, despite differing clinical etiologies, ranging from chronic mucosal defects to ROS-driven malignancies like OSCC, various oral diseases share a reliance on this upstream signaling network. Their molecular targets consistently center on pro-inflammatory factors, apoptotic effectors, and matrix remodeling enzymes, such as Type I collagen and matrix metalloproteinases (MMPs)[92,98].

While the distinct pathological characteristics of each disease dictate specific downstream target molecules, these conditions remain unified by their coordinated response to this shared upstream signaling network.

2.2.2 Disease-specific regulatory mechanisms

Beyond activating universal inflammatory cascades, ROS accelerate periodontal destruction through targeted mechanisms. Pathogens such as P. gingivalis suppress the host Kelch-like ECH-associated protein 1/nuclear factor erythroid 2-related factor 2 (Keap1/Nrf2) (Keap1/Nrf2) antioxidant axis and evade NADPH oxidase 2 (NOX2) -derived ROS, thereby sustaining chronic infection[104,105]. Furthermore, ROS-induced mitochondrial damage causes mitochondrial DNA (mtDNA) leakage into the cytoplasm, activating the cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) pathway. This alters the receptor activator of nuclear factor-κB ligand ((RANKL) to osteoprotegerin (OPG) ratio, promoting osteoclastogenesis. Concurrently, the buildup of mitochondrial oxidative radicals initiates the functional activation of the NLRP3 complex. Consequently, local cells excessively secrete potent proinflammatory mediators, specifically IL-1β alongside interleukin-18 (IL-18). This molecular molecular cascade directly compounds the severity of localized mucosal deterioration and drives rampant bone resorption[105-108].

In OSF, ROS dysregulate collagen metabolism primarily via the transforming growth factor-β1 (TGF-β1)/Smad signaling axis[109]. Elevated intracellular ROS stimulate mucosal fibroblasts to secrete TGF-β1, which phosphorylates Smad2/3 to drive the transcription and deposition of Type I and III collagen[110-111]. Additionally, ROS inhibit interstitial collagenase activity and upregulate tissue inhibitor of metalloproteinases 1(TIMP-1), preventing matrix degradation[112]. ROS also activate the JNK/activating transcription factor 2 (ATF2)/c-Jun network, establishing a positive feedback loop for TGF-β1 transcription that acts synergistically with NF-κB to sustain fibrotic progression[111,113-115].

In debilitating oral and maxillofacial skeletal pathologies, including BRONJ and critical-sized periodontal bone defects, ROS regulation is dictated by a bidirectional breakdown of mitochondrial redox hubs coupled with severe osteoclast-osteoblast uncoupling. Crucially, the ultimate cellular sources of ROS and their corresponding downstream cascades differ profoundly depending on the specific clinical background[88]. In skeletal pathologies like BRONJ, nitrogen-containing bisphosphonates block the mevalonate pathway, leading to intracellular ROS accumulation. This ROS buildup suppresses the ERK1/2 pathway, inducing cell cycle arrest in endothelial cells and keratinocytes. It also inhibits the sirtuin 1 (SIRT1)/peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) axis, causing mitochondrial collapse and apoptosis via Caspase-3 activation[6,106,116]. Conversely, in aggressive periodontal bone defects, ROS generation is frequently driven by the dendritic cell-associated C-type lectin 2 (Dectin-2)/spleen tyrosine kinase (Syk)/NOX2 axis. The resulting ROS output activates MAPK networks (p38, JNK, ERK) to upregulate osteoclastogenic genes, including nuclear factor of activated T cells 1 (*NFATc1*), cathepsin K (*CTSK*), and *MMP-9*[117]. Secondary mitochondrial ROS leakage further activates cGAS-STING signaling, perpetuating osteolytic expansion[106].

In mucosal healing defects, such as diabetic oral trauma, the impairment of the Nrf2/heme oxygenase-1 (HO-1) pathway delays wound closure[118]. Targeted delivery of specific oligonucleotides, such as *microRNA-132* (*miR-132*), via DNA nanostructures restores Nrf2/HO-1 expression. This intervention neutralizes ROS, normalizes mitochondrial ultrastructure, suppresses inflammatory cytokines, and promotes angiogenesis and collagen deposition[119].

In summary, across various stomatological and maxillofacial diseases, ROS function as central molecular regulators. While they engage conserved transcription networks, they execute distinct, tissue-specific morphological changes. This mechanistic understanding provides a foundational framework for designing targeted nanomaterial therapies.

2.3 Effects of the oral microenvironment on ROS regulation

The complex oral microenvironment dictates the fundamental equilibrium between ROS generation and clearance[120,121]. Pathogens like P. gingivalis secrete butyric acid and hydrogen sulfide, actively inhibiting host antioxidant enzymes[122,123]. Additionally, salivary flushing limits the retention of exogenous antioxidants, inflammatory acidity (pH 5.5–6.8) impairs CAT and GPX activities[124], and dense extracellular biofilms physically restrict scavenger penetration[125,126]. Conventional clinical regimens relying on mechanical debridement combined with systemic or localized antibiotic administration successfully reduce absolute microbial loads but fail entirely to restore local redox homeostasis Consequently, underlying tissue destruction frequently progresses unabated.

In direct contrast, advanced self-assembled nanoscale delivery platforms exemplified by tFNAs, provide an exceptionally elegant engineering solution capable of systematically surmounting these dual host and microenvironmental clearance barriers. Combining a exceptionally rigid, remarkably highly compact nanoscale geometry with dense, highly accessible multivalent surface functionalization sites, tFNAs directly quench excessive localized ROS pools while simultaneously delivering therapeutic payloads to precisely modulate primary upstream transcription networks, including canonical NF-κB, MAPK, and the central PI3K/Akt survival axis[29,30]. An in-depth, rigorous comprehension of this highly dynamic, two-tiered regulatory paradigm combining intracellular signaling cascades with hostile external microenvironmental parameters establishes the mandatory theoretical foundation driving the advanced mechanical design and subsequent clinical translation of multifunctional tFNAs therapeutics[108,127].

3 Construction of ROS-scavenging materials using tFNAs as delivery vectors

tFNAs serve as nanoscale delivery platforms for ROS scavenging therapeutics due to their structural rigidity, biocompatibility, spatial editability, and biodegradability[29]. As a structural core, tFNAs enable the simultaneous attachment of various pharmacological agents. Specifically, researchers can easily load these architectural foundations with functional peptides, conventional pharmaceutical compounds, and therapeutic genetic sequences. This spatial integration allows for targeted tissue delivery and coordinated ROS scavenging, thereby improving localized cellular uptake and bioavailability within the oral microenvironment.

3.1 Advantages and functionalization strategies of tFNA-based delivery platforms

The successful assembly of tFNA-vehicles relies entirely upon the programmed folding of four unique nucleic acid polymers. This well-defined supramolecular structure emerges smoothly during a simple temperature-regulating step, where the components are heated simultaneously and then allowed to naturally equilibrate. These strands assemble via Watson-Crick base-pairing into a rigid three-dimensional tetrahedron with dimensions typically ranging from 10 to 20 nm[29,30]. Compared to conventional vectors such as liposomes or synthetic polymers, tFNAs exhibit favorable physicochemical stability, which helps maintain the structural integrity of sensitive ROS scavengers in mucosal and skeletal defects. Furthermore, researchers can customize incorporation methods by considering the specific electrostatic properties, lipid solubility, and physical size of the encapsulated agents. This personalized design ultimately maximizes the structural integrity of the therapeutics while enhancing their subsequent delivery into target cells[128-131].

The functional advantages of tFNAs carriers are primarily attributed to several intrinsic properties (Fig. 3a-b)[29]. First, because they are constructed from natural nucleotides, tFNAs demonstrate high biocompatibility and negligible immunogenicity. Host nucleases degrade the framework into non-toxic monomeric nucleotides that are readily metabolized or excreted, making the platform suitable for sustained delivery into sensitive oral mucosal layers and periodontal attachment sites[30,33]. Second, the tetrahedral geometry provides a rigid internal cavity and four distinct external vertices, enabling the concurrent loading of diverse therapeutics via

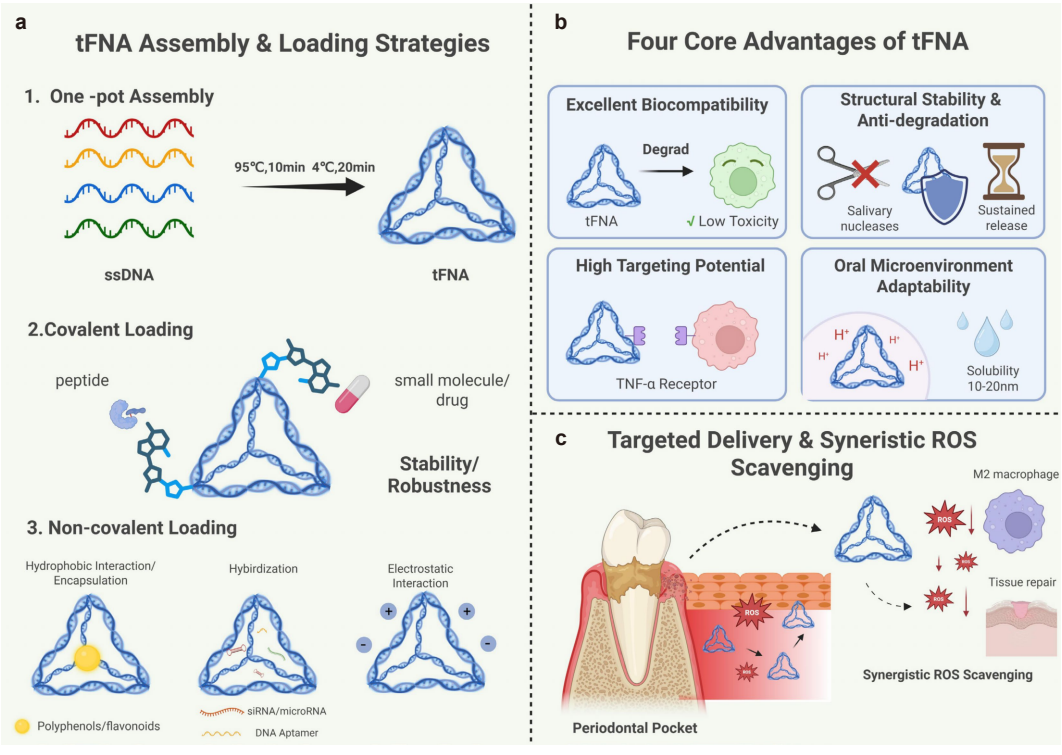


Figure 3 Schematic illustration of the assembly, cargo loading protocols, core advantages, and localized applications of tFNAs. (a) The one-pot thermal annealing process of constituent single-stranded DNA molecules alongside covalent surface immobilization and non-covalent payload strategies; (b) The four foundational biochemical parameters consisting of biocompatibility, anti-degradation stability, receptor-targeted capability, and microenvironmental adaptability; (c) Targeted intracellular delivery and mechanical free-radical clearance within infected periodontal pockets to promote tissue regeneration. Created by BioRender.com.

non-covalent partitioning or covalent conjugation. This spatial arrangement shields fragile payloads, such as unmodified siRNAs or polyphenols, from salivary nucleases and proteases while allowing controlled release into target tissues[34,132]. Third, the external vertices permit the stoichiometric conjugation of targeting ligands, including cell-penetrating peptides or DNA aptamers that recognize specific inflammatory markers like TNF-α. This targeting capability promotes the accumulation of ROS scavengers within periodontitis lesions, fibrotic zones, or skeletal defects, minimizing off-target distribution[133]. Finally, tFNAs nanocarriers maintain structural integrity within humid and acidic inflammatory zones, such as deep periodontal pockets, and their nanoscale dimensions facilitate navigation through dense mucosal subepithelial spaces and extracellular matrices[32,134,135]. Notably, the unfunctionalized tFNAs framework can intrinsically scavenge intracellular free radicals, providing a mechanical synergy with the encapsulated cargo[39].

To accommodate various types of cargo, tFNAs employ two primary functionalization strategies, namely covalent linkage and non-covalent assembly (Fig. 3a)[30].

Covalent loading involves coupling therapeutic agents to the tFNAs backbone via stable chemical bonds to prevent premature dissociation during transit, making it suitable for low-molecular-weight drugs, targeting ligands, and therapeutic peptides[136]. This surface immobilization can shield sensitive molecules from oral proteases and extend their functional half-life[137]. Optimizing these reaction parameters is necessary to ensure that chemical cross-linking does not distort the three-dimensional geometry of the tFNAs core or compromise the biological activity of the cargo[138].

Conversely, non-covalent loading relies on encapsulating payloads within the central cavity or along the charged external edges through hydrogen bonding, hydrophobic partitioning, electrostatic complexation, or base-stacking. This approach preserves the native structure of the cargo and is suitable for functional oligonucleotides and lipophilic polyphenols[137,139]. Hydrophobic compounds partition directly into the central cavity, whereas oligonucleotides hybridize with complementary single-stranded DNA extensions engineered into the primary tFNAs strands[17,19,130]. Additionally, the inherent anionic polarity of the nucleic acid framework permits spontaneous binding with various basic proteins and other positively ionized compounds through ionic attraction. Researchers can systematically design these physical attachments to break apart when exposed to distinct physiological triggers, particularly low pH conditions. Ultimately, this ensures on-demand delivery of the medicinal cargo precisely inside the intended cellular populations[140].

By utilizing these distinct functionalization capabilities, a single tFNAs platform can co-deliver multiple therapeutic modalities for synchronized release triggered by localized pathological stimuli, thereby enhancing therapeutic outcomes while minimizing systemic toxicity[139]. Consequently, customized tFNAs delivery networks represent a viable strategy for precision medicine applications in complex tissue microenvironments(Fig. 3c).

3.2 Classification and functions of ROS-scavenging materials delivered by tFNA carriers

Using tFNAs as a delivery platform enables the co-delivery of structurally diverse ROS-scavenging agents, integrating physical quenching mechanisms with upstream signaling pathways to achieve coordinated antioxidant therapy[141]. The characteristics and delivery applications of various materials are detailed below (Table 1).

Table 1 Existing tFNA-based ROS-scavenging materials.

Nanoconstruct	Therapeutic Payload	Loading Strategy/ Interaction Mode	Experimental Disease Model	Regulatory Mechanism	Therapeutic Outcomes	Advantages (+)	Disadvantages (−)
Tsi [142-144]	siRNA (targeting *RAGE/NF-κB/TLR4*)	Nucleic acid hybridization/base complementary pairing	Diabetic complications; Temporomandibular osteoarthritis (TMJOA); BRONJ	Downregulates RAGE/NF-κB pathway; inhibits NLRP3/Caspase-1 axis; modulates macrophage polarization.	Effectively silences target genes, reduces inflammatory cytokines, improves mitochondrial function, and promotes matrix regeneration.	(+) High silencing specificity; synergistic anti-inflammatory/antioxidant effects.	(−) Long-term stability and *in vivo* delivery efficiency require verification.
DNS/DNS@Cap [145]	siRNA targeting *Galectin-3*	Multipoint internal integration via base complementary pairing	Liver fibrosis/cirrhosis (*in vitro/in vivo*)	Silences Galectin-3; inhibits STAT1/NF-κB; upregulates Nrf2/HO-1; reduces M1 polarization.	Inhibits pro-inflammatory cytokines, significantly alleviates fibrosis, restores liver function, and reduces collagen deposition.	(+) First oral tFNA-siRNA complex; pH-responsive liver targeting.	(−) Needs continuous monitoring for systemic off-target effects.
siR-TDNbox [146]	siRNA targeting *Raptor*	Internal encapsulation/pH-responsive release ("nano box")	Cellular and systemic aging	Silences Raptor to inhibit mTORC1/S6 pathway; reduces senescence markers and SASP factors.	Reverses aging phenotype, downregulates aging proteins, prolongs lifespan (53.8%), and improves motor function.	(+) "Nano box" perfectly protects siRNA; synergistic anti-aging effects.	(−) Complex preparation; potential impact on mTORC2 needs evaluation.
TR21@TS [147]	*miR-21-5p*	Hybridization	Diabetic wounds	Inhibits NF-κB and activates Akt pathway.	Promotes M2 macrophage polarization, enhances angiogenesis, and accelerates healing.	(+) Multifunctional synergistic integration.	(−) Complex multi-component system; high cost and scaling challenges.

(To be continued on the next page)

(Continued)

Nanoconstruct	Therapeutic Payload	Loading Strategy/ Interaction Mode	Experimental Disease Model	Regulatory Mechanism	Therapeutic Outcomes	Advantages (+)	Disadvantages (−)
P-T-M/P-T-M@GMs [148]	*miR-34a-5p* inhibitor	Hybridization + chemical coupling	Fat-associated osteoarthritis	Activates AMPK/ACC pathway, regulates lipid metabolism, and inhibits ferroptosis.	Protects chondrocytes, maintains extracellular matrix balance, and reduces joint injury.	(+) Targeted lipid metabolism regulation.	(−) Long-term safety and degradation of GMs need further evaluation.
BiRDS [149]	*miR-150*	Encapsulation	Sepsis	Inhibits NF-κB and Notch1 pathways.	Reduces systemic inflammation, limits multi-organ injury, and improves survival rate.	(+) Stable structure, high loading, synergistic.	(−) Notch1's role in sepsis remains poorly understood.
Tm [150]	*miR-34a* inhibitor	Hybridization	Metabolic dysfunction-associated steatohepatitis (MASH)	Inhibits NF-κB and activates Nrf2/HO-1 pathway.	Reduces steatosis, fibrosis, and liver enzymes; promotes M2 anti-inflammatory macrophage polarization.	(+) Dual action on inflammation and oxidative stress.	(−) Hepatocyte impact and long-term safety require verification.
T-29b [132]	*miR-29b*	Hybridization	OSF	Inhibits TGF-β/Smad and activates Nrf2/HO-1 pathway.	Effectively reduces ROS in cells stimulated by TGF-β and arecoline.	(+) Offers new treatment possibilities for OSF.	(−) Impact on long-term cancer risk is unknown.
MiDs [151]	*miR-22*	Hybridization	Peripheral nerve injury	Activates ERK1/2 to regulate M2 polarization by inhibiting NF-κB and activating Nrf2.	Promotes Schwann cell proliferation, neuron regeneration, and facial nerve recovery.	(+) Simultaneously regulates two key microenvironment cells.	(−) Efficacy in severe nerve defects remains unverified.
T-miR3 [152]	*miR-124*	Three-vertex connection	Osteoarthritis (OA)	Inhibits NF-κB catabolic factors; promotes anabolic factors (Sox9, Col-II).	Inhibits chondrocyte apoptosis, smooths cartilage, and delays OA progression.	(+) Improved miRNA stability/uptake; enhanced therapeutic effect via three loci.	(−) Long-term *in vivo* safety lacks direct comparison.
Tapt-tFNA (TT)/MTT [133]	TNF-α aptamer+ methotrexate (MTX)	Covalent + electrostatic	Rheumatoid arthritis	Inhibits NF-κB and ERK signaling pathways.	Targets TNF-α, enhances MTX bioavailability, promotes M2 polarization, and reduces joint damage.	(+) Active targeting with synergistic immunomodulation.	(−) Complex system; potential MTX side effects.
tFNAs Ap MN (AP) [153]	IL-6 aptamer	Covalent linkage	Inflammatory wound healing	Inhibits IL-6 and downstream factors (TNF-α).	Binds IL-6, inhibits inflammation, promotes keratinocyte migration, and accelerates healing.	(+) Strong targeting and synergistic healing.	(−) Targets only IL-6 within a complex inflammatory network.
tFNA-Cur/Cur-tFNAs [40]	Curcumin	Groove binding	Postmenopausal osteoporosis; Acute gouty arthritis	Inhibits JNK (bone) and NF-κB (gout); regulates Nrf2 and apoptotic proteins.	Enhances Curcumin bioavailability, resists apoptosis, promotes bone repair, and inhibits inflammation.	(+) Improves stability and water solubility synergistically.	(−) Universality across different bone diseases is unverified.
tFNA-Que/TTQ [154–155]	Quercetin	Hole groove; Chemical crosslinking	Sepsis; Diabetic periodontitis	Inhibits ERK/NF-κB and upregulates Nrf2/HO-1.	Alleviates systemic inflammation/organ injury; reduces alveolar bone absorption.	(+) High antioxidant activity; mitochondria targeting.	(−) Chemical modification increases complexity.
tFNA-Resveratrol (TR) [134]	Resveratrol	Groove binding	Acute gouty arthritis	Activates p53/Bcl-2/Bax; inhibits NLRP3 and NF-κB.	Induces M1 apoptosis, inhibits pyroptosis, and rapidly relieves joint inflammation.	(+) Fast-acting synergistic anti-inflammatory action.	(−) Effects on normal cell apoptosis need monitoring.
tFNA@ Cep [156]	Cepharanthine	Groove binding	TMJOA	Inhibits cGAS-STING/NF-κB and promotes M2 polarization.	Relieves cartilage degeneration and protects subchondral bone.	(+) Synergistic immunomodulation.	(−) Precise TMJ mechanism requires more study.
TNC (tFNA-Nar) [157]	Naringin	Groove binding	Alveolar bone defect	Activates BMP/Runx2/Osx pathway.	Promotes BMSC proliferation/osteogenesis and repairs bone defects.	(+) Improves natural medicine bioavailability.	(−) Short animal observation time; long-term stability unverified.

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Nanoconstruct	Therapeutic Payload	Loading Strategy/ Interaction Mode	Experimental Disease Model	Regulatory Mechanism	Therapeutic Outcomes	Advantages (+)	Disadvantages (−)
TMC (tFNA-Met) [158]	Metformin	Electrostatic adsorption/Groove binding	Diabetic periodontitis	Activates AMPK to inhibit NF-κB and NLRP3.	Inhibits periodontal inflammation, collagen degradation, and osteoclast formation.	(+) Synergistic metabolic and inflammatory regulation.	(−) Systemic administration risks side effects.
TK-VLA@TAT [159]	Atorvastatin (AT)	Click chemistry+ physical coating	Atherosclerosis	AT lowers lipids; tFNA activates Nrf2/HO-1 to inhibit NF-κB/iNOS.	Inhibits macrophage frothing, targets plaques, and increases fiber cap thickness.	(+) Active targeting with ROS-responsive release; improved pharmacokinetics.	(−) Complex preparation; long-term metabolism unevaluated.
Pt [160]	Pirfenidone (PFD)	groove binding	Idiopathic pulmonary fibrosis (IPF)	Inhibits TGF-β1/Smad2/3 (EMT) and NLRP3/NOX4; activates HO-1.	Inhibits fibroblast activation and improves lung function via low-dose atomization.	(+) Tracheal atomization lowers systemic toxicity and required dose.	(−) Device clinical standardization needed.
APTB [161]	Baicalin + ACPGP targeting peptide	Covalently linked + minor groove binding	Sepsis	Targets inflammatory sites via neutrophils; promotes M2 polarization and downregulates IL-6/IL-1β.	Improves survival rate (95%) and reduces organ damage by regulating neutrophils.	(+) "Hitchhiking" neutrophil targeting prolongs half-life.	(−) Complex multi-step preparation.
tFNA-P [162]	Polydatin (P)	groove binding	Kidney stones	Inhibits ferroptosis: reduces lipid peroxidation, maintains GSH, restores GPX4/FSP1.	Reduces calcium oxalate deposition, protects renal tubules, and restores cell viability.	(+) First use targeting ferroptosis for calculi; increased bioavailability.	(−) Focuses heavily on ferroptosis over other antioxidant paths.
tFNA @Rapa [163]	Rapamycin (Rapa)	Groove binding/hydrophobicity	Senile osteoporosis/bone aging	Inhibits cGAS-STING pathway by restoring mitochondria and preventing mtDNA leakage.	Reverses BMSC aging, promotes bone regeneration, and improves microarchitecture.	(+) Effectively targets inflammatory aging.	(−) Lacks evaluation on other interconnected aging pathways.
TLA [164]	Lipoic acid (LA)	groove binding	Skin light injury (UVB)	Clears ROS, inhibits MAPK/NF-κB, and promotes Bcl-2 and collagen synthesis.	Reduces erythema/scabs and restores collagen via transdermal delivery.	(+) Solves LA water solubility; good skin penetration.	(−) Deep tissue penetration and long-term safety need verification.
tFNA-GL13K/HAMA hydrogel[165]	Antimicrobial peptide (GL13K)	Electrostatic adsorption	Wound healing after infection	Inhibits inflammatory factors (IL-1β, TNF-α, IL-6).	Broad-spectrum antibacterial, promotes wet healing, and reduces scars.	(+) Hydrogel suits wet healing; combines antibacterial/anti-inflammatory.	(−) AMP stability requires improvement.
Cur-de-tFNA[166]	Curcumin + defensin	Covalent linkage + groove binding	Periodontitis	Clears ROS, inhibits TLR4/NF-κB, and upregulates osteogenic proteins.	Strong bactericidal action, reduces bone absorption, and promotes regeneration.	(+) Triple function integration; safe natural degradation.	(−) Dual-drug loading complicates quality control.
B/L [167]	*miR-146a* + Levofloxacin (Lev)	Multipoint connection/electrostatic	Infected wound	Targets TRAF6/IRAK1 to inhibit NF-κB; clears ROS.	Antibacterial action; accelerates epithelialization and collagen deposition.	(+) Transdermal delivery avoids systemic side effects; simultaneous dual delivery.	(−) Complex structure complicates preparation.
S-T-N composite hydrogel [168]	*miR-455-3p* +CeO_2 nanoenzyme	Physical encapsulation/co-delivery	Meniscus tear	CeO_2 clears ROS; miRNA promotes SMSC fibrocartilage differentiation.	Protects articular cartilage, repairs meniscus tear, and delays osteoarthritis.	(+) Triple function (repair, immunity, gene therapy).	(−) Extremely complex system; long-term metabolism unstudied.
Cu-Tsi@Gel [169]	Cu^{2+} ion/Cu^{+} ion + *TNF-α* siRNA	Biomineralization /electrostatic + hydrogel	Infectious wound	Dual ROS regulation: pro-oxidant in bacteria (Fenton), antioxidant in host cells.	Efficient sterilization (MRSA), accelerates healing, and promotes angiogenesis.	(+) Innovative differential ROS regulation.	(−) Multi-component complexity; long-term safety unverified.

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Nanoconstruct	Therapeutic Payload	Loading Strategy/ Interaction Mode	Experimental Disease Model	Regulatory Mechanism	Therapeutic Outcomes	Advantages (+)	Disadvantages (−)
APT [170]	Modified AC PGP targeting peptide	Covalent linkage	Sepsis	Targets CXCR2 on neutrophils, inhibiting NOX2/iNOS/MPO oxidative burst.	Reduces neutrophil excessive migration and multiple organ damage.	(+) Direct neutrophil regulation; prolongs half-life via "free riding".	(−) Lacks additional therapeutic drug loading.
Ha-β 3TC hydrogel [171]	Curcumin+ anti-TGF-β1 peptide	Covalently linked +Groove binding	Skin wound healing	Early: inhibits NF-κB. Late: peptide captures TGF-β1 to activate Smad2/3.	Sequential regulation of inflammation and regeneration; reduces scar formation.	(+) Sequential immunity-regeneration strategy; high TGF-β1 capture.	(−) Very complex system preparation.

Abbreviations: **RAGE**, receptor for advanced glycation endproducts; **TLR4**, Toll-like receptor 4; **STAT1**, signal transducer and activator of transcription 1; **Raptor**, regulatory-associated protein of mTOR; **mTORC1**, mechanistic target of rapamycin complex 1; **S6**, ribosomal protein S6; **SASP**, senescence-associated secretory phenotype; **AMPK**, AMP-activated protein kinase; **ACC**, acetyl-CoA carboxylase; **BMP**, bone morphogenetic protein; **Runx2**, runt-related transcription factor 2; **Osx**, osterix; **iNOS**, inducible nitric oxide synthase; **GSH**, glutathione; **FSP1**, ferroptosis suppressor protein 1; **TRAF6**, TNF receptor-associated factor 6; **IRAK**, interleukin-1 receptor-associated kinase; **SMSC**, synovial mesenchymal stem cell; **CXCR2**, C-X-C motif chemokine receptor 2; **MPO**, myeloperoxidase.

3.2.1 *Oligonucleotide materials*

Therapeutic oligonucleotides, including regulatory miRNAs, gene-silencing siRNAs, and single-stranded DNA aptamers, represent a major class of payloads deployed on tFNAs platforms. These molecules modulate upstream signaling networks governing cellular redox homeostasis, complementing the intrinsic ROS-scavenging capabilities of the tFNAs backbone[19,39,133,142].

MicroRNAs (miRNAs) are endogenous, non-coding single-stranded RNAs that regulate oxidative stress equilibrium by binding to the 3'-untranslated regions (3'-UTRs) of target mRNAs involved in ROS synthesis and antioxidant defense[172]. When hybridized to tFNAs structural extensions, these fragile RNA backbones are protected against rapid enzymatic cleavage by systemic and salivary nucleases[29]. For example, a tFNAs complex loaded with *miRNA-200c* (*miR-200c*), termed T-200c, targets periodontal ligament stem cells (PDLSCs) within periodontitis lesions. Upon endocytosis, the delivered *miR-200c* silences Myeloid Differentiation Primary Response 88 (*MyD88*) transcripts, thereby inhibiting the MyD88/NF-κB signaling cascade, suppressing pro-inflammatory cytokine secretion, and preventing secondary intracellular ROS accumulation. Simultaneously, this engineered formulation stimulates the Akt/β-Catenin cellular preservation signaling cascade. As a result, the overall survivability and redox defense mechanisms of PDLSCs are significantly improved. Ultimately, these combined cellular responses drive the comprehensive restoration of both gingival architectures and the surrounding maxillofacial skeletal defects[130]. Similarly, in OSF, a tFNAs vector functionalized with *miR-29b*, designated T-29b suppresses the TGF-β1/Smad signaling axis in mucosal fibroblasts while upregulating the endogenous Nrf2/HO-1 network, neutralizing intracellular ROS and reducing pathological Type I collagen overproduction[132].

Small interfering RNAs (siRNAs) utilize the endogenous RNA interference (RNAi) machinery to achieve sequence-specific translational silencing of genes governing ROS synthesis, such as *NF-κB* p65, *NOX1*, and *NOX4*, thereby arresting pathological ROS generation at the transcriptional level[173]. The tFNAs core facilitates intracellular transport directly into the cytoplasm, which increases intracellular bioavailability and limits non-specific systemic off-target effects[174]. In models of diabetic microvascular complications and temporomandibular joint osteoarthritis, tFNAs loaded with siRNAs targeting the receptor for advanced glycation endproducts (RAGE) or the NF-κB p65 subunit downregulate these pro-inflammatory pathways and reduce ROS-induced cytokines. This action works in coordination with the native tFNAs core, which stimulates the Nrf2/HO-1 pathway and preserves mitochondrial integrity (Fig. 4a-c)[142-143]. Furthermore, in BRONJ models, tFNAs carrying siRNAs against Toll-Like Receptor 4 (*TLR4*) silence TLR4 expression in infiltrating M1 macrophages. This down-regulation prevents TLR4-mediated mitochondrial collapse and secondary mitochondrial ROS (mtROS) generation by restoring the expression of inner mitochondrial membrane fusion proteins (Mfn1/Mfn2) and respiratory chain complexes. This genetic intervention promotes the polarization of infiltrating macrophages from the M1 phenotype toward the M2 phenotype, reducing oxidative stress and skeletal necrosis[144].

Single-stranded DNA aptamers, developed via the Systematic Evolution of Ligands by Exponential Enrichment (SELEX) process, fold into specific three-dimensional structures that bind target proteins with high affinity and specificity. For example, aptamers targeting the TNF-α protein can be integrated into tFNAs to neutralize pro-inflammatory cytokines (Fig. 4d-f)[133,175-177]. Integrating aptamers into the tFNAs framework creates dual-function delivery platforms capable of simultaneous tissue targeting and ROS clearance. Surface-displayed aptamers drive the concentration of the nanocarrier into target tissues via molecular recognition, while the central tFNAs core addresses underlying oxidative stress[133]. For instance, a tFNAs delivery vehicle functionalized with BACE1-targeting aptamers has been developed to cross the blood-brain barrier and target amyloid-beta (Aβ) plaques in Alzheimer's disease models. The displayed aptamers inhibit β-site amyloid precursor protein cleaving enzyme 1 (BACE1) enzymatic cleavage activity to halt pathological Aβ synthesis, while the tFNA core neutralizes localized ROS pools within surrounding neuronal networks, preventing ROS-induced apoptotic cascades (Fig. 5a-c)[178-180].

3.2.2 *Small-molecule drugs*

Low-molecular-weight antioxidant agents, primarily plant-derived polyphenols and flavonoids, exhibit direct free-radical quenching activity. Although these compounds are widely available and possess significant intrinsic ROS-scavenging capacities, their clinical application is often limited by hydrophobicity, rapid physiological

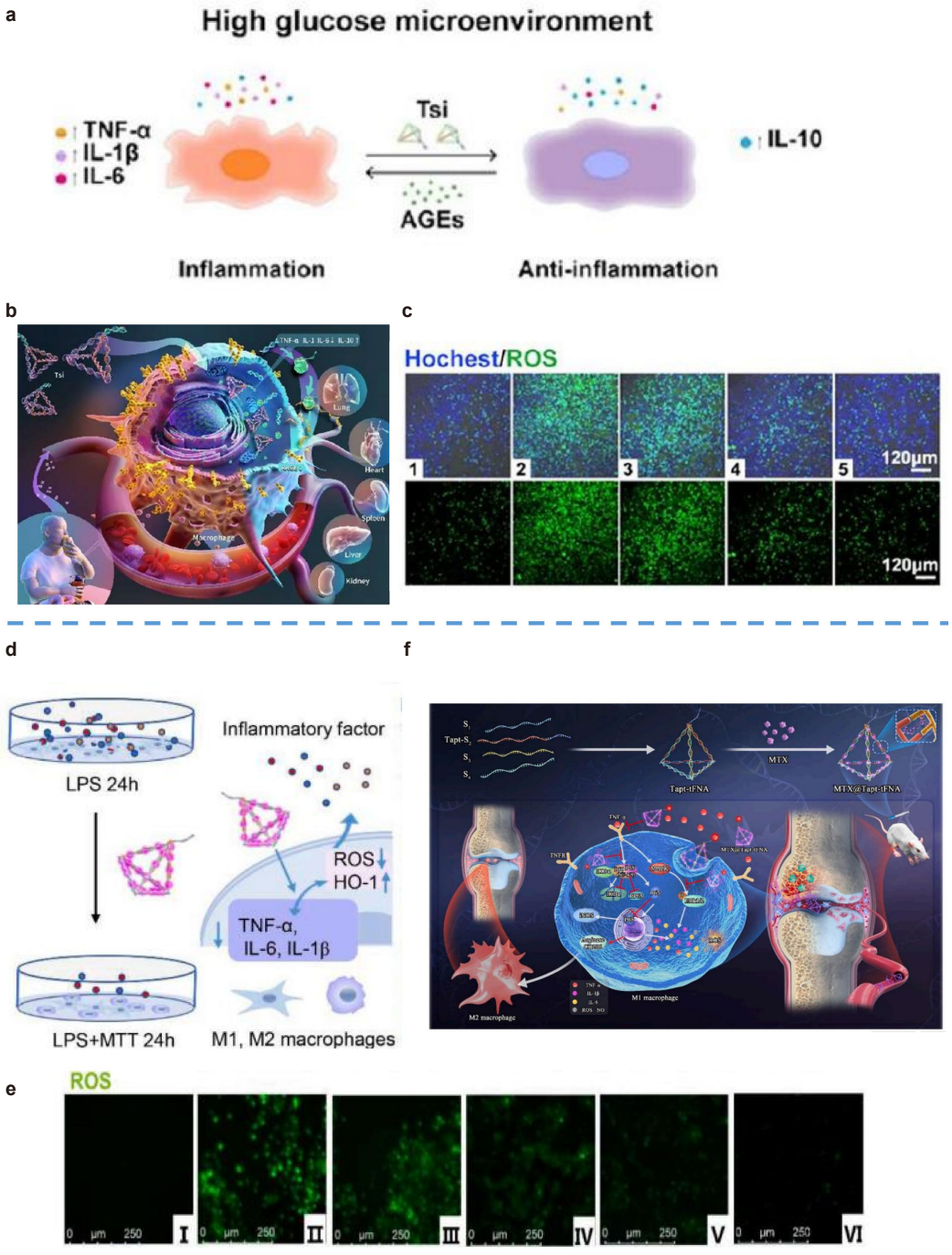


Figure 4 Drug loading profiles of tFNAs, including siRNA, DNA aptamer, and small-molecule drugs. Tetrahedral Framework Nucleic Acids Based Small Interfering RNA Targeting Receptor for Advanced Glycation End Products for Diabetic Complications Treatment. (a) Schematic diagram illustrating the protective effect of Tsi against AGEs-induced inflammation in macrophages; (b) Graphic illustration of this study; (c)Fluorescence microscopy assay detected the ROS level after different treatments[140] (blue: nuclei; green: ROS. Scale bar = 120 μm). Copyright 2023, ACS Nano. Targeted therapy for autoimmune diseases based on multifunctional frame nucleic acid system: Blocking TNF-α-NF-κB signaling and mediating macrophage polarization. (d) Schematic illustration of MTX@Tapt-tFNAs suppressed LPS-induced inflammation; (e) Immunofluorescence images of ROS in RAW264.7 cells after different treatment for 24 h. (ROS: green). Scale bars are 200 μm; (f) MTX@Tapt-tFNAs was developed to combine the dual roles of MTX and TNF-α-targeted DNA aptamer for the targeted therapy of rheumatoid arthritis[126]. Copyright 2023, Chemical Engineering Journal.

oxidation, and low bioavailability. Encapsulating these small molecules within tFNAs structures successfully resolves these limitations, improving their aqueous solubility, stability, and localized delivery[17,181–182].

Plant-derived phenolic molecules, namely tannic acid, resveratrol, and curcumin, possess abundant hydroxyl moieties capable of quenching reactive oxidative species via the donation of individual electrons or hydrogen atoms. Furthermore, these natural biochemicals function as powerful stimulants for internal cellular defense mechanisms. Specifically, they upregulate the Nrf2/HO-1 signaling cascade to induce the biological synthesis of native radical-scavenging proteins[183]. The stable core of the tFNAs framework

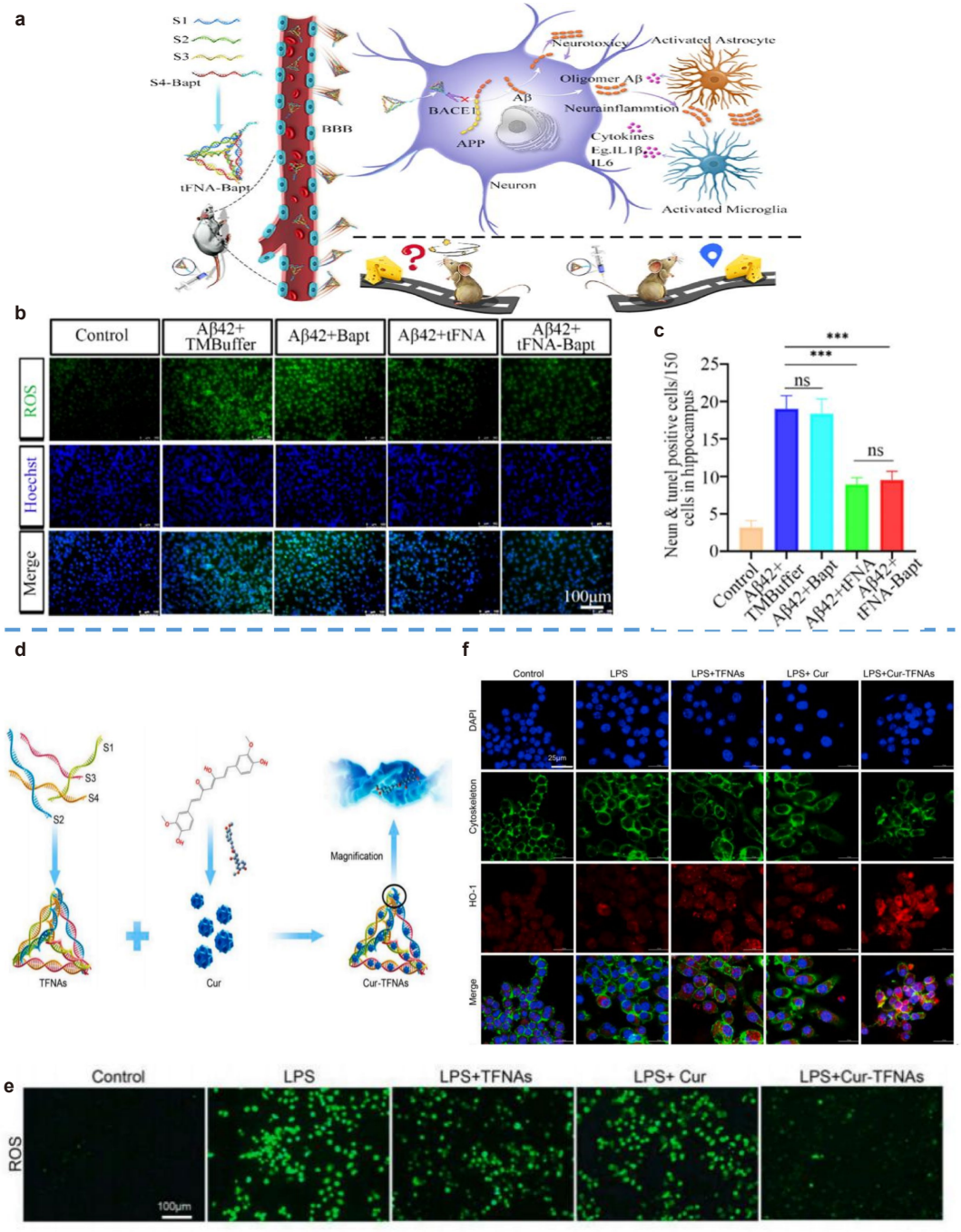


Figure 5 Drug loading profiles of tFNAs, including siRNA, DNA aptamer, and small-molecule drugs. BACE1 Aptamer-Modified Tetrahedral Framework Nucleic Acid to Treat Alzheimer's Disease in an APP-PS1 Animal Model. (a) Graphic illustration of this study; (b) Fluorescence image of ROS in SH-SY5Y cells;(c) Statistics of the mean fluorescence intensity of ROS in SH-SY5Y. n = 4. *p < 0.05; **p < 0.01; ns = no significance[146]. Copyright 2022, ACS Applied Materials & Interfaces. Anti-inflammatory activity of curcumin-loaded tetrahedral framework nucleic acids on acute gouty arthritis. (d) A structure diagram showing the composition of Cur-TFNAs; (e) Immunofluorescence images of ROS in RAW264.7 cells (ROS: green). Scale bars are 100 μm; (f) Immunofluorescence micrographs of LPS-treated RAW264.7 cells[15] (cytoskeleton: green; nucleus: blue; HO-1: red). Scale bars = 25 μm. Copyright 2022, Bioactive Materials.

shields these hydrophobic molecules from premature physiological oxidation or enzymatic degradation within mucosal fluids. For example, tFNAs encapsulate curcumin within their internal cavities via hydrophobic partitioning and electrostatic adsorption. This formulation facilitates the sustained localized accumulation of curcumin directly into the inflamed joint spaces of acute gouty arthritis models. Once internalized, the complex undergoes controlled intracellular payload release, directly quenching ROS while concurrently suppressing upstream pro-inflammatory transcription networks (Fig. 5d-f)[17]. Similarly, non-covalent loading of resveratrol into the tFNAs framework increases its aqueous stability and physiological half-life, allowing it to clear free radicals and inhibit pro-inflammatory cytokine release within inflamed lesions (Fig. 6a-c)[134].

Plant-based flavonoid structures, particularly quercetin combined with naringin, control reactive radical accumulation via

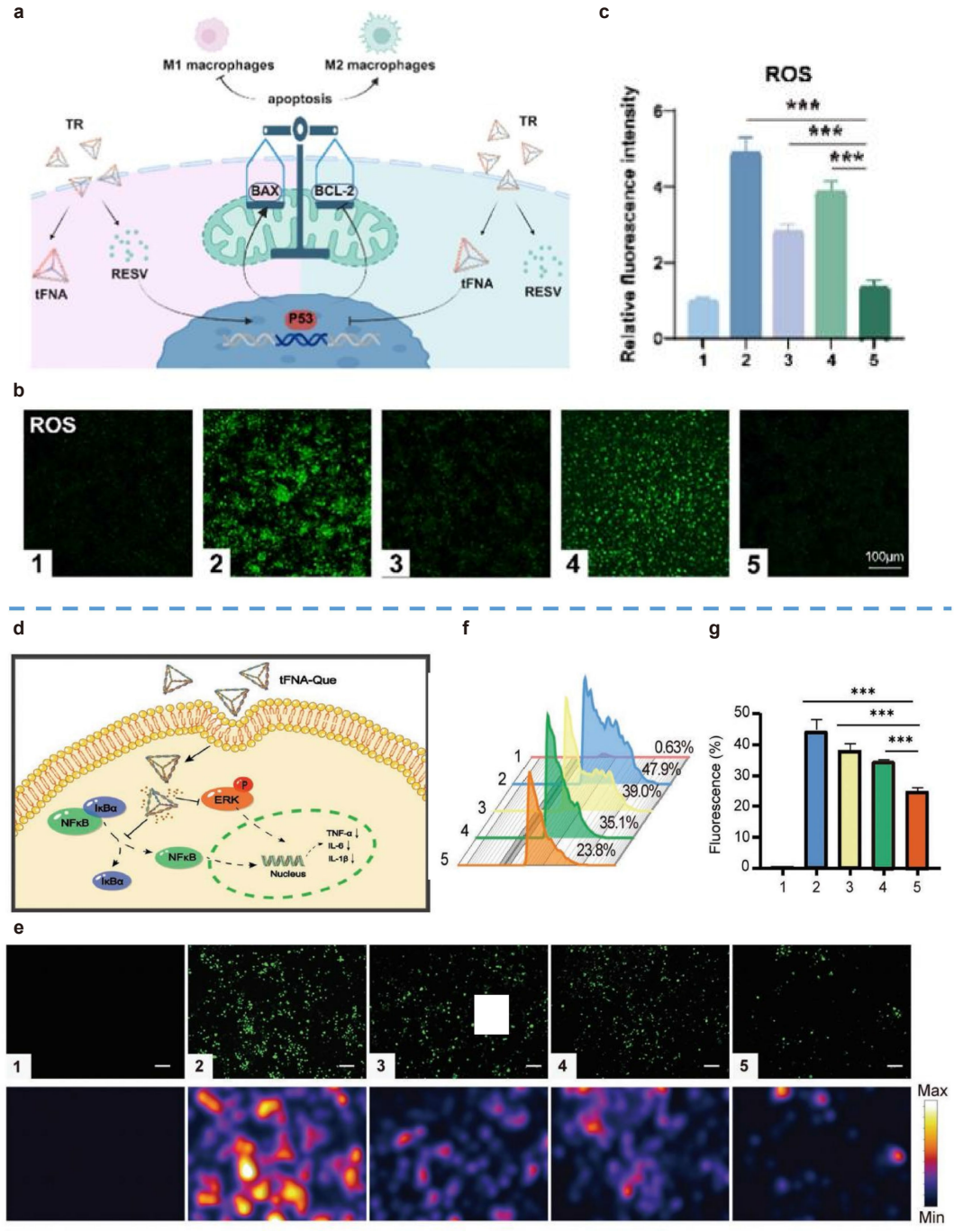


Figure 6 Drug loading profiles of tFNAs, including small-molecule drugs and peptides. Resveratrol-loaded DNA tetrahedron nanocarrier attenuates acute gouty arthritis via dual modulation of apoptosis and pyroptosis pathways. (a) Schematic diagram illustrating the proapoptotic effect of RESV on M1 macrophages and the anti-apoptotic effect of tFNA on M2 macrophages; (b) Fluorescence microscopy images showing intracellular ROS levels after different treatments (blue: nuclei; green: ROS; scale bar = 100 μm); (c) Quantification of intracellular ROS fluorescence intensity[127]. Copyright 2025, Chemical Engineering Journal. Suppression of Lipopolysaccharide-Induced Sepsis by Tetrahedral Framework Nucleic Acid Loaded with Quercetin. (d) Schematic diagram of key inflammatory signaling molecules getting involved in antiinflammatory effect of tFNA-Que; (e) Fluorescence microscope observation and thermal imaging of intracellular ROS level. Scale bar: 100 μm. Green: ROS; (f, g) Quantitative detection and analysisof intracellular ROS levels by flow cytometry[152]. Copyright 2022, Advanced Functional Materials.

distinct electron-donating or hydrogen-yielding mechanisms. Additionally, they readily bind unattached transition metals like free copper and iron elements. Sequestering these catalytic ions crucially blocks any secondary production of dangerous hydroxyl radicals typically fueled by Fenton chemistry. Physiologically, these multitasking compounds accelerate Nrf2/HO-1 protective signaling and simultaneously inhibit standard ERK/NF-κB inflammatory signal transduction. Consequently, researchers highly value their ability to unite profound oxidative radical scavenging with exceptional immunoregulatory benefits[184]. Incorporating flavonoids into the tFNAs platform enables sustained intracellular delivery via caveolin-dependent endocytic pathways, maximizing their

bioavailability[29]. For instance, a tFNAs nanocarrier loaded with quercetin suppresses ERK1/2 phosphorylation and halts the nuclear translocation of the NF-κB p65 subunit. Concurrently, the complex drives intracellular ROS clearance via hyperactivation of the Nrf2/HO-1 axis. This multi-pathway modulation has been shown to suppress LPS-induced macrophage inflammatory cascades, alleviate systemic inflammation in septicemia models, and reduce acute lung, liver, and kidney injury scores (Fig. 6d-f)[185,154].

3.2.3 Polypeptides

Therapeutic peptides are low-molecular-weight amino acid sequences engineered for intrinsic ROS-scavenging activity, biocompatibility, and cellular targeting. These peptides neutralize ROS free radicals through reactive amino acid side chains and function as ligands that activate endogenous host antioxidant networks. Covalently conjugating or electrostatically complexing these peptides onto the external surfaces of tFNAs vectors protects them from proteolytic degradation and rapid clearance, thereby extending their local stability and cellular delivery efficiency[140].

The primary therapeutic peptides loaded onto tFNAs platforms include dual-function anti-inflammatory/antimicrobial sequences, such as GL13K and pro-regenerative healing motifs, such as REGRT. These peptides operate in synergy with the free-radical quenching properties of the native tFNAs core to support soft-tissue and skeletal wound repair. For example, the host-defense peptide GL13K possesses anti-inflammatory, free-radical quenching, and antimicrobial properties. The polyanionic tFNAs framework loads cationic GL13K peptides onto its external surfaces via electrostatic adsorption. When applied to infected dermal or mucosal defects, the complex neutralizes LPS-induced ROS bursts and downregulates the transcription of pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, thereby breaking the cycle of microbial infection and tissue inflammation in cutaneous wounds, mucosal ulcers, and periodontitis lesions (Fig. 7a-c)[140,165]. Similarly, the pro-regenerative peptide REGRT acts as an agonist that promotes localized neoangiogenesis by triggering ERK1/2 phosphorylation, while also demonstrating independent antioxidant capacity and •OH quenching kinetics. Covalently conjugating REGRT to the external vertices of the tFNAs framework shields it from enzymatic cleavage by tissue proteases, enhancing intracellular delivery into wound cell populations. Once internalized, the complex upregulates the expression of endogenous HO-1 to neutralize intracellular oxidative stress induced by Advanced Glycation End products (AGEs), accelerating closure in refractory diabetic cutaneous ulcers and chronic mucosal wounds (Fig. 7d-f)[186].

3.3 Design and optimization strategies for tFNA nanocarriers

To optimize the localized delivery efficiency of tFNAs carriers, improve intracellular bioavailability, and accommodate the distinct biochemical parameters of specific pathological microenvironments, the structural architecture of tFNAs vectors requires rational optimization. To address challenges such as deep anatomical concealment, continuous fluid erosion, enzymatic degradation, and localized tissue acidity, various advanced engineering methodologies have been developed. These primarily focus on combining tFNAs with functionalized hydrogels, embedding intensely specific lysosomal escape mechanics, and displaying targeted surface ligands (Fig. 8).

3.3.1 tFNA-hydrogel composite delivery systems

Biomedical hydrogels possess favorable biological compatibility, tunable hydrophilicity, mechanical support, and sustained-release characteristics. Integrating functionalized tFNAs networks directly into hydrogel matrices addresses the limitations of rapid fluid washout and short localized tissue retention times associated with aqueous tFNAs formulations. This structural combination establishes stable reservoirs that facilitate long-term ROS clearance and sustained transcriptional regulation within challenging wound beds[187]. Mechanistically, the surrounding hydrogel functions as a controlled sustained-release depot wherein intact tFNAs nanostructures or pre-assembled tFNA-drug complexes are uniformly embedded.

When applied topically to extensive tissue defects, such as thermal burns or deep chronic diabetic ulcers, the hydrogel matrix undergoes controlled swelling upon absorbing inflammatory wound exudates. This degradation process slowly releases the embedded tFNAs complexes into the underlying wound bed over extended periods. Concurrently, the cross-linked polymer network physically shields the embedded tFNAs frameworks from immediate attack by tissue endonucleases, thereby increasing carrier biological stability[165,188–189]. For example, topical application of an optimized composite tFNAs hydrogel to contaminated thermal burns allows the matrix to immediately quench excessive extracellular ROS. Simultaneously, the persistent discharge of these DNA frameworks facilitates their deep tissue infiltration, leading to the profound deactivation of subsequent NF-κB inflammatory signal transduction. Ultimately, this localized immunomodulation strictly prompts invading wound macrophages to transition into the restorative M2 subpopulation, thereby accelerating complete structural healing[187]. Similarly, in applications designed to accelerate the closure of refractory diabetic ulcers, an injectable composite hydrogel incorporating tFNAs loaded with therapeutic *miR-21-5p* (TR21@TS) has demonstrated therapeutic efficacy. The released complexes activate the intracellular Nrf2/HO-1 axis while suppressing canonical NF-κB signaling, reducing localized oxidative stress and cytokine output, including TNF-α, IL-1β, and IL-6. Concurrently, the delivered miRNA drives downstream signaling through the pro-survival Akt cascade, stimulating localized neoangiogenesis and organized Type I collagen matrix deposition to promote wound closure[147]. Additionally, these hydrogels possess injectability, shear-thinning, and self-healing properties, which allow them to conform to irregular wound geometries and improve administration convenience.

3.3.2 Construction of pH-responsive tFNA vectors

Following cellular endocytosis, unfunctionalized tFNAs delivery vectors are typically routed through the classical endolysosomal pathway. The acidic environment (pH 4.5–5.5) and enzymatic profile of the lysosomal lumen can cause structural degradation of the carrier and chemical inactivation of sensitive payloads, thereby reducing cytosolic bioavailability. To bypass this biological checkpoint, specialized pH-sensitive single-stranded DNA sequences such as specifically cytosine-rich i-motif domains, are embedded into the tFNAs skeleton to construct lysosomal-responsive nanoboxes[190–191]. Under neutral conditions (pH 8.0), the i-motif sequence remains linear, and the tFNAs structure remains closed to protect the internal payload. However, when the carrier is internalized into the lysosome, the acidic environment (pH 4.5–5.5) induces the i-motif sequence to form a four-stranded quadruplex

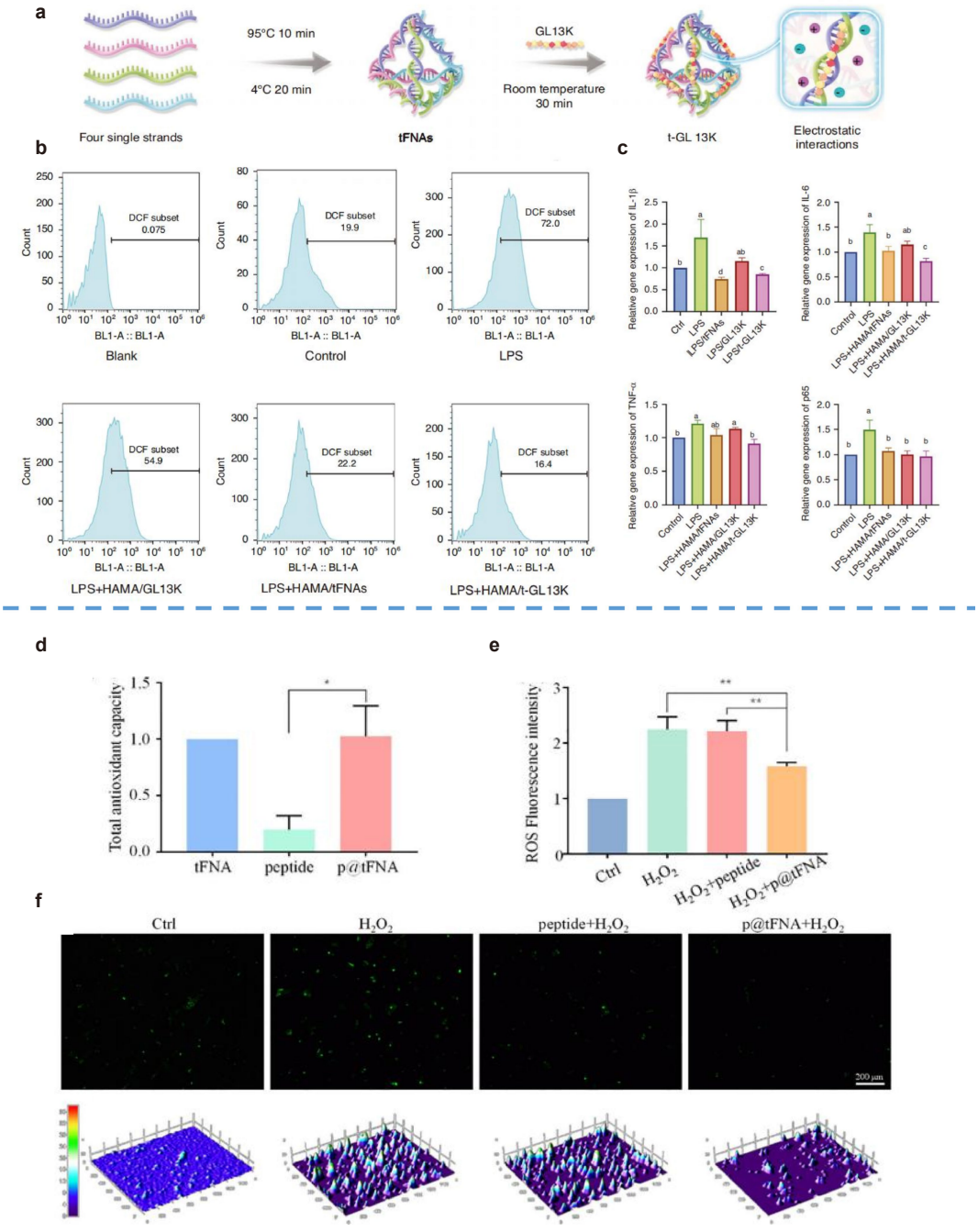


Figure 7 Drug loading profiles of tFNAs, including small-molecule drugs and peptides. Tetrahedral framework nucleic acids/hyaluronic acid-methacrylic anhydride hybrid hydrogel with antimicrobial and anti-inflammatory properties for infected wound healing. (a) Schematic diagram of the preparation of HAMA/tFNA-GL13K hydrogel; (b) Quantification of ROS in HaCaT cells; (c) Quantification of expression of inflammatory factors (IL-1β, IL-G, TNF-α, and p65) in HaCaT cells[154]. Copyright 2024, International Journal of Oral Science. Tetrahedral framework nucleic acids-based delivery promotes intracellular transfer of healing peptides and accelerates diabetic would healing. (d) Total antioxidant capacity assay results of tFNA and p@tFNA; (e) Fluorescence quantitative detection of ROS production with equalization by cell counting in control group, H_2O_2 group, $H_2O_2^+$ peptide group and $H_2O_2^+$ p@tFNA group; (f) croscope examinations and interactive 3D surface plot reconstruction of intracellular ROS levels of endothelial cells in the control group, H_2O_2 group, $H_2O_2^+$ peptide group and $H_2O_2^+$ p@tFNA group[156]. Copyright 2022, Cell Proliferation.

structure. This conformational change triggers the dissociation of the tFNAs skeleton, opening the nanocage to release the internal load[190]. For example, when anti-inflammatory siRNA is encapsulated within a lysosome-responsive tFNAs nanobox, the acidic lysosomal pH triggers structural opening and payload release. The released siRNA silences pro-inflammatory genes such as *TNF-α* via RNA interference, significantly inhibiting lipopolysaccharide-induced intracellular ROS production. Concurrently, the tFNAs framework itself degrades within the lysosome, preventing carrier accumulation[191]. This pH-gated responsive design improves intracellular delivery efficiency and endolysosomal escape kinetics for fragile nucleic acid therapeutics, ensuring precise upstream gene silencing and redox regulation[192].

3.3.3 *Active targeting strategies for enhanced delivery precision*

The specific pathological localizations and subcellular organelles

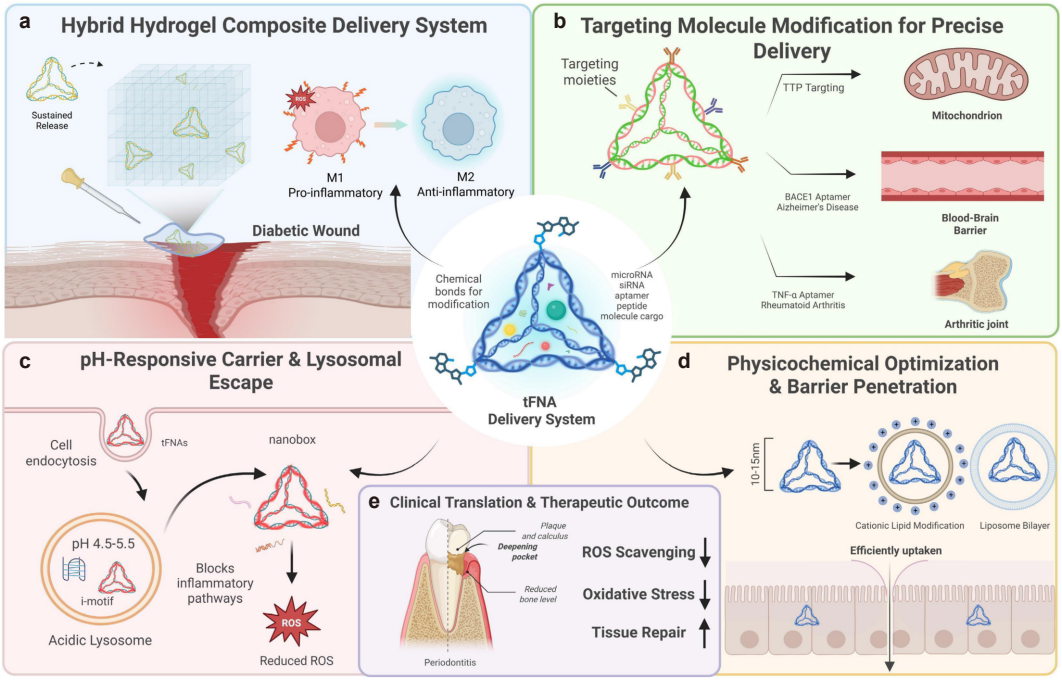


Figure 8 Structural optimization workflows and clinical translation modalities of advanced tFNA delivery vectors. (a) Hybrid hydrogel composite delivery platforms for macro-environmental adaptation and sustained cargo delivery in chronic wounds; (b) Surface ligand modification for active cellular and subcellular targeting; (c) Acid-responsive i-motif configuration transformations driving endolysosomal escape kinetics; (d) Physicochemical geometric modifications and lipid coatings to accelerate structural mucosal barrier penetration. Middle (Bottom): Practical targeted clinical deployment within destructive periodontitis lesions to suppress underlying inflammation lines and facilitate tissue remodeling. Created by BioRender.com.

driving severe oxidative stress pathologies exhibit immense clinical heterogeneity. For instance, Alzheimer's disease lesions are restricted to deep cerebral networks, rheumatoid arthritis predominantly involves hyperactive synovial macrophages, and diabetic periodontitis is characterized by metabolic dysregulation localized within the mitochondrial matrices of PDLSCs[116,133,155,179]. By modifying the surface of the tFNAs carrier with exogenous targeting molecules, accurate delivery of antioxidant or nucleic acid drugs to specific lesion sites and subcellular structures can be achieved, minimizing non-specific distribution and improving safety.

The selection of surface targeting ligands must be customized to match the molecular fingerprint of individual disease states. In rheumatoid arthritis models, modifying the tFNAs surface with a TNF-α aptamer for the co-delivery of methotrexate targets macrophages in inflammatory joints, blocking the TNF-α/NF-κB pathway, reducing ROS levels, and promoting M2 macrophage polarization[133]. For Alzheimer's disease, conjugation with a BACE1 aptamer enables tFNAs to cross the blood-brain barrier, inhibit β-amyloid production, and clear neuronal ROS to mitigate oxidative stress injury[179]. Similarly, in diabetes-related periodontitis, triphenylphosphine (TPP), a small mitochondrial targeting molecule, can be covalently linked to the tFNAs surface to deliver loaded quercetin directly to the mitochondria of PDLSCs, thereby activating the Nrf2/HO-1 pathway to eliminate excessive ROS and restore osteogenic differentiation[155]. Furthermore, for ischemia-reperfusion induced acute renal injury, functionalizing tFNAs with renal tubular epithelial cell-specific ligands, such as integrin-binding peptides, enables active targeting to renal tubular cells, delivering antioxidant payloads into the cytoplasm to reduce mitochondrial dysfunction and apoptosis[193].

3.3.4 *Other optimization strategies*

Beyond primary functionalization methods, tFNAs delivery efficiency and transmucosal penetration can be improved by optimizing framework dimensions, modifying surface charge, and constructing hybrid lipid-nucleic acid nanocarriers[33,194–195]. Compressional tuning of individual DNA strands can reduce the tFNAs framework to an ultra-compact size of 10 to 15 nm, which facilitates penetration through dense oral mucosal layers and subepithelial extracellular matrices[33,196]. Concurrently, coating the polyanionic tFNAs surface with cationic lipids, such as 1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA) , reverses the net surface charge to positive values, enhancing cellular endocytosis via electrostatic interactions with negatively charged membranes of target cells[194]. Furthermore, hybrid tFNA-liposome systems integrate the targeting specificity of the structural nucleic acid core with the high payload capacity of lipid bilayers for multi-drug co-delivery. Crucially, even unfunctionalized tFNAs exhibit intrinsic bioactivity, characterized by the suppression of malondialdehyde (MDA) output, upregulation of intracellular SOD activity, and inhibition of canonical NLRP3 inflammasome assembly to alleviate oxidative stress and neuroinflammation[196]. This dual role as both an adjustable carrier and an active therapeutic agent provides a solid rationale for the translation of composite tFNAs systems in regulating tissue redox parameters within complex stomatological and orthopedic microenvironments.

4 Applications of tFNA-based drugs in oral-related diseases

tFNAs exhibit exceptional preclinical efficacy in treating oral soft-

tissue and maxillofacial inflammatory diseases due to its stable nanoscale geometry, biocompatibility, spatial editability, and intrinsic capacity to quench excessive ROS[29,30]. Functionalized tFNAs therapeutics effectively resolve complex oxidative stress networks across various disease states (Fig. 9a).

4.1 Applications in soft tissue inflammation-related diseases

Excessive ROS accumulation constitutes a primary pathological hallmark of acute and chronic oral soft tissue inflammation. This

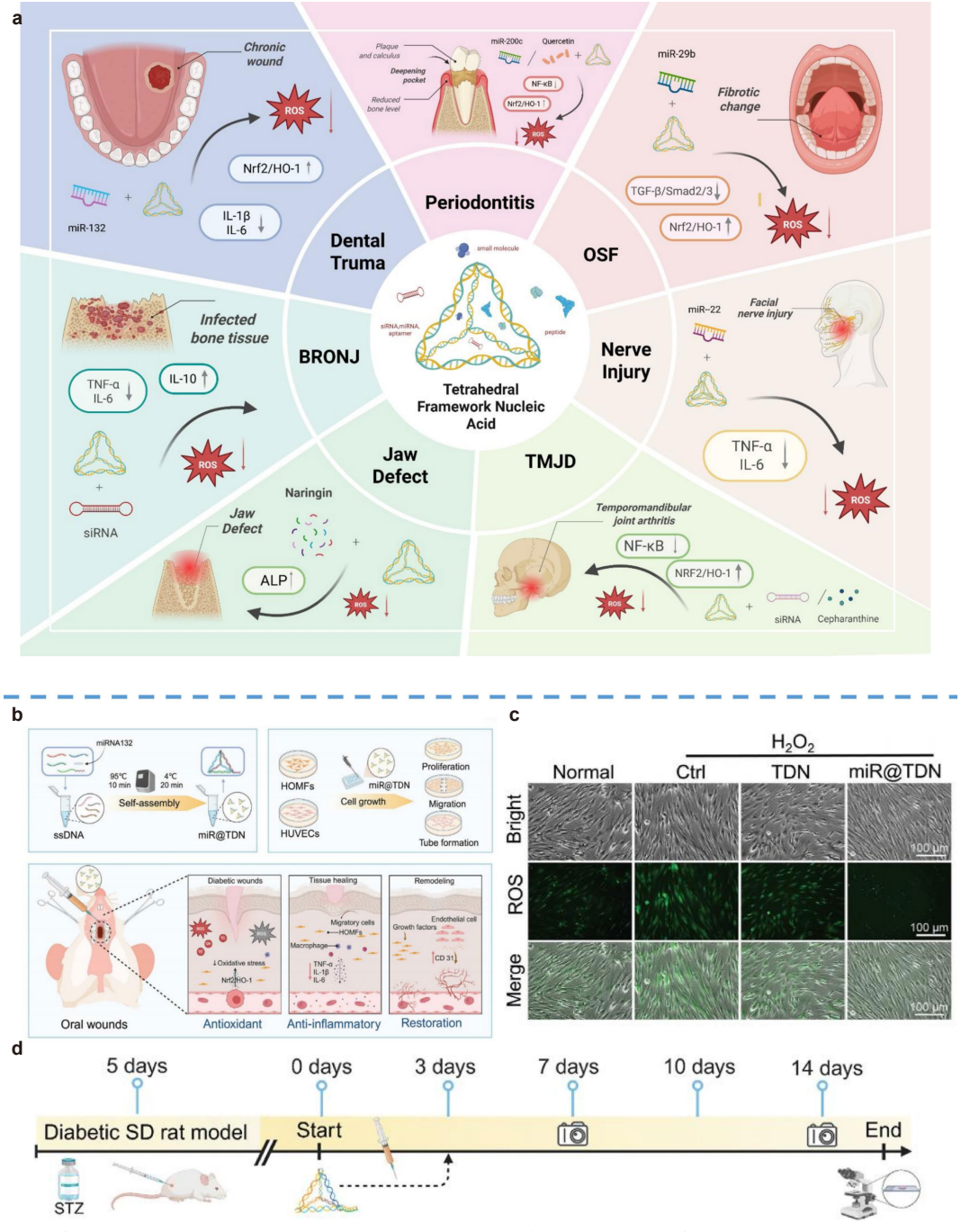


Figure 9 Applications of tFNA-based nanomedicines in stomatological diseases. (a) Schematic summary of tFNA-based therapeutic applications across oral and maxillofacial diseases. The central tFNA nanocarrier can be loaded with specific therapeutic payloads (miRNAs, siRNAs, aptamers, small molecules, or peptides) to target distinct pathological microenvironments. Surrounding panels detail the corresponding disease models—including diabetic oral wounds, periodontitis, oral submucous fibrosis (OSF), facial nerve injury, temporomandibular joint osteoarthritis (TMJOA), alveolar bone defects, and bisphosphonate-related osteonecrosis of the jaw (BRONJ)—highlighting the specific upstream signaling pathways modulated by tFNAs to achieve effective ROS clearance and structural tissue regeneration; Created by BioRender.com. Enhancing Diabetic Oral Wound Healing with miR-132 Delivered Through Tetrahedral DNA Nanostructures. (b) Schematic representation of the fabrication of miR@TDN and its application in a diabetic rat oral mucosal wound model; (c) Representative images of HOMFs stained with ROS under different treatment conditions. Scale bar: 100 μm; (d) Timeline of the wound treatment process[114]. Copyright 2025, Small.

oxidative stress hyperactivates inflammatory signaling networks and cytokine output, thereby compromising cellular integrity and extracellular matrices[1,120,141]. Self-assembled tFNAs permanently resolve soft-tissue hyper-inflammation by combining their intrinsic free-radical quenching capacities with the potent antioxidant and anti-inflammatory activities of their cargo. Their compact nanoscale dimensions and biocompatibility allow these nanostructures to smoothly navigate sensitive mucosal layers and resist rapid salivary washout[29,30].

4.1.1 Perioral skin trauma

During oral mucosal and perioral wound healing such as diabetic defects or severe lacerations, substantial bursts of toxic ROS are generated. This unbuffered oxidative output induces fibroblast apoptosis, halts Type I collagen synthesis, disrupts mitochondrial networks, delays wound closure, and elevates infection risks[118,197]. Conventional treatments, relying on passive barriers and antimicrobials, fail to restore the localized host redox balance[198]. Advanced tFNA-based biomaterials provide an active intervention strategy. For instance, tFNAs loaded with functional *miR-132*, designated as miR@TDN precisely modulate inflammatory and cytoprotective networks to achieve synergistic ROS clearance and accelerated repair.

In vitro assays show that miR@TDN efficiently penetrates compromised oral fibroblasts, reducing H_2O_2-induced intracellular ROS by up to 80.39%. This preserves mitochondrial integrity and stimulates survival, proliferation, migration, and capillary tube formation in primary human umbilical vein endothelial cells (HUVECs). *In vivo* evaluations using diabetic rat palatal defect models demonstrate that subepithelial injection of miR@TDN significantly accelerates wound closure and Type I collagen deposition. Mechanistically, it upregulates the Nrf2/HO-1 antioxidant axis, suppresses pro-inflammatory cytokines, including IL-1β and IL-6, and drives neoangiogenesis as evidenced by increased $CD31^+$ density, confirming its clinical value in resolving diabetic oral mucosal trauma (Fig. 9b-d)[119].

4.1.2 Oral submucous fibrosis

OSF is a chronic disease where excessive ROS accumulation abnormally activates mucosal fibroblasts, causing excessive collagen deposition, mucosal sclerosis, and restricted mouth opening. Traditional treatments only alleviate symptoms without reversing fibrosis[109]. tFNA-based materials achieve disease intervention through targeted delivery and pathway regulation. Specifically, tFNAs loaded with *miR-29b*, termed T-29b, targets mucosal fibroblasts with high ROS expression. *In vitro*, T-29b significantly inhibits the TGF-β1/Smad2/3 pathway, reduces ROS-induced collagen deposition, and downregulates fibrosis-related proteins, such as α-SMA, Collagen I, fibronectin and vimentin. Simultaneously, it activates the Nrf2/HO-1 antioxidant pathway to clear ROS and restores E-cadherin to maintain epithelial integrity. In animal models, T-29b improves oral mucosa pathology in arecoline-induced fibrosis, reduces collagen volume fraction, and reverses sclerosis, offering a precise nanostrategy for OSF treatment (Fig. 10a)[132].

4.1.3 Oral-related nerve injury

Severe oral and maxillofacial trauma often damages peripheral nerve structures, specifically trigeminal and facial nerve networks, triggering immediate, substantial bursts of toxic ROS. Unbuffered oxidative stress induces neuronal apoptosis, suppresses axonal sprouting, degrades Schwann cell networks, and causes permanent paresthesia, neuropathic pain, and motor deficits[199]. Traditional nerve repair methods fail to effectively clear ROS, resulting in low repair efficiency[200]. tFNA-based ROS scavenging materials protect nerve cells and promote axonal regeneration. For example, loading these tetrahedral frameworks with neuro-modulating *miR-22* creates a specific therapeutic complex designated as MiDs. This engineered system effectively drives resident immune populations toward the healing, anti-inflammatory M2 classification. Working cooperatively, the foundational DNA scaffold actively eliminates harmful oxidative radicals while severely limiting programmed neural cell death. Furthermore, this combined molecular action encourages local Schwann cells to adopt a regenerative cellular profile, ultimately expediting the regrowth of damaged nerve fibers. *In vitro*, MiDs significantly reduce LPS-induced ROS and NO levels in macrophages, downregulate pro-inflammatory factors, primarily TNF-α and IL-6, and enhance Schwann cell proliferation and migration. In animal models, the system improves motor function in facial nerve injury, promotes structural recovery of nerve axons and myelin sheaths, and shortens repair time (Fig. 10b-d)[151].

4.2 Applications in oral and maxillofacial inflammatory bone diseases

Complex oral and maxillofacial inflammatory pathologies are universally characterized by persistent, destructive ROS accumulation across the compromised bone bed. This concentrated oxidative output directly damages mineralized matrices, triggers widespread osteoblast apoptosis, shuts down critical osteogenic transcription factors, and hyper-activates pre-osteoclasts. This cascade leads to unregulated osteoclast differentiation, severe pathological bone resorption, critical-sized defects, and avascular bone necrosis[6,8,9,12]. Self-assembled tFNA-based ROS-scavenging biomaterials offer an exceptionally superior intervention strategy to resolve skeletal hyper-inflammation and drive robust bone regeneration. By utilizing targeted delivery to directly quench ROS while delivering pro-osteogenic or anti-osteolytic cargo, tFNAs reconstruct the localized skeletal metabolic balance. Furthermore, their optimal physical dimensions and absolute biocompatibility perfectly navigate the dense matrices of maxillofacial bone.

4.2.1 Temporomandibular joint osteoarthritis

The core pathology of TMJOA involves excessive ROS accumulation following articular cartilage injury, which aggravates cartilage damage and inflammation, ultimately limiting joint activity[201]. Traditional anti-inflammatory treatments fail to reverse cartilage injury. However, tFNA-based materials simultaneously scavenge ROS and protect cartilage. For instance, tFNAs can load NF-κB-targeting siRNA, designated as Tsi, or the natural alkaloid cepharanthine, termed tFNA@Cep, for targeted delivery to the TMJ lesion. In vitro experiments demonstrate that Tsi significantly reduces IL-1β-induced ROS, inhibits the NF-κB pathway, activates the Nrf2/HO-1 antioxidant pathway, reduces matrix metalloproteinases, specifically MMP-3, MMP-9 and MMP-13), and protects chondrocyte viability. Conversely, tFNA@Cep regulates the cGAS-STING-NF-κB axis, promotes M2 macrophage polarization, reduces intracellular ROS, and indirectly enhances chondrocyte anabolism by upregulating Sox9, Col II, and Aggrecan. In animal models, both Tsi and tFNA@Cep successfully alleviate

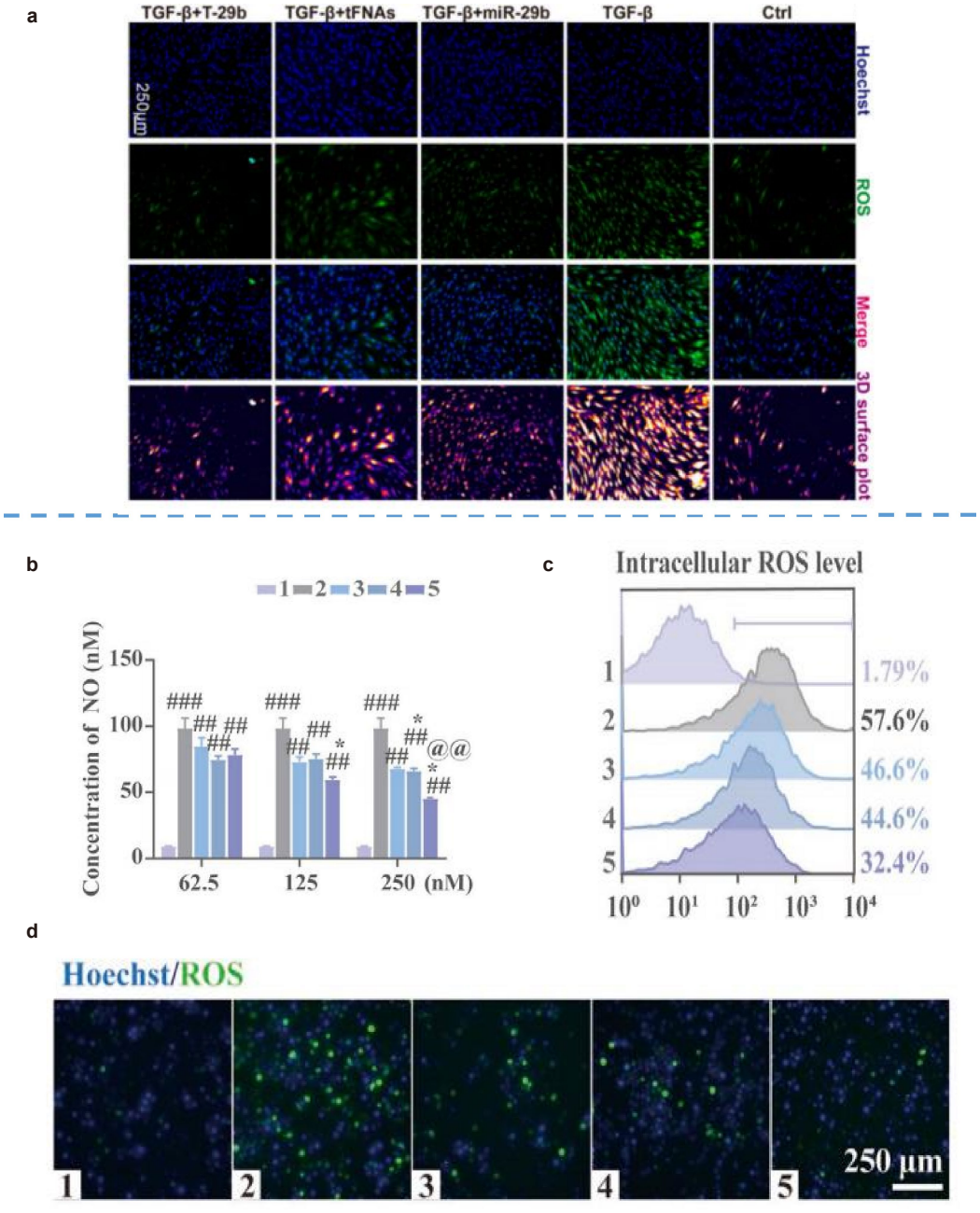


Figure 10 Applications of tFNA-based nanomedicines in stomatological diseases. Tetrahedral framework nucleic acid-based delivery of microRNA-29b: A precision nanotherapeutic strategy for oral submucous fibrosis. (a) Reduction of ROS in hOMF after different treatments was detected by fluorescence pictures[125]. Copyright 2025, Chemical Engineering Journal. Modulation of the Crosstalk between Schwann Cells and Macrophages for Nerve Regeneration: A Therapeutic Strategy Based on a Multifunctional Tetrahedral Framework Nucleic Acids System. (b) The effects of different concentrations of MiDs, tFNAs, and miR-22 on NO release from RAW264.7 after injury were detected within 24 h; (c) The expression of ROS in RAW264.7 after 24 h of different treatments was detected by flow cytometry; (d) Images of ROS expression in RAW264.7 after 24 h different treatments[162]. Scale bars = 250 μm. Copyright 2022, Advanced Materials.

cartilage degeneration and subchondral bone loss, improve joint structure, and inhibit TMJOA progression (Fig. 11a-b)[143,156].

4.2.2 *Bone defects*

Clinical situations demanding extensive osseous repair, primarily including widespread skeletal fragility and complex jawbone lesions, are frequently complicated by severe local oxidative stress. High concentrations of reactive oxygen intermediates critically paralyze the mitotic expansion and functional specialization of local osteoblast populations. In addition to suppressing the activation of essential bone-synthesizing genes, this extreme oxidative state aggressively drives osteoclast-mediated structural breakdown, thereby completely undermining the overall formation of healthy skeletal architectures[8,202]. tFNA-based materials accelerate jaw formation by scavenging ROS and promoting osteoblast activity. In related studies, tFNAs were utilized to carry the natural flavonoid naringin (forming the TNC complex) targeted to jaw defects. The intrinsic radical-scavenging capacity of tFNAs significantly reduces

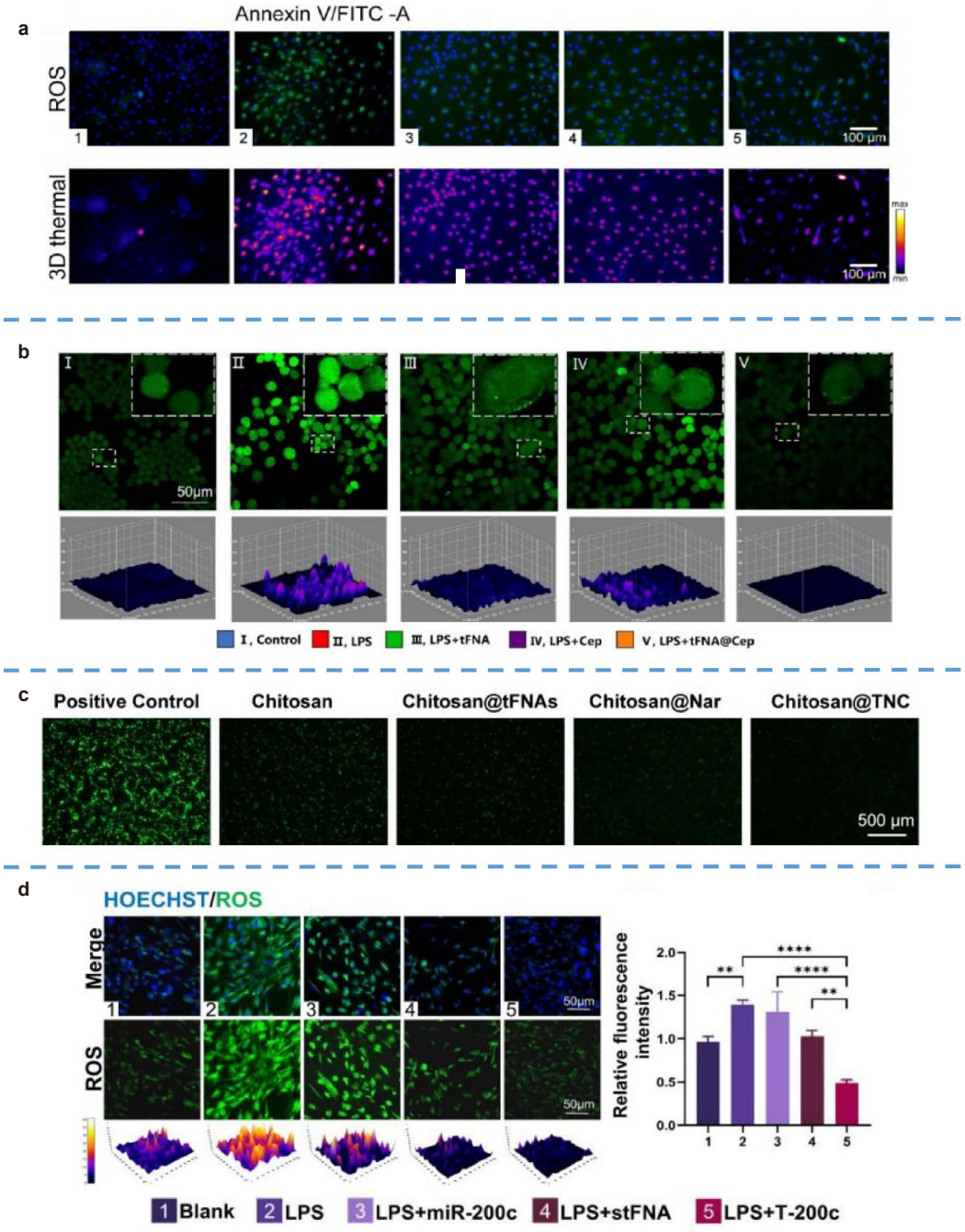


Figure 11 Applications of tFNA-based nanomedicines in stomatological diseases. Efficient Delivery of siRNA via Tetrahedral Framework Nucleic Acids: Inflammation Attenuation and Matrix Regeneration in Temporomandibular Joint Osteoarthritis. (a) Fluorescence microscopy to determine the reactive oxygen species (ROS) levels of chondrocytes after different treatments (blue: nuclei; green: ROS. Scale bar: 100 μm)[141]. Copyright 2024, ACS Applied Materials & Interfaces. Tetrahedral Framework Nucleic Acid-Based Cepharanthine Attenuates TMJOA via cGAS–STING–NF-κB Pathway Modulation and Macrophage Reprogramming. (b) Representative ROS staining images (nucleus: blue; ROS: green, scale bar: 50 μm). Group I: Control group; Group II: LPS group; Group III: LPS group under tFNA treatment; Group IV: LPS group under Cep treatment; Group V: LPS group under tFNA@Cep treatment[166]. Copyright 2026, ACS Applied Materials & Interfaces. Tetrahedral Framework Nucleic Acid Composite Hydrogel Loaded with Naringin for Full Alveolar Bone Regeneration. (c) The ROS test of the co-culture system of Chitosan Hydrogels and BMSCs[167]. Copyright 2025, ACS Applied Materials & Interfaces. A Multifunctional miRNA Delivery System Based on Tetrahedral Framework Nucleic Acids for Regulating Inflammatory Periodontal Ligament Stem Cells and Attenuating Periodontitis Bone Loss. (d) Immunofluorescence images of cellular ROS. (Scale bar: 50μm) and the quantitative analysis of immunofluorescence results[124]. Copyright 2025, ACS Applied Materials & Interfaces.

oxidative stress damage in bone marrow mesenchymal stem cells (BMSCs), thereby promoting their proliferation and osteogenic differentiation. *In* vitro, TNC treatment significantly enhanced BMSC alkaline phosphatase (ALP) activity, mineralized nodule formation, and the expression of osteogenic proteins, including runt-related transcription factor 2 (Runx2), OSX, and bone morphogenetic protein 4 (BMP4). In animal models, applying a TNC-composite chitosan hydrogel to a full-thickness alveolar bone defect accelerated new bone formation, improved bone volume fraction (BV/TV) and trabecular thickness, and promoted the dual

reconstruction of cortical and cancellous bone (Fig. 11c)[157].

4.2.3 Periodontitis

Periodontitis involves pathogenic bacterial infections such as P. gingivalis that trigger local inflammation and excessive ROS accumulation. This oxidative stress destroys the periodontal ligament, inhibits alveolar osteogenesis, promotes bone absorption, and causes tooth loosening[5,12,98]. Traditional scaling removes bacteria but cannot reverse ROS-induced injury. However, tFNA-based materials scavenge ROS and protect bone through synergistic therapies, such as using tFNAs alone, loading them with *miR-200c*, termed T-200c, or loading quercetin modified with a mitochondrial-targeting molecule, designated as TTQ. tFNAs intrinsically reduce ROS and inflammatory factors by inhibiting the MAPK/ERK pathway. T-200c inhibits the MyD88/NF-κB pathway and activates Akt/β-Catenin to promote periodontal ligament stem cell proliferation and osteogenesis. TTQ targets mitochondria to deliver quercetin, activating Nrf2/HO-1 to clear ROS and inhibit NF-κB-mediated inflammation. *In vitro*, these systems significantly reduced ROS in stem cells and macrophages while inhibiting IL-1β and TNF-α. *In vivo*, they alleviated gingivitis and alveolar bone absorption in periodontitis rats; additionally, TTQ effectively improved bone microstructure in diabetic periodontitis models (Fig. 11d, 12a)[130,155].

4.2.4 Bisphosphonate-related osteonecrosis of the jaw (BRONJ)

BRONJ is a severe complication driven by excessive ROS accumulation, leading to osteocyte apoptosis, osteonecrosis, and local inflammation[6,90]. Traditional treatments struggle to alleviate this oxidative damage. Recent studies covalently coupled tetrahedral DNA nanomaterials with *TLR4*-targeting siRNA, forming the TDN-TLR4-4siR complex, targeting overactivated M1 macrophages at

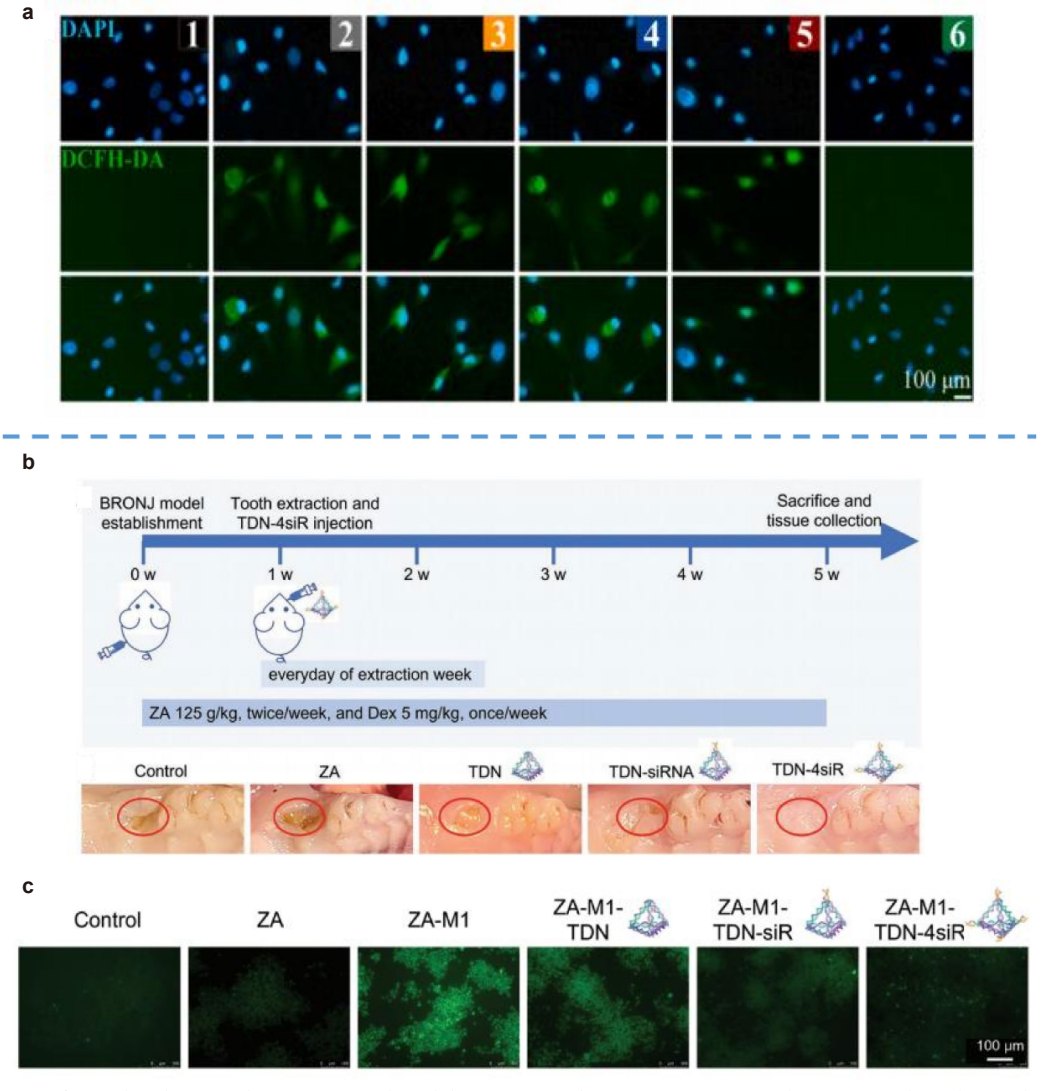


Figure 12 Applications of tFNA-based nanomedicines in stomatological diseases. Mucosal Gingipain Vaccine Based on Framework Nucleic Acid Engineering for the Treatment of Periodontitis. (a) ROS levels in T2DM-PD cells after different treatment[165]. Scale bar = 100 μm. Copyright 2024, Chemical Engineering Journal. Functionalized DNA Nanomaterials Targeting Toll-Like Receptor 4 Prevent Bisphosphonate-Related Osteonecrosis of the Jaw via Regulating Mitochondrial Homeostasis in Macrophages. (b) Graphic illustration of the establishment and treatment procedure of rat BRONJ and the photographs of wound healing after tooth extraction in rats (normal control, ZA-induced BRONJ, ZA+TDNs treatment, ZA+TDN-siRNA treatment, and ZA+TDN-4siR treatment groups. Red circle refers to tooth extraction site; (c) Mitochondrial ROS levels in macrophages treated with ZA and TDN-TLR4-4siRNA[195]. Scale bar = 100 μm. Copyright 2023, Advanced Functional Materials.

the osteonecrosis site. This system effectively silences TLR4, blocks mitochondrial dysfunction, significantly reduces mitochondrial ROS (mtROS), and restores mitochondrial membrane potential. It also upregulates mitochondrial fusion proteins (Mfn1/Mfn2) and respiratory chain complexes to reverse M1/M2 polarization imbalance. *In vitro*, TDN-TLR4-4siR significantly reduced ROS in zoledronic acid-treated macrophages, decreased pro-inflammatory factors, such as TNF-α and IL-6, and promoted anti-inflammatory interleukin-10 (IL-10) release. In animal experiments, the system accelerated extraction socket healing in BRONJ rats, reduced dead bone formation, and promoted the regeneration of new bone and collagen fibers (Fig. 12b-c)[144].

5 Current progress, translational bottlenecks, and future perspectives

Based on existing literature, the development of tFNA-based ROS-scavenging biomaterials has shown systematic progression. The current research landscape exhibits several defining characteristics across material construction, mechanistic exploration, and preclinical validation.

5.1 Evolution of active tFNA therapeutic platforms

To address complex oral osteo-inflammatory diseases, the construction of tFNAs has evolved from passive delivery vehicles into highly active, multifunctional interventions. Recent design strategies heavily emphasize precision delivery by loading small-molecule antioxidants such as curcumin or regulatory siRNAs/miRNAs to improve localized target tissue retention and overcome the traditional limitations of systemic administration[17,132,143]. Furthermore, researchers are increasingly incorporating nanozymes, which are nanomaterials with enzyme-like catalytic properties—into the tFNAs framework to provide intrinsic, continuous ROS scavenging against persistent oral oxidative stress[30]. Alongside these developmental strides, researchers have successfully fabricated intelligent nanoscale vehicles engineered to sense their immediate biological surroundings. This approach enables controlled therapeutic unloading in specific spatial and temporal contexts. Specifically, the medicinal payload is liberated only when activated by unique physiological changes, notably the localized low pH environments typically found within inflammatory lesions[115,155,190]. Together, these advancements drive the development of immensely efficient, spatiotemporally controllable nanoplatforms tailored for localized oral and maxillofacial therapies.

5.2 Elucidation of multiplexed therapeutic mechanisms

Early studies primarily focused on the direct, physical neutralization of ROS by tFNAs complexes[30]. Current understanding, however, reveals that their core efficacy stems from the systematic regulation of complex pathological signaling networks. Rather than acting through a single pathway, tFNA-based materials intervene in the ROS, inflammation and tissue destruction axis through multiplexed modulation. Specifically, these complexes attenuate pro-inflammatory cytokines and substantial ROS bursts by inhibiting NF-κB signaling and NLRP3 inflammasome activation[39,156,158]. Simultaneously, they enhance cellular antioxidant defenses by activating the Nrf2 pathway in periodontal stem cells and local macrophages[155,150], while actively governing cell survival and extracellular matrix metabolism via the PI3K/AKT axis[203]. This comprehensive network intervention effectively disrupts the vicious cycle driving chronic oral inflammatory diseases.

5.3 Preclinical validation in complex *in vivo* models

With exceptional biosafety and *in vitro* antioxidant activity widely verified, tFNAs platforms have demonstrated robust efficacy across various complex *in vivo* models, including periodontitis, oral mucositis, jaw necrosis, and critical-sized bone defects[119,145,157–158]. These preclinical studies conclusively confirm the powerful anti-inflammatory effects of tFNAs and highlight their profound potential for oral and maxillofacial tissue regeneration via targeted microenvironmental modulation. Consequently, the primary therapeutic objective has fundamentally shifted from mere symptom alleviation to driving root-cause structural tissue reconstruction[17,204].

5.4 Crucial translational challenges and limitations

Despite the encouraging preclinical trajectory of tFNA-based ROS-scavenging biomaterials, their transition into standardized clinical modalities is hindered by several formidable barriers. The primary challenge lies in elucidating the precise *in vivo* behavior of tFNAs within the highly dynamic, heterogeneous microenvironments characteristic of oral diseases, such as periodontitis and BRONJ[30]. Current mechanistic insights heavily rely on static *in vitro* assays or end-stage animal models, which fail to accurately capture the spatiotemporal fluctuations of ROS or the localized metabolic fate of the nanocarriers[205]. Consequently, the specific long-term interactions between tFNAs and critical local cell populations including gingival fibroblasts, reparative osteoblasts and infiltrating immune cells, remain poorly understood[30]. Furthermore, a significant design gap persists. Most existing tFNAs platforms employ a "universal" scavenging approach rather than being rationally tailored to the specific molecular signatures of distinct diseases or varying pathological stages, such as distinguishing acute infection from chronic fibrosis. Finally, substantial translational hurdles impede large-scale clinical application. These include the lack of cost-effective, high-purity, Good Manufacturing Practice (GMP)-compliant production protocols, alongside unresolved concerns regarding long-term immunogenicity and chronic toxicity. Additionally, while the ultra-small size of tFNAs, approximately 10 nm, facilitates tissue penetration, it paradoxically accelerates systemic clearance, thereby limiting sustained localized bioavailability.

5.5 Future perspectives and clinical roadmap

To shift the therapeutic paradigm from passive symptom relief to active, precision tissue repair, future research must pioneer innovative, interdisciplinary strategies. Mechanistically, integrating advanced real-time in situ imaging with high-resolution ROS-sensitive molecular probes will be crucial for visualizing the spatiotemporal distribution and clearance kinetics of tFNAs[206]. Concurrently, leveraging spatial transcriptomics and single-cell sequencing can decode the exact transcriptional programs and signaling networks, such as NF-κB, NLRP3, and Nrf2, altered by tFNAs interventions at a systems biology level.

Based on these mechanistic insights, the next generation of tFNAs platforms must evolve into highly autonomous, intelligent therapeutic systems. Future designs will likely incorporate sophisticated pathological logic gating, requiring the concurrent presence of specific triggers, including elevated MMPs, acidic pH,

and severe ROS bursts, to initiate accurately localized cargo release and prevent off-target leakage. Integrated with artificial intelligence (AI) and computational simulation, these advanced biomaterials can be customized to match the unique "ROS signal fingerprints" of specific patient profiles. Ultimately, AI-driven in silico modeling and digital twins could predict therapeutic efficacies and guide adaptive, closed-loop treatment regimens.

From a clinical translation perspective, targeted localized administration for chronic periodontitis represents the most viable initial breakthrough. Its large patient base, direct clinical accessibility, and the availability of mature, standardized large animal models make it an ideal candidate for evaluating long-term safety and pharmacodynamics. To successfully bridge the gap between bench and bedside, establishing standardized dosing regimens and practical administration routes is paramount. While systemic intravenous delivery often requires higher relative doses, typically ranging from 1 to 5 mg/kg in preclinical murine models, and risks rapid physiological clearance, localized administration represents a far more translatable and efficacious strategy for stomatological lesions[29–30]. For conditions like periodontitis, direct subgingival injection of aqueous tFNAs or the topical application of tFNA-loaded sustained-release hydrogels into the periodontal pocket are highly recommended[39,157,165]. These localized routes maximize drug retention and bioavailability at the specific defect site while avoiding systemic off-target effects. Future clinical trial designs must meticulously delineate the optimal therapeutic window, likely within the low nanomolar to micromolar concentration range such as 50 to 250 nM for local application, to perfectly balance potent ROS-scavenging efficacy with long-term biosafety[33,151]. Once validated, this versatile nanoplatform can progressively expand its application boundaries to address broader stomatological challenges, including mucosal trauma regeneration, critical-sized maxillofacial defects, and synergistic treatments for jaw osteomyelitis. Through rigorous interdisciplinary collaboration across materials science, molecular biology, and regulatory medicine, tFNA-based therapeutics are poised to establish a new frontier in precision osteo-inflammatory medicine.

6 Conclusion

ROS serve as a central molecular hub bridging cellular inflammatory responses with downstream progressive tissue destruction, establishing targeted redox modulation as a key therapeutic objective in modern inflammatory and orthopedic medicine[207]. tFNAs successfully overcome the delivery and stability limitations associated with conventional low-molecular-weight antioxidants, evolving into multifunctional nanoscale platforms owing to their rigid three-dimensional geometry, biocompatibility, customizable spatial editability, and intrinsic bioactivity[29–30]. Crucially, functionalized tFNA delivery complexes therapeutics do not merely passively quench extracellular ROS; they precisely transport therapeutic payloads into the cytoplasm to modulate upstream intracellular transcription networks, effectively arresting the chronic oxidative stress, inflammation, and tissue destruction pathological cascade at the molecular level[208]. Accordingly, customized tFNAs delivery networks have demonstrated therapeutic efficacy and robust tissue regeneration capacity across various animal models of complex oral soft-tissue and skeletal inflammatory diseases[119,151,156].

To transition these advanced formulations into clinically translatable modalities, future investigations must shift from empirical mapping toward precise spatiotemporal mechanistic elucidation within living biological systems, execute rationally designed, computationally driven structural customizations, and systematically resolve industrial bottlenecks spanning from large-scale, GMP-compliant synthesis to comprehensive long-term systemic biosafety evaluation. Through the interdisciplinary convergence of nanotechnology, synthetic biology, computational modeling, and clinical medicine, next-generation tFNA-based ROS regulatory platforms are poised to offer definitive solutions for refractory inflammatory and skeletal pathologies. This advancement is expected to drive the evolution of pharmacotherapy toward autonomous pathological perception, dynamic precision intervention, and targeted structural tissue regeneration.

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Data available statement

N/A

Author contribution

Conceptualization, J.X. and M.Z.; literature search and screening, J.X. and W.C.; writing—original draft preparation, J.X.; writing—review and editing, X.F.; visualization (figures and tables), Z.Z. and Y.L.; supervision, M.Z.; project administration, B.H.; funding acquisition, Y.L. and M.Z. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent

N/A

Consent for publication

Authors agree to publish.

Conflicts of interest

Author Yunfeng Lin is an executive editors-in-chief of this journal, but he is not involved in the peer-review or decision of this article

References

[1] Medzhitov, R. Origin and physiological roles of inflammation.

Nature **2008**, *454*, 428–435.
[2] Schmid-Schönbein, G. W. Analysis of inflammation. *Annu. Rev. Biomed. Eng.* **2006**, *8*, 93–151.
[3] Medzhitov, R. The spectrum of inflammatory responses. *Science* **2021**, *374*, 1070–1075.
[4] Cicchese, J. M.; Evans, S.; Hult, C.; et al. Dynamic balance of pro- and anti-inflammatory signals controls disease and limits pathology. *Immunol. Rev.* **2018**, *285*, 147–167.
[5] Hajishengallis, G.; Chavakis, T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. *Nat. Rev. Immunol.* **2021**, *21*, 426–440.
[6] Zhu, S. Q.; Cui, Y. J.; Zhang, W. D.; et al. Inflammation can be a high-risk factor for mucosal nonunion of MRONJ by regulating SIRT1 signaling when treated with an oncologic dose of zoledronate. *Drug Des. Dev. Ther.* **2024**, *18*, 2793–2812.
[7] Wright, H. L.; Moots, R. J.; Edwards, S. W. The multifactorial role of neutrophils in rheumatoid arthritis. *Nat. Rev. Rheumatol.* **2014**, *10*, 593–601.
[8] Sapra, L.; Saini, C.; Mishra, P. K.; et al. *Bacillus coagulans* ameliorates inflammatory bone loss in post-menopausal osteoporosis *via* modulating the "Gut-Immune-Bone" axis. *Gut Microbes* **2025**, *17*, 2492378.
[9] Adam-Vizi, V.; Chinopoulos, C. Bioenergetics and the formation of mitochondrial reactive oxygen species. *Trends Pharmacol. Sci.* **2006**, *27*, 639–645.
[10] Sies, H.; Belousov, V. V.; Chandel, N. S.; et al. Defining roles of specific reactive oxygen species (ROS) in cell biology and physiology. *Nat. Rev. Mol. Cell Biol.* **2022**, *23*, 499–515.
[11] Sies, H.; Jones, D. P. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. *Nat. Rev. Mol. Cell Biol.* **2020**, *21*, 363–383.
[12] Sczepanik, F. S. C.; Grossi, M. L.; Casati, M.; et al. Periodontitis is an inflammatory disease of oxidative stress: We should treat it that way. *Periodontology 2000* **2020**, *84*, 45–68.
[13] Smallwood, M. J.; Nissim, A.; Knight, A. R.; et al. Oxidative stress in autoimmune rheumatic diseases. *Free Radic. Biol. Med.* **2018**, *125*, 3–14.
[14] Hayes, J. D.; Dinkova-Kostova, A. T.; Tew, K. D. Oxidative stress in cancer. *Cancer Cell* **2020**, *38*, 167–197.
[15] Li, X. Y.; Cao, Z. C.; Chen, M.; et al. Redox signaling and homeostasis. *Oral Sci. Homeost. Med.* **2025**, *1*, 9610003.
[16] Peng, B. Z.; Zhang, H. B. Mitochondrial homeostasis in stem cell senescence. *Oral Sci. Homeost. Med.* **2025**, *1*, 9610006.
[17] Zhang, M.; Zhang, X. L.; Tian, T. R.; et al. Anti-inflammatory activity of curcumin-loaded tetrahedral framework nucleic acids on acute gouty arthritis. *Bioact. Mater.* **2022**, *8*, 368–380.
[18] Wang, L. C.; Wang, Z. Q.; Pan, Y. Y.; et al. Polycatechol-derived mesoporous polydopamine nanoparticles for combined ROS scavenging and gene interference therapy in inflammatory bowel disease. *ACS Appl. Mater. Interfaces* **2022**, *14*, 19975–19987.
[19] Xiao, D. X.; Li, Y. J.; Tian, T. R.; et al. Tetrahedral framework nucleic acids loaded with aptamer AS1411 for siRNA delivery and gene silencing in malignant melanoma. *ACS Appl. Mater. Interfaces* **2021**, *13*, 6109–6118.
[20] Yao, Y. X.; Lei, X. Y.; Wang, Y.; et al. A mitochondrial nanoguard modulates redox homeostasis and bioenergy metabolism in diabetic peripheral neuropathy. *ACS Nano* **2023**, *17*, 22334–22354.
[21] Arfeen, M.; Srivastava, A.; Srivastava, N.; et al. Design, classification, and adverse effects of NSAIDs: A review on recent advancements. *Bioorg. Med. Chem.* **2024**, *112*, 117899.
[22] McDonough, A. K.; Curtis, J. R.; Saag, K. G. The epidemiology of glucocorticoid-associated adverse events. *Curr. Opin. Rheumatol.* **2008**, *20*, 131–137.
[23] Aftab, M.; Ali, H.; Ullah, M.; et al. Biomedical applications of carbon dots: Advances in antimicrobial therapy and targeted delivery systems. *Biomed. Mater. Devices* **2026**, *4*, 3136–3157.
[24] Zhang, H. L.; Chen, H. X.; Hu, X. M.; et al. Inflammation-modulating polymeric nanoparticles: Design strategies, mechanisms, and therapeutic applications. *eBioMedicine* **2025**, *118*, 105837.
[25] Allen, T. M.; Cullis, P. R. Liposomal drug delivery systems: From concept to clinical applications. *Adv. Drug Deliv. Rev.* **2013**, *65*, 36–48.
[26] Abu Lila, A. S.; Ishida, T. Liposomal delivery systems: Design optimization and current applications. *Biol. Pharm. Bull.* **2017**, *40*, 1–10.
[27] Huang, K. X.; Guo, R.; Luo, H. Y.; et al. Mucoadhesive liposomal delivery system synergizing anti-inflammation and anti-oxidation for enhanced treatment against dry eye disease. *J. Control. Release* **2024**, *368*, 318–328.
[28] Choi, S. J.; Lee, J. K.; Jeong, J.; et al. Toxicity evaluation of inorganic nanoparticles: Considerations and challenges. *Mol. Cell. Toxicol.* **2013**, *9*, 205–210.
[29] Zhang, T.; Tian, T. R.; Lin, Y. F. Functionalizing framework nucleic-acid-based nanostructures for biomedical application. *Adv. Mater.* **2022**, *34*, 2107820.
[30] Gu, J. J.; Liang, J. L.; Tian, T. R.; et al. Current understanding and translational prospects of tetrahedral framework nucleic acids. *JACS Au* **2025**, *5*, 486–520.
[31] Tan, T. T.; Li, J. J.; Fan, W. S.; et al. Tetrahedral framework nucleic acid relieves sepsis-induced intestinal injury by regulating M2 macrophages. *Cell Prolif.* **2025**, *58*, e13803.
[32] Walsh, A. S.; Yin, H. F.; Erben, C. M.; et al. DNA cage delivery to mammalian cells. *ACS Nano* **2011**, *5*, 5427–5432.
[33] Shi, S. R.; Li, Y. J.; Zhang, T.; et al. Biological effect of differently sized tetrahedral framework nucleic acids: Endocytosis, proliferation, migration, and biodistribution. *ACS Appl. Mater. Interfaces* **2021**, *13*, 57067–57074.
[34] Xu, J. P.; Wang, G. A.; Gao, L.; et al. Enabling programmable dynamic DNA chemistry using small-molecule DNA binders. *Nat. Commun.* **2023**, *14*, 4248.
[35] Li, C.; Feng, X. R.; Li, S. H.; et al. Tetrahedral DNA loaded siCCR2 restrains M1 macrophage polarization to ameliorate pulmonary fibrosis in chemoradiation-induced murine model. *Mol. Ther.* **2024**, *32*, 766–782.
[36] Li, Z. H.; Tang, Y. L.; Wang, L. H.; et al. Tetrahedral framework nucleic acids-based delivery of microRNA-155 alleviates intervertebral disc degeneration through targeting Bcl-2/Bax apoptosis pathway. *Cell Prolif.* **2024**, *57*, e13689.
[37] Xu, X. X.; Fu, Y. Y.; Luo, D. L.; et al. Therapeutic effects of tetrahedral framework nucleic acids and tFNAs-miR22 on retinal ischemia/reperfusion injury. *Cell Prolif.* **2024**, *57*, e13695.
[38] Qi, P. P.; Cao, M.; Song, L. J.; et al. The biological activity of cationic liposomes in drug delivery and toxicity test in animal models. *Environ. Toxicol. Pharmacol.* **2016**, *47*, 159–164.
[39] Zhou, M.; Gao, S.; Zhang, X. L.; et al. The protective effect of tetrahedral framework nucleic acids on periodontium under inflammatory conditions. *Bioact. Mater.* **2021**, *6*, 1676–1688.
[40] Bai, L.; Feng, M. G.; Li, Q. M.; et al. Curcumin delivery using tetrahedral framework nucleic acids enhances bone regeneration in osteoporotic rats. *Chem. Eng. J.* **2023**, *472*, 144978.
[41] Sies, H.; Mailloux, R. J.; Jakob, U. Fundamentals of redox regulation in biology. *Nat. Rev. Mol. Cell Biol.* **2024**, *25*, 701–719.
[42] Davies, M. J. Protein oxidation and peroxidation. *Biochem. J.* **2016**, *473*, 805–825.
[43] Murphy, M. P.; Holmgren, A.; Larsson, N. G.; et al. Unraveling the biological roles of reactive oxygen species. *Cell Metab.* **2011**, *13*, 361–366.
[44] Ferrer-Sueta, G.; Campolo, N.; Trujillo, M.; et al. Biochemistry of peroxynitrite and protein tyrosine nitration. *Chem. Rev.* **2018**, *118*, 1338–1408.

[45] van Dam, L.; Pagès-Gallego, M.; Polderman, P. E.; et al. The human 2-cys peroxiredoxins form widespread, cysteine-dependent- and isoform-specific protein-protein interactions. *Antioxid. Basel Switz.* **2021**, *10*, 627.

[46] Sies, H. Hydrogen peroxide as a central redox signaling molecule in physiological oxidative stress: Oxidative eustress. *Redox Biol.* **2017**, *11*, 613–619.

[47] Thomas, C.; MacKey, M. M.; Diaz, A. A.; et al. Hydroxyl radical is produced *via* the Fenton reaction in submitochondrial particles under oxidative stress: Implications for diseases associated with iron accumulation. *Redox Rep.* **2009**, *14*, 102–108.

[48] di Mascio, P.; Martinez, G. R.; Miyamoto, S.; et al. Singlet molecular oxygen reactions with nucleic acids, lipids, and proteins. *Chem. Rev.* **2019**, *119*, 2043–2086.

[49] Lim, P.; Wuenschell, G. E.; Holland, V.; et al. Peroxyl radical mediated oxidative DNA base damage: Implications for lipid peroxidation induced mutagenesis. *Biochemistry* **2004**, *43*, 15339–15348.

[50] Nauser, T.; Gebicki, J. M. Reaction rates of glutathione and ascorbate with alkyl radicals are too slow for protection against protein peroxidation *in vivo*. *Arch. Biochem. Biophys.* **2017**, *633*, 118–123.

[51] Eiserich, J. P.; Hristova, M.; Cross, C. E.; et al. Formation of nitric oxide-derived inflammatory oxidants by myeloperoxidase in neutrophils. *Nature* **1998**, *391*, 393–397.

[52] Pak, V. V.; Ezeriņa, D.; Lyublinskaya, O. G.; et al. Ultrasensitive genetically encoded indicator for hydrogen peroxide identifies roles for the oxidant in cell migration and mitochondrial function. *Cell Metab.* **2020**, *31*, 642–653.e6.

[53] Salvador, A.; Sousa, J.; Pinto, R. E. Hydroperoxyl, superoxide and pH gradients in the mitochondrial matrix: A theoretical assessment. *Free Radic. Biol. Med.* **2001**, *31*, 1208–1215.

[54] Marquis, R. Oxygen metabolism, oxidative stress and acid-base physiology of dental plaque biofilms. *J. Ind. Microbiol.* **1995**, *15*, 198–207.

[55] Wang, Y. B.; Ren, Y. R.; Zhang, Y. T.; et al. Periodontitis therapy with iron alginate and glucose oxidase based on the Fenton reaction. *Mater. Des.* **2023**, *235*, 112426.

[56] Girotti, A. W. Lipid hydroperoxide generation, turnover, and effector action in biological systems. *J. Lipid Res.* **1998**, *39*, 1529–1542.

[57] Zhang, B. Y.; Pan, C. Y.; Feng, C.; et al. Role of mitochondrial reactive oxygen species in homeostasis regulation. *Redox Rep.* **2022**, *27*, 45–52.

[58] Kračun, D.; Zurich, U. H.; et al. NADPH oxidases: Redox regulation of cell homeostasis and disease. *Physiol. Rev.* **2025**, *105*, 1291–1428.

[59] Jiang, A. W.; Wang, L. Y.; Liu, X. Y.; et al. ROS-Drp1-mitophagy feedback loop regulates myogenic differentiation *via* actin cytoskeleton remodeling-mediated MRTF-A/SRF axis. *Redox Rep.* **2025**, *30*, 2536400.

[60] Obrador, E.; Montoro, A. Ionizing radiation, antioxidant response and oxidative damage: Radiomodulators. *Antioxidants* **2023**, *12*, 1219.

[61] Chen, Y. S.; Tian, H. X.; Rong, D. C.; et al. ROS homeostasis in cell fate, pathophysiology, and therapeutic interventions. *Mol. Biomed.* **2025**, *6*, 89.

[62] Forrester, S. J.; Kikuchi, D. S.; Hernandes, M. S.; et al. Reactive oxygen species in metabolic and inflammatory signaling. *Circ. Res.* **2018**, *122*, 877–902.

[63] Lennicke, C.; Cochemé, H. M. Redox metabolism: ROS as specific molecular regulators of cell signaling and function. *Mol. Cell* **2021**, *81*, 3691–3707.

[64] Averill-Bates, D. Reactive oxygen species and cell signaling. *Review. Biochim. Biophys. Acta BBA Mol. Cell Res.* **2024**, *1871*, 119573.

[65] Chen, G.; Kroemer, G.; Kepp, O. Mitophagy: An emerging role in aging and age-associated diseases. *Front. Cell Dev. Biol.* **2020**, *8*, 200.

[66] Leiding, J. W.; Mathews, C. E.; Arnold, D. E.; et al. The role of NADPH oxidase 2 in leukocytes. *Antioxidants* **2025**, *14*, 309.

[67] Bode, K.; Hauri-Hohl, M.; Jaquet, V.; et al. Unlocking the power of NOX2: A comprehensive review on its role in immune regulation. *Redox Biol.* **2023**, *64*, 102795.

[68] Bae, T.; Hallis, S. P.; Kwak, M. K. Hypoxia, oxidative stress, and the interplay of HIFs and NRF2 signaling in cancer. *Exp. Mol. Med.* **2024**, *56*, 501–514.

[69] Kovac, S.; Angelova, P. R.; Holmström, K. M.; et al. Nrf2 regulates ROS production by mitochondria and NADPH oxidase. *Biochim. Biophys. Acta BBA Gen. Subj.* **2015**, *1850*, 794–801.

[70] Schieber, M.; Chandel, N. S. ROS function in redox signaling and oxidative stress. *Curr. Biol.* **2014**, *24*, R453–R462.

[71] Chahla, C.; Kovacic, H.; Ferhat, L.; et al. Pathological impact of redox post-translational modifications. *Antioxid. Redox Signal.* **2024**, *41*, 152–180.

[72] Yadav, D. K.; Kumar, S.; Choi, E. H.; et al. Molecular dynamic simulations of oxidized skin lipid bilayer and permeability of reactive oxygen species. *Sci. Rep.* **2019**, *9*, 4496.

[73] Omari Shekaftik, S.; Nasirzadeh, N. 8-Hydroxy-2'-deoxyguanosine (8-OHdG) as a biomarker of oxidative DNA damage induced by occupational exposure to nanomaterials: A systematic review. *Nanotoxicology* **2021**, *15*, 850–864.

[74] Blaser, H.; Dostert, C.; Mak, T. W.; et al. TNF and ROS crosstalk in inflammation. *Trends Cell Biol.* **2016**, *26*, 249–261.

[75] Morris, G.; Gevezova, M.; Sarafian, V.; et al. Redox regulation of the immune response. *Cell. Mol. Immunol.* **2022**, *19*, 1079–1101.

[76] Sendtner, N.; Seitz, R.; Brandl, N.; et al. Reactive oxygen species across death pathways: Gatekeepers of apoptosis, ferroptosis, pyroptosis, paraptosis, and beyond. *Int. J. Mol. Sci.* **2025**, *26*, 10240.

[77] Komaroff, A. L.; Dantzer, R. Causes of symptoms and symptom persistence in long COVID and myalgic encephalomyelitis/chronic fatigue syndrome. *Cell Rep. Med.* **2025**, *6*, 102259.

[78] Fiadeiro, M. B.; Diogo, J. C.; Silva, A. A.; et al. NADPH oxidases in neurodegenerative disorders: Mechanisms and therapeutic opportunities. *Antioxid. Redox Signal.* **2024**, *41*, 522–541.

[79] Zhang, Z. S.; Guo, J. W. Deciphering oxidative stress in cardiovascular disease progression: A blueprint for mechanistic understanding and therapeutic innovation. *Antioxid. Basel Switz.* **2024**, *14*, 38.

[80] Kowalczyk, P.; Krych, S.; Kramkowski, K.; et al. Effect of oxidative stress on mitochondrial damage and repair in heart disease and ischemic events. *Int. J. Mol. Sci.* **2024**, *25*, 12467.

[81] Muro, P.; Zhang, L.; Li, S. X.; et al. The emerging role of oxidative stress in inflammatory bowel disease. *Front. Endocrinol.* **2024**, *15*, 1390351.

[82] Jomova, K.; Alomar, S. Y.; Alwasel, S. H.; et al. Several lines of antioxidant defense against oxidative stress: Antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants. *Arch. Toxicol.* **2024**, *98*, 1323–1367.

[83] Irato, P.; Santovito, G. Enzymatic and non-enzymatic molecules with antioxidant function. *Antioxidants* **2021**, *10*, 579.

[84] Fukai, T.; Ushio-Fukai, M. Superoxide dismutases: Role in redox signaling, vascular function, and diseases. *Antioxid. Redox Signal.* **2011**, *15*, 1583–1606.

[85] Baker, A.; Lin, C. C.; Lett, C.; et al. Catalase: A critical node in the regulation of cell fate. *Free Radic. Biol. Med.* **2023**, *199*, 56–66.

[86] Iglesias-Matesanz, P.; Lacalle-Gonzalez, C.; Lopez-Blazquez, C.; et al. Glutathione peroxidases: An emerging and promising therapeutic target for pancreatic cancer treatment. *Antioxid. Basel Switz.* **2024**, *13*, 1405.

[87] Stancill, J. S.; Broniowska, K. A.; Oleson, B. J.; et al. Pancreatic β-cells detoxify H_2O_2 through the peroxiredoxin/thioredoxin

antioxidant system. *J. Biol. Chem.* **2019**, *294*, 4843–4853.
[88] Zhang, Y. W.; Zhang, Y. F.; Mei, Y. K.; et al. Reactive oxygen species enlightened therapeutic strategy for oral and maxillofacial diseases-art of destruction and reconstruction. *Biomedicines* **2022**, *10*, 2905.
[89] Yang, S. Y.; Yang, X. The role of reactive oxygen species (ROS) in periodontitis: A potential therapeutic target. *Immun. Inflamm. Dis.* **2025**, *13*, e70301.
[90] Taniguchi, N.; Osaki, M.; Onuma, K.; et al. Bisphosphonate-induced reactive oxygen species inhibit proliferation and migration of oral fibroblasts: A pathogenesis of bisphosphonate-related osteonecrosis of the jaw. *J. Periodontology* **2020**, *91*, 947–955.
[91] Hu, Z. Y.; Liu, Y. L.; Qiu, J. K.; et al. Oral submucous fibrosis: Regulatory mechanism of collagen metabolism and management. *Biomed. Pharmacother.* **2026**, *196*, 119053.
[92] Rauf, A.; Khalil, A. A.; Awadallah, S.; et al. Reactive oxygen species in biological systems: Pathways, associated diseases, and potential inhibitors-a review. *Food Sci. Nutr.* **2024**, *12*, 675–693.
[93] Lu, X. L.; Zhao, C. H.; Yao, X. L.; et al. Quercetin attenuates high fructose feeding-induced atherosclerosis by suppressing inflammation and apoptosis *via* ROS-regulated PI3K/AKT signaling pathway. *Biomedecine Pharmacother.* **2017**, *85*, 658–671.
[94] Kang, W. Y.; Jia, Z. L.; Tang, D.; et al. *Fusobacterium nucleatum* facilitates apoptosis, ROS generation, and inflammatory cytokine production by activating AKT/MAPK and NF-κB signaling pathways in human gingival fibroblasts. *Oxid. Med. Cell. Longev.* **2019**, *2019*, 1681972.
[95] Yu, Y. J.; Zhao, S.; Gu, D. A.; et al. Cerium oxide nanozyme attenuates periodontal bone destruction by inhibiting the ROS-NFκB pathway. *Nanoscale* **2022**, *14*, 2628–2637.
[96] Son, Y.; Kim, S.; Chung, H. T.; et al. Reactive oxygen species in the activation of MAP kinases. *Hydrogen Peroxide and Cell Signaling, Part C*. Amsterdam: Elsevier, **2013**, 27–48.
[97] Kma, L.; Baruah, T. J. The interplay of ROS and the PI3K/Akt pathway in autophagy regulation. *Biotechnol. Appl. Biochem.* **2022**, *69*, 248–264.
[98] de Molon, R. S.; Vernal, R.; Oliveira, G. E.; et al. Inflammatory bone loss and signaling pathways in periodontitis: Mechanistic insights and emerging therapeutic strategies. *Bone Res.* **2026**, *14*, 1.
[99] Chen, Z. L.; Lang, G. P.; Xu, X.; et al. The role of NF-kappaB in the inflammatory processes related to dental caries, pulpitis, apical periodontitis, and periodontitis-a narrative review. *PeerJ* **2024**, *12*, e17953.
[100] Chen, Y. T.; Kao, S. H.; Chuang, C. Y.; et al. Alisol a exerts anti-proliferative activity against human oral cancer cells through triggering JNK/p38 MAPK-mediated apoptotic cascade. *Oncol. Res.* **2025**, *33*, 3387–3404.
[101] Wang, Z.; Wang, J. X.; Liu, J. C.; et al. Platinum nanoparticles enhance osteogenic differentiation of human dental follicle stem cells *via* scavenging ROS. *Smart Mater. Med.* **2023**, *4*, 621–638.
[102] Chuhuaicura, P.; Rodríguez-Niklitschek, C.; Oporto, G. H.; et al. Distinct molecular mechanisms in oral mucosal wound healing: Translational insights and future directions. *Int. J. Mol. Sci.* **2025**, *26*, 10660.
[103] Mu, H. L.; Yang, B. N.; Wang, Y.; et al. Inhibition of fibulin-3 ameliorates periodontal inflammation through reducing M1 macrophage polarization *via* EGFR/PI3K/AKT pathway. *J. Periodontology* **2025**, *96*, 440–454.
[104] Tian, Y. J.; Li, Y.; Liu, J. L.; et al. Photothermal therapy with regulated Nrf2/NF-κB signaling pathway for treating bacteria-induced periodontitis. *Bioact. Mater.* **2022**, *9*, 428–445.
[105] Roberts, J. S.; Atanasova, K. R.; Lee, J.; et al. Opportunistic pathogen *Porphyromonas gingivalis* modulates danger signal ATP-mediated antibacterial NOX2 pathways in primary epithelial cells. *Front. Cell. Infect. Microbiol.* **2017**, *7*, 291.
[106] Huang, N.; Cao, L. Y.; Xu, Y.; et al. A mitochondria-targeted nanoantioxidant restores alveolar bone homeostasis in periodontitis by quenching ROS and suppressing the cGAS-STING pathway. *Bioact. Mater.* **2026**, *60*, 574–589.
[107] Xiu, Z. L.; Zhu, Y. J.; Li, X. F.; et al. A multifunctional injectable microsphere with enhanced near-infrared photo-antibacterial, ROS scavenging, and anti-inflammatory properties for periodontitis treatment. *Theranostics* **2025**, *15*, 3750–3780.
[108] Gou, H. Q.; Chen, X.; Zhu, X. M.; et al. Sequestered SQSTM1/p62 crosstalk with Keap1/NRF2 axis in hPDLCs promotes oxidative stress injury induced by periodontitis. *Free Radic. Biol. Med.* **2022**, *190*, 62–74.
[109] Saso, L.; Reza, A.; Ng, E.; et al. A comprehensive analysis of the role of oxidative stress in the pathogenesis and chemoprevention of oral submucous fibrosis. *Antioxid. Basel Switz.* **2022**, *11*, 868.
[110] Hsieh, Y. P.; Wu, K. J.; Chen, H. M.; et al. Arecoline activates latent transforming growth factor β1 *via* mitochondrial reactive oxygen species in buccal fibroblasts: Suppression by epigallocatechin-3-gallate. *J. Formos. Med. Assoc.* **2018**, *117*, 527–534.
[111] Pant, I.; Rao, S. G.; Kondaiah, P. Role of *Areca* nut induced JNK/ATF2/Jun axis in the activation of TGF-β pathway in precancerous Oral Submucous Fibrosis. *Sci. Rep.* **2016**, *6*, 34314.
[112] Chang, M. C.; Lin, L. D.; Wu, H. L.; et al. *Areca* nut-induced buccal mucosa fibroblast contraction and its signaling: A potential role in oral submucous fibrosis: A precancer condition. *Carcinogenesis* **2013**, *34*, 1096–1104.
[113] Chang, M. C.; Chen, Y. J.; Chang, H. H.; et al. *Areca* Nut components affect COX-2, cyclin B1/cdc25C and keratin expression, PGE2 production in keratinocyte is related to reactive oxygen species, CYP1A1, Src, EGFR and Ras signaling. *PLoS One* **2014**, *9*, e101959.
[114] Chang, M. C.; Chan, C. P.; Chen, Y. J.; et al. *Areca* nut components stimulate ADAM17, IL-1α, PGE2 and 8-isoprostane production in oral keratinocyte: Role of reactive oxygen species, EGF and JAK signaling. *Oncotarget* **2016**, *7*, 16879–16894.
[115] Zeng, Y. Y.; Luo, M. S.; Yao, Z. L.; et al. Adiponectin inhibits ROS/NLRP3 inflammatory pathway through FOXO3A to ameliorate oral submucosal fibrosis. *Odontology* **2024**, *112*, 811–825.
[116] Feng, Y.; Tu, S. Q.; Hou, Y. L.; et al. Alendronate sodium induces G1 phase arrest and apoptosis in human umbilical vein endothelial cells by inhibiting ROS-mediated ERK1/2 signaling. *Toxicology* **2024**, *508*, 153917.
[117] Ye, W.; Liao, Y. L.; Liu, X. Y.; et al. Dectin-2 depletion alleviates osteoclast-induced bone loss in periodontitis *via* Syk/NOX2/ROS signaling. *Free Radic. Biol. Med.* **2025**, *229*, 13–29.
[118] Ko, K. I.; Sculean, A.; Graves, D. T. Diabetic wound healing in soft and hard oral tissues. *Transl. Res.* **2021**, *236*, 72–86.
[119] Zhou, Q. Q.; Zhou, M. Q.; Yang, G. F.; et al. Enhancing diabetic oral wound healing with miR-132 delivered through tetrahedral DNA nanostructures. *Small* **2025**, *21*, 2411353.
[120] Zhao, W.; Zhang, Y.; Chen, J.; et al. Revolutionizing oral care: Reactive oxygen species (ROS)-Regulating biomaterials for combating infection and inflammation. *Redox Biol.* **2025**, *79*, 103451.
[121] Xiao, L. Y.; Feng, M. G.; Chen, C.; et al. Microenvironment-regulating drug delivery nanoparticles for treating and preventing typical biofilm-induced oral diseases. *Adv. Mater.* **2025**, *37*, 2304982.
[122] Sun, W. M.; Yang, T. R.; Wang, C. X.; et al. Mitochondrial ROS participates in *Porphyromonas gingivalis*-induced pyroptosis in cementoblasts. *Heliyon* **2024**, *10*, e30814.
[123] Chang, M. C.; Tsai, Y. L.; Chen, Y. W.; et al. Butyrate induces reactive oxygen species production and affects cell cycle progression in human gingival fibroblasts. *J. Periodontal Res.* **2013**, *48*, 66–73.
[124] Toczewska, J.; Zalewska, A.; Konopka, T.; et al. Enzymatic

antioxidants activity in gingival crevicular fluid and saliva in advanced periodontitis. *Oral Dis.* **2023**, *29*, 3559–3570.
[125] Socransky, S. S.; Haffajee, A. D. Dental biofilms: Difficult therapeutic targets. *Periodontology 2000* **2002**, *28*, 12–55.
[126] Jamal, M.; Ahmad, W.; Andleeb, S.; et al. Bacterial biofilm and associated infections. *J. Chin. Med. Assoc.* **2018**, *81*, 7–11.
[127] Liu, W.; Guo, D. Y. Oxidative stress in periodontitis and the application of antioxidants in treatment: A narrative review. *Front. Physiol.* **2025**, *16*, 1485367.
[128] Wiraja, C.; Zhu, Y.; Lio, D. C. S.; et al. Framework nucleic acids as programmable carrier for transdermal drug delivery. *Nat. Commun.* **2019**, *10*, 1147.
[129] Kim, K. R.; Kim, H. Y.; Lee, Y. D.; et al. Self-assembled mirror DNA nanostructures for tumor-specific delivery of anticancer drugs. *J. Control. Release* **2016**, *243*, 121–131.
[130] Wu, H. Y.; Lyu, X. Y.; Xu, M. Z.; et al. A multifunctional miRNA delivery system based on tetrahedral framework nucleic acids for regulating inflammatory periodontal ligament stem cells and attenuating periodontitis bone loss. *ACS Appl. Mater. Interfaces* **2025**, *17*, 560–571.
[131] Xie, X. P.; Ma, W. J.; Zhan, Y. X.; et al. Methods to improve the stability of nucleic acid-based nanomaterials. *Curr. Drug Metab.* **2023**, *24*, 315–326.
[132] Fu, X.; Zhang, M.; Chen, C. P.; et al. Tetrahedral framework nucleic acid-based delivery of microRNA-29b: A precision nanotherapeutic strategy for oral submucous fibrosis. *Chem. Eng. J.* **2025**, *515*, 163736.
[133] Zhang, M.; Wen, Y. T.; Huang, Z. H.; et al. Targeted therapy for autoimmune diseases based on multifunctional frame nucleic acid system: Blocking TNF-α-NF-κB signaling and mediating macrophage polarization. *Chem. Eng. J.* **2023**, *454*, 140399.
[134] Zhao, Z.; Zhang, M.; Zhang, W. F.; et al. Resveratrol-loaded DNA tetrahedron nanocarrier attenuates acute gouty arthritis *via* dual modulation of apoptosis and pyroptosis pathways. *Chem. Eng. J.* **2025**, *526*, 170962.
[135] Fan, Q.; Sun, B. C.; Chao, J. Advancements in engineering tetrahedral framework nucleic acids for biomedical innovations. *Small Meth.* **2025**, *9*, 2401360.
[136] Ma, W. J.; Yang, Y. T.; Zhu, J. W.; et al. Biomimetic nanoerythrosome-coated aptamer–DNA tetrahedron/maytansine conjugates: pH-responsive and targeted cytotoxicity for HER2-positive breast cancer. *Adv. Mater.* **2022**, *34*, 2109609.
[137] Zhang, T.; Tian, T. R.; Zhou, R. H.; et al. Design, fabrication and applications of tetrahedral DNA nanostructure-based multifunctional complexes in drug delivery and biomedical treatment. *Nat. Protoc.* **2020**, *15*, 2728–2757.
[138] Goodman, R. P.; Schaap, I. A.; Tardin, C. F.; et al. Rapid chiral assembly of rigid DNA building blocks for molecular nanofabrication. *Science* **2005**, *310*, 1661–1665.
[139] Zhang, T.; Cui, W. T.; Tian, T. R.; et al. Progress in biomedical applications of tetrahedral framework nucleic acid-based functional systems. *ACS Appl. Mater. Interfaces* **2020**, *12*, 47115–47126.
[140] Liu, Y. H.; Sun, Y.; Li, S. H.; et al. Tetrahedral framework nucleic acids deliver antimicrobial peptides with improved effects and less susceptibility to bacterial degradation. *Nano Lett.* **2020**, *20*, 3602–3610.
[141] Liu, J. T.; Han, X. Y.; Zhang, T. Y.; et al. Reactive oxygen species (ROS) scavenging biomaterials for anti-inflammatory diseases: From mechanism to therapy. *J. Hematol. Oncol.* **2023**, *16*, 116.
[142] Cai, Z. W.; Li, Y.; Bai, L.; et al. Tetrahedral framework nucleic acids based small interfering RNA targeting receptor for advanced glycation end products for diabetic complications treatment. *ACS Nano* **2023**, *17*, 22668–22683.
[143] Liao, S. N.; Liu, Z. Q.; Lv, W. T.; et al. Efficient delivery of siRNA *via* tetrahedral framework nucleic acids: Inflammation attenuation and matrix regeneration in temporomandibular joint osteoarthritis. *ACS Appl. Mater. Interfaces* **2024**, *16*, 53499–53514.
[144] Zhang, T.; Ma, H. S.; Zhang, X. L.; et al. Functionalized DNA nanomaterials targeting toll-like receptor 4 prevent bisphosphonate-related osteonecrosis of the jaw *via* regulating mitochondrial homeostasis in macrophages. *Adv. Funct. Mater.* **2023**, *33*, 2213401.
[145] Liu, Z. Q.; Wang, B. W.; Li, S. H.; et al. Oral administration of a tetrahedral framework DNA-based nanoshot attenuates liver fibrosis *via* targeting galectin-3. *ACS Nano* **2025**, *19*, 23876–23892.
[146] Yue, Z. Q.; Yang, Y. C.; Nie, L.; et al. A binary siRNA-loaded tetrahedral DNA nanobox for synergetic anti-aging therapy. *Small* **2025**, *21*, 2408323.
[147] Zhang, M.; Fu, X.; Wang, Y.; et al. A sprayable nucleic acid hydrogel for diabetic wound healing *via* immunomodulation and angiogenesis. *Small* **2025**, *21*, e06587.
[148] Zhang, Z. C.; Fu, L. W.; Zheng, Y. Z.; et al. Antilipotoxic framework nucleic acid-loaded injectable hydrogel microspheres for the targeted delivery of miR-34a-5p inhibitors to attenuate dietary fat-associated osteoarthritis. *Chem. Eng. J.* **2025**, *522*, 168281.
[149] He, Y. T.; Liu, Z. Q.; Li, S. H.; et al. A tetrahedral framework DNA-based bioswitchable miR-150 delivery system for sepsis. *ACS Appl. Mater. Interfaces* **2024**, *16*, 58477–58488.
[150] Wang, R. Q.; Yang, Y. C.; Liang, J. L.; et al. Tetrahedral framework nucleic acid-based delivery of miR-34a inhibitor for the treatment of metabolic dysfunction-associated steatohepatitis. *ACS Appl. Mater. Interfaces* **2025**, *17*, 66460–66474.
[151] Li, J. J.; Yao, Y. X.; Wang, Y.; et al. Modulation of the crosstalk between schwann cells and macrophages for nerve regeneration: A therapeutic strategy based on a multifunctional tetrahedral framework nucleic acids system. *Adv. Mater.* **2022**, *34*, 2202513.
[152] Shi, S. R.; Chen, T. Y.; Lu, W. T.; et al. Amelioration of osteoarthritis *via* tetrahedral framework nucleic acids delivering microrna-124 for cartilage regeneration. *Adv. Funct. Mater.* **2023**, *33*, 2305558.
[153] Wang, Y. Q.; Liang, J. L.; Chen, Y.; et al. DNA tetrahedron functionalized microneedles blocking IL-6 to promote skin wound healing. *ACS Appl. Mater. Interfaces* **2025**, *17*, 42717–42734.
[154] Liu, Z. Q.; Chen, X. Y.; Ma, W. J.; et al. Suppression of lipopolysaccharide-induced sepsis by tetrahedral framework nucleic acid loaded with quercetin. *Adv. Funct. Mater.* **2022**, *32*, 2204587.
[155] Li, Y. J.; Li, J. Y.; Chang, Y. Q.; et al. Mitochondria-targeted drug delivery system based on tetrahedral framework nucleic acids for bone regeneration under oxidative stress. *Chem. Eng. J.* **2024**, *496*, 153723.
[156] Liu, S. B.; Liu, H. H.; Yang, Q. H.; et al. Tetrahedral framework nucleic acid-based cepharanthine attenuates TMJOA *via* cGAS-STING-NF-κB pathway modulation and macrophage reprogramming. *ACS Appl. Mater. Interfaces* **2026**, *18*, 4183–4197.
[157] Tian, Y.; Shi, S. R.; Lu, W. T.; et al. Tetrahedral framework nucleic acid composite hydrogel loaded with naringin for full alveolar bone regeneration. *ACS Appl. Mater. Interfaces* **2025**, *17*, 47985–47999.
[158] Han, Q.; Li, J. Q.; Deng, H.; et al. Tetrahedral framework nucleic acid (tFNA)-loaded metformin (met) modulates cellular pyroptosis and AMPK to ameliorate type II diabetic periodontitis. *Small* **2025**, *21*, 2411740.
[159] Chen, T. Y.; Lv, W. T.; Yang, M. X.; et al. Treatment of atherosclerosis by biomimetic responsive-targeting hybrid nanoparticles enabled by genetically engineering cell membranes and nucleic acid nanostructures for atorvastatin delivery. *Chem. Eng. J.* **2025**, *511*, 162130.
[160] Xie, Y. T.; Shi, S. R.; Lv, W. T.; et al. Tetrahedral framework nucleic acids delivery of pirfenidone for anti-inflammatory and antioxidative effects to treat idiopathic pulmonary fibrosis. *ACS Nano* **2024**, *18*, 26704–26721.
[161] Zhou, M.; Tang, Y. L.; Lu, Y. F.; et al. Framework nucleic acid-

based and neutrophil-based nanoplatform loading baicalin with targeted drug delivery for anti-inflammation treatment. *ACS Nano* **2025**, *19*, 3455–3469.

[162] Feng, S. J.; Yan, R.; Tang, C.; et al. Modulating ferroptosis for the prevention of urinary stone recurrence: An innovative strategy employing Tetrahedral Framework Nucleic acids and Polydatin conjugates. *Chem. Eng. J.* **2024**, *496*, 153655.

[163] Liu, S. B.; Yang, Q. H.; Liu, H. H.; et al. Engineering a tetrahedral framework nucleic acid-based nanomedicine for precise intracellular delivery of rapamycin to rescue senescent bone mesenchymal stem cells. *Chem. Eng. J.* **2026**, *536*, 175445.

[164] Xie, Y.; He, J. J.; Li, S. H.; et al. A transdermal drug delivery system based on nucleic acid nanomaterials for skin photodamage treatment. *Adv. Funct. Mater.* **2023**, *33*, 2303580.

[165] Qi, C.; Sun, Q.; Xiao, D. X.; et al. Tetrahedral framework nucleic acids/hyaluronic acid-methacrylic anhydride hybrid hydrogel with antimicrobial and anti-inflammatory properties for infected wound healing. *Int. J. Oral Sci.* **2024**, *16*, 30.

[166] Zhang, G. R.; Cui, W. T.; Wu, H. Y.; et al. DNA framework-based nanomedicine platform: A triple-function strategy for treating periodontitis *via* antibacterial, anti-inflammatory, and osteogenesis-promoting activities. *Int. J. Oral Sci.* **2026**, *18*, 39.

[167] Lyu, X. Y.; Wu, H. Y.; Chen, Y.; et al. A multifunctional nano complex as miRNA/antibiotic co-delivery system based on tetrahedral framework DNA: Application to infected wound healing. *Small* **2024**, *20*, 2406629.

[168] Ning, C.; et al. Silk fibroin hydrogel adhesive combined with miR-455 modified framework nucleic acids/ROS-responsive CeO_2 nanozymes for *Meniscus tears* reconstruction. *Regen. Biomater.* **2026**, *13*, rbag014.

[169] Yang, Y. C.; Liang, J. L.; Qin, Z. Q.; et al. Programmable metal-nucleic acid biomineralized hydrogel for infected wound healing *via* mitochondrial regulation. *Acta Biomater.* **2026**, *215*, 302–316.

[170] Zhou, M.; Lu, Y. F.; Tang, Y. L.; et al. A DNA-based nanorobot for targeting, hitchhiking, and regulating neutrophils to enhance sepsis therapy. *Biomaterials* **2025**, *318*, 123183.

[171] Yin, W. M.; Yang, Y. C.; Yue, Z. Q.; et al. Framework nucleic acid-based hydrogel for sequential immune regulation and endogenous TGF-β1 capture in wound healing. *Biomaterials* **2026**, *327*, 123780.

[172] Rupaimoole, R.; Slack, F. J. microRNA therapeutics: Towards a new era for the management of cancer and other diseases. *Nat. Rev. Drug Discov.* **2017**, *16*, 203–222.

[173] Wang, M.; Wang, Y. B.; Zhang, P. Q.; et al. Neutrophil-like cell membrane-coated metal-organic frameworks for siRNA delivery targeting NOX4 to alleviate oxidative stress in acute ischemic injury. *Acta Biomater.* **2025**, *196*, 487–505.

[174] Liao, S. N.; Li, S. H.; Liu, Z. Q.; et al. A bioswitchable siRNA delivery system: RNAi therapy based on tetrahedral framework nucleic acids for bone defect repair. *Nanoscale* **2024**, *16*, 21531–21544.

[175] Sefah, K.; Shangguan, D. H.; Xiong, X. L.; et al. Development of DNA aptamers using cell-SELEX. *Nat. Protoc.* **2010**, *5*, 1169–1185.

[176] Afrasiabi, S.; Pourhajibagher, M.; Raoofian, R.; et al. Therapeutic applications of nucleic acid aptamers in microbial infections. *J. Biomed. Sci.* **2020**, *27*, 6.

[177] Wan, L. Y.; Yuan, W. F.; Ai, W. B.; et al. An exploration of aptamer internalization mechanisms and their applications in drug delivery. *Expert Opin. Drug Deliv.* **2019**, *16*, 207–218.

[178] Butterfield, D. A.; Halliwell, B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. *Nat. Rev. Neurosci.* **2019**, *20*, 148–160.

[179] Wang, Y. Y.; Zhu, J. W.; Jia, W. Q.; et al. BACE1 aptamer-modified tetrahedral framework nucleic acid to treat Alzheimer's disease in an APP-PS1 animal model. *ACS Appl. Mater. Interfaces* **2022**, *14*, 44228–44238.

[180] Xiang, J.; Zhang, W.; Cai, X. F.; et al. DNA aptamers targeting BACE1 reduce amyloid levels and rescue neuronal deficiency in cultured cells. *Mol. Ther. Nucleic Acids* **2019**, *16*, 302–312.

[181] Bas, T. G. Dietary polyphenols (flavonoids) derived from plants for use in therapeutic health: Antioxidant performance, ROS, molecular mechanisms, and bioavailability limitations. *Int. J. Mol. Sci.* **2026**, *27*, 1404.

[182] Rudrapal, M.; Khairnar, S. J.; Khan, J.; et al. Dietary polyphenols and their role in oxidative stress-induced human diseases: Insights into protective effects, antioxidant potentials and mechanism(s) of action. *Front. Pharmacol.* **2022**, *13*, 806470.

[183] Rao, M. J.; Zheng, B. S. The role of polyphenols in abiotic stress tolerance and their antioxidant properties to scavenge reactive oxygen species and free radicals. *Antioxid. Basel Switz.* **2025**, *14*, 74.

[184] Tumilaar, S. G.; Hardianto, A.; Dohi, H.; et al. A comprehensive review of free radicals, oxidative stress, and antioxidants: Overview, clinical applications, global perspectives, future directions, and mechanisms of antioxidant activity of flavonoid compounds. *J. Chem.* **2024**, *2024*, 5594386.

[185] Biswas, P.; Dey, D.; Biswas, P. K.; et al. A comprehensive analysis and anti-cancer activities of quercetin in ROS-mediated cancer and cancer stem cells. *Int. J. Mol. Sci.* **2022**, *23*, 11746.

[186] Lin, S. Y.; Zhang, Q.; Li, S. H.; et al. Tetrahedral framework nucleic acids-based delivery promotes intracellular transfer of healing peptides and accelerates diabetic would healing. *Cell Prolif.* **2022**, *55*, e13279.

[187] Liu, Z. Q.; Chen, X. Y.; Xu, Z. A.; et al. Diamond-inspired DNA hydrogel based on tetrahedral framework nucleic acids for burn wound healing. *Adv. Mater.* **2025**, *37*, e09727.

[188] Qin, X.; Zhang, Z. Y.; Wei, T.; et al. Mucosal gingipain vaccine based on framework nucleic acid engineering for the treatment of periodontitis. *ACS Appl. Mater. Interfaces* **2026**, *18*, 21562–21578.

[189] Xu, Z. A.; Liu, Z. Q.; Li, Y. J.; et al. An immunomodulatory DNA hydrogel based on tetrahedral framework nucleic acids for treating psoriasis. *ACS Appl. Mater. Interfaces* **2026**, *18*, 794–809.

[190] Tian, T. R.; Zhang, T.; Shi, S. R.; et al. A dynamic DNA tetrahedron framework for active targeting. *Nat. Protoc.* **2023**, *18*, 1028–1055.

[191] Gao, Y.; Chen, X. Y.; Tian, T. R.; et al. A lysosome-activated tetrahedral nanobox for encapsulated siRNA delivery. *Adv. Mater.* **2022**, *34*, 2201731.

[192] Ding, H. T.; Tan, P.; Fu, S. Q.; et al. Preparation and application of pH-responsive drug delivery systems. *J. Control. Release* **2022**, *348*, 206–238.

[193] Yan, R.; Cui, W. T.; Ma, W. J.; et al. Typhaneoside-tetrahedral framework nucleic acids system: Mitochondrial recovery and antioxidation for acute kidney injury treatment. *ACS Nano* **2023**, *17*, 8767–8781.

[194] Singh, R.; Yadav, P.; Naveena A, H.; et al. Cationic lipid modification of DNA tetrahedral nanocages enhances their cellular uptake. *Nanoscale* **2023**, *15*, 1099–1108.

[195] Lim, D. Y.; Hwang, B. H. Aptamer-modified tetrahedral DNA nanostructure-immobilized liposome for specific gene delivery and potential cancer theragnostic. *Biotechnol. J.* **2024**, *19*, 2300156.

[196] Zhang, G. R.; Gao, Y.; Yao, L.; et al. Tetrahedral framework nucleic acids as an efficient nasal-to-brain delivery carrier *via* neural transport pathways. *Adv. Funct. Mater.* **2025**, *35*, 2419914.

[197] Holzer-Geissler, J. C. J.; Schwingenschuh, S.; Zacharias, M.; et al. The impact of prolonged inflammation on wound healing. *Biomedicines* **2022**, *10*, 856.

[198] Shi, R.; Zhu, Y. J.; Chen, Y.; et al. Advances in DNA nanotechnology for chronic wound management: Innovative functional nucleic acid nanostructures for overcoming key challenges. *J. Control. Release* **2024**, *375*, 155–177.

[199] Zhang, F. C.; Miao, Y.; Liu, Q. Y.; et al. Changes of pro-inflammatory and anti-inflammatory macrophages after peripheral

nerve injury. *RSC Adv.* **2020**, *10*, 38767–38773.
[200] Yoo, M. C.; Chon, J.; Jung, J.; et al. Potential therapeutic strategies and substances for facial nerve regeneration based on preclinical studies. *Int. J. Mol. Sci.* **2021**, *22*, 4926.
[201] Hu, S. Y.; Li, H. M.; Jiang, H. H.; et al. Macrophage activation in synovitis and osteoarthritis of temporomandibular joint and its relationship with the progression of synovitis and bone remodeling. *Am. J. Pathol.* **2024**, *194*, 296–306.
[202] Liang, L. L.; Li, X. W.; Liang, H.; et al. Navigating oxidative stress in oral bone regeneration: Mechanisms and reactive oxygen species-regulating biomaterial strategies. *Regen. Biomater.* **2025**, *12*, rbaf091.
[203] Yao, Y. X.; Wen, Y. T.; Li, Y. J.; et al. Tetrahedral framework nucleic acids facilitate neurorestoration of facial nerves by activating the NGF/PI3K/AKT pathway. *Nanoscale* **2021**, *13*, 15598–15610.
[204] Huang, K.; Li, Q. M.; Lin, H. X.; et al. Cartilage-penetrating framework nucleic acid nanoparticles ameliorate osteoarthritis by promoting drug delivery and chondrocyte uptake. *Adv. Sci.* **2025**, *12*, 2502661.
[205] D'Autréaux, B.; Toledano, M. B. ROS as signalling molecules: Mechanisms that generate specificity in ROS homeostasis. *Nat. Rev. Mol. Cell Biol.* **2007**, *8*, 813–824.
[206] Hu, M. H.; Zhang, Y. Y.; Zhang, J.; et al. Double self-amplified programmable allosteric DNA nanomachine for enzymatically triggered spatially controllable molecular imaging. *Adv. Funct. Mater.* **2025**, *35*, 2501940.
[207] Riegger, J.; Schoppa, A.; Ruths, L.; et al. Oxidative stress as a key modulator of cell fate decision in osteoarthritis and osteoporosis: A narrative review. *Cell. Mol. Biol. Lett.* **2023**, *28*, 76.
[208] Zhu, Y. J.; Shi, R.; Lu, W. T.; et al. Framework nucleic acids as promising reactive oxygen species scavengers for anti-inflammatory therapy. *Nanoscale* **2024**, *16*, 7363–7377.

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