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Tetrahedral framework nucleic acids in the prevention and treatment of skin and mucosal diseases: Advances and prospects

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ABSTRACT

The application of DNA hybridization technology, grounded in Watson-Crick base pairing, has facilitated the rational design of framework nucleic acids (FNAs) featuring adaptable shapes and dimensions. These nanostructures exhibit remarkable stability and reproducibility, making them promising candidates for biomedical applications. Among various FNAs, tetrahedral FNAs (tFNAs), first introduced by Turberfield, are nanoscale assemblies of oligonucleotides that possess unique physical, chemical, and biological properties. Previous studies have demonstrated that tFNAs exhibit excellent cellular uptake, enhanced tissue permeability, and strong capabilities to promote cell migration, proliferation, and differentiation. Moreover, the intrinsic ability of tFNAs to efficiently penetrate cell membranes allows tFNAs to serve as versatile carriers for small-molecule drugs or functional oligonucleotides, thereby exerting significant anti-inflammatory, antioxidant, antibacterial, and immunomodulatory effects. These features highlight the therapeutic potential of tFNA-based complexes in skin, mucosal, and barrier tissue repair and regeneration. This review provides a comprehensive analysis of recent advances in the application of tFNAs for the prevention and treatment of skin, mucosal, and barrier tissue diseases, with a focus on their mechanisms of action and future prospects in regenerative medicine and targeted therapies.

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1. Introduction

Recent advances in precision medicine and nanobiotechnology have positioned nucleic acid-based therapies as a key research area of biomedicine. This is largely attributable to the unique mechanisms of action and broad application prospects of these therapies [1]. Nucleic acid drugs (NADs) provide novel strategies for treating a range of refractory diseases through precise gene regulation, including mRNA silencing, gene editing, and RNA activation. From foundational research to clinical trials [2], and now edging toward commercialization, NADs have demonstrated significant promise and enormous growth potential [1]. These drugs play a crucial role in managing genetic disorders [2], viral infections, and cancer [3,4] through the control of certain gene expression at the mRNA stage [5,6]. To date, the U.S. Food and Drug Administration (FDA) has approved 19 NADs based on different mechanisms, including antisense oligonucleotides (ASO) [7], small interfering RNA (siRNA), microRNA (miRNA), and mRNA vaccines [8], greatly facilitating the clinical translation of these drugs [9,10].

Nonetheless, challenges still remain. To enhance the bioavailability of various small-molecule drugs, peptides, and multiple types of oligonucleotides and address poor cellular uptake efficiency and stability, numerous delivery strategies have been developed. While conventional delivery methods such as liposomes, polymer nanoparticles, and viral vectors have shown utility in certain contexts, each presents inherent limitations. For example, liposomes often exhibit poor targeting ability and an uneven biodistribution throughout the body during drug delivery, and are susceptible to opsonization by serum proteins. These attributes reduce their therapeutic efficacy [11,12]. In terms of polymer nanoparticles, despite enhanced drug stability, certain materials degrade slowly, leading to accumulation in the body and potential toxicity [13,14]. Viral vectors, though highly efficient for gene delivery, trigger strong immunogenic responses in the host, limiting their broader clinical applications [15,16]. These limitations underscore the urgent need for more efficient delivery systems. Against such a backdrop, DNA origami technology and framework nucleic acid (FNA)-based delivery systems have emerged as compelling strate-

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gies due to the excellent editability of FNAs that facilitate the construction of precise nanoscale structures through DNA origami technology or self-assembly [17–19]. Additionally, the superior biocompatibility and modifiability of FNAs [20–22] are ideal for optimizing drug delivery and enhancing the therapeutic efficacy of NADs in different scenarios such as immune regulation [23,24]. In particular, tetrahedral FNAs (tFNAs) have attracted significant attention due to their simple synthesis, excellent biocompatibility, and efficient cellular uptake [25]. These structures have been widely applied in diverse biomedical fields such as cancer therapy, neurodegenerative disease management [26], and tissue regeneration [27–31]. DNA tetrahedral (Td), three-dimensional nanostructures self-assembled from four complementary single strands *via* Watson-Crick base pairing [32], exhibit several distinct advantages. First, their rigid structure and cationic surface properties confer resistance to nuclease degradation and enhance cell membrane penetration [32–34]. Second, their natural nucleic acid composition ensures low immunogenicity and good biodegradability, significantly reducing systemic toxicity [33]. Third, the chemical modifiability at the vertices and edges supports multifunctional integration: targeting ligands (*e.g.*, folate, arginine-glycine-aspartic acid (RGD) peptides) can be covalently linked *via* thiol-maleimide reactions [35–37], while certain therapeutic cargoes (*e.g.*, chemotherapy drugs, siRNA) can be loaded *via* electrostatic adsorption/hydrophobic interactions [34]. This structural-functional synergy addresses the limitations of traditional drug carriers and enables controlled, site-specific drug release [35].

As primary barriers against external environmental factors, skin and mucous membranes are frequently exposed to physical, chemical, and biological threats that can result in diseases. When the integrity of skin and mucous tissue is compromised or flawed, it is defined as a wound [38]. Skin wounds can be classified as acute or chronic based on their clinical healing time. Acute wounds are characterized by rapid onset, predictable healing stages, short duration, and minimal complications. However, there are still challenges during the healing process, such as infection, pain, and scarring [39]. Compared to acute wounds, the healing process of chronic wounds is weakened and disordered [40]. Chronic wounds, often caused by infections or blood circulation disorders, are a major dermatological concern that may progress to chronic ulcers, severely compromising patients' quality of life. Therefore, accelerating wound closure, reducing scarring, and enhancing tissue regeneration capabilities have long been a focus of in-depth research and innovation [41]. Developing safe and effective treatment methods is not only crucial for accelerating the wound healing (WH) process and alleviating patients' pain and discomfort but also essential for reducing the risk of infection and other complications, thereby improving patients' quality of life [42]. Likewise, mucosal damage in the oral cavity, digestive system, and urogenital system causes intense pain, triggers local infections, and elicits systemic inflammation. Fibrotic diseases, characterized by excessive extracellular matrix (ECM) deposition, frequently affect skin and mucosal tissues, impairing the structure and function of organs [43]. Current treatment options largely rely on symptomatic therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), growth factors, glucocorticoid drugs, and immunomodulators. Despite some therapeutic benefits, these agents often pose significant toxicity risks for chronic conditions. Moreover, drawbacks such as low solubility, poor bioavailability, and insufficient targeting ability hinder efficiency and precision, limiting the efficacy of conventional drug therapies. Surgical interventions can be used to remove lesions in some cases, but are associated with high risks of large or deep injuries, prolonged recovery, and potential scarring. Physical therapies, such as laser and cryotherapy, also have limitations, including incomplete lesion clearance and collateral tissue damage [44,45].

In contrast, Td offer unique advantages for treating skin, mucosal, and barrier tissue diseases. Their excellent biocompatibility and low immunogenicity enhance safety *in vivo* [46], while their efficient cellular uptake facilitates precise delivery of therapeutic agents to target cells, significantly improving treatment efficacy [47]. Modifications on the surface of Td with targeting ligands enable further enhance delivery precision [48]. In recent years, researchers have made significant breakthroughs in this field. For example, Td carrying genes that promote cell proliferation and collagen synthesis have been shown to significantly accelerate healing, enhance tissue regeneration, and reduce scar formation in skin wound repair [49]. In mucosal applications, Td carrying anti-inflammatory drugs or genetic payloads can effectively alleviate inflammation and promote tissue repair [50].

In summary, the rapid development of nucleic acid-based therapies presents new opportunities for disease treatment. FNAs and DNA origami technology provide powerful tools for constructing functional nanostructures, and Td, with their distinct advantages, have demonstrated extraordinary potential in addressing skin, mucosal, and barrier tissue diseases. For challenges facing NADs, such as enzymatic degradation *in vivo*, high costs in clinical translation, difficulties in large-scale production, and insufficient long-term safety data, numerous studies have been conducted [51]. For instance, the combination of tFNAs with composite hydrogels can effectively delay degradation and thereby prolong the bioactivity, while the incorporation of i-motif structures facilitates lysosomal escape, thereby enhancing the cellular uptake efficiency and bioavailability of the drugs. Further exploration of the properties and applications of Td is expected to provide more effective strategies to overcome current clinical challenges. This review highlights recent progress in tFNA-based therapies for skin, mucosal, and barrier tissue diseases and discusses future directions in this promising field.

2. Potential roles of tFNAs in the prevention and treatment of skin diseases

The skin serves as the body's primary defense against external threats and a critical barrier to both internal and external pathogens and injuries. The wide variety of skin diseases, such as wounds and skin cancer, often associated with slow WH, prolonged inflammation, and loss of tissue function, significantly affect patient quality of life [52,53]. Current treatment methods include topical drugs, surgical interventions, and physical therapies. However, many commonly used drugs, such as topical antibiotic ointments, may cause severe allergic reactions [54]. For instance, erythromycin ointment can trigger swelling of the face, lips, or throat, difficulty in breathing, and severe skin rashes. Moisturizing ointments lack bioactive functions, while long-term use of glucocorticoids can result in a wide range of side effects, including osteoporosis, hypertension, diabetes, skin atrophy, and increased susceptibility to infections [55]. In response to these limitations, alternatives such as small-molecule, peptide, and oligonucleotide drugs have been explored. However, issues like poor solubility, low bioavailability, and limited targeting capacity persist, particularly for complex wounds or refractory skin diseases, leading to unsatisfactory efficacy [56,57]. Therefore, there is an urgent need for innovative treatment strategies to improve clinical outcomes. tFNAs, a class of novel nucleic acid nanomaterials, have shown tremendous potential in various fields due to their excellent biocompatibility, efficient cellular uptake, and superior targeting abilities. In the treatment of skin diseases, tFNAs provide structural stability to therapeutic cargos, protect them from degradation, and allow surface modifications to enhance targeted delivery [58–60]. Compared with traditional drug delivery systems, tFNAs can more precisely deliver therapeutic molecules to the lesion site [61], offering sig-

nificant advantages in wound repair and fibrotic disease treatment [62]. Studies have shown that tFNAs can accelerate WH by regulating inflammation [36], promoting cell proliferation, and facilitating tissue repair [63,64]. Furthermore, their ability to co-deliver anti-inflammatory and growth-promoting factors offers improved therapeutic efficacy [65]. Therefore, tFNAs represent a promising new direction for addressing the limitations of current skin disease treatments and may play a crucial role in future clinical applications.

2.1. Promoting WH

WH is an intricate process involving multiple cell types, such as keratinocytes and fibroblasts, as well as growth factors [66]. Commonly, this process is segmented into four overlapping phases: blood clotting, inflammation, growth, and skin restructuring. Each stage requires precisely regulated intercellular communication to guarantee the reestablishment of standard tissue architecture and an environment conducive to function [67,68]. Based on healing progression, wounds can be categorized into acute and chronic. Acute wounds are typically associated with rapid healing, with therapeutic goals centered on infection control and scar minimization [69]. In contrast, chronic wounds, such as diabetic wounds, as severe complications of diabetes, display prolonged healing due to persistent pathological stimuli like hyperglycemia and persistent inflammation, resulting in sustained tissue damage and impaired regeneration [70]. Management of chronic wounds remains challenging due to factors such as bacterial infections, oxidative stress, persistent inflammation, and disrupted tissue repair and regeneration [68]. Conventional approaches, such as wound dressings and antibiotic application, provide partial relief but are often limited by inadequate infection control, poor healing outcomes, and low patient comfort [71]. Therefore, the development of more efficient and innovative therapeutic strategies is a central focus of current research. Nucleic acid nanodrugs, particularly tFNA-based systems, have attracted growing interest due to their unique structural and biological advantages. tFNAs and their functionalized complexes have been extensively studied for the management of various skin defects, demonstrating satisfactory therapeutic efficacy.

2.1.1. Application of pure tFNAs in WH

As a novel class of nanostructures, tFNAs exhibit superior biocompatibility and versatile functionality, making them a research hotspot in the field of WH. tFNAs significantly promote skin WH by activating specific cellular signaling pathways, enhancing tissue repair in both acute and chronic wounds.

(1) Acute wounds

For acute wounds, the primary therapeutic objectives include infection control and scar minimization. Zhu *et al.* [49] found that tFNAs stimulated the protein kinase B (Akt) signaling route, thereby promoting growth and movement of keratinocytes (HaCaT cell line) and fibroblasts (HSF cell line). This significantly enhances the release of VEGF and basic fibroblast growth factor (bFGF) by HSF cells while impeding the release of pro-inflammatory cytokines (tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β)) in HaCaT cells. These effects collectively contribute to cellular repair mechanisms. *In vivo* experiments revealed that tFNAs enhanced reepithelialization, improved the quality of WH, inhibited inflammation, and reduced skin fibrosis to promote skin repair in rat models. This research pioneered in showing how a nucleic acid nanostructure can hasten the healing of skin wounds and reduce scar development, offering strong proof for the possible use of tFNAs in skin regeneration treatments (Fig. S1A in Supporting information).

(2) Chronic wounds

In the context of chronic wounds, especially diabetes-associated ones, tFNAs demonstrate considerable therapeutic potential. Diabetic WH is a complex pathological process [72,73]. The hyperglycemic environment disrupts the normal function of keratinocytes, causing prolonged WH. Under diabetic conditions, endoplasmic reticulum stress (ERS) and ER-mitochondria (ER-MITO) interactions are enhanced, leading to mitochondrial dysfunction and subsequently impairing WH. Persistent hyperglycemia exacerbates intracellular dysfunction, and oxidative stress and inflammation further complicate the wound repair process. tFNAs can regulate the ER-MITO axis, significantly alleviating mitochondrial dysfunction, thereby aiding in the recovery of chronic diabetic injuries and rejuvenating the skin's mechanical barrier (Fig. S1B in Supporting information) [74].

Wang *et al.* further illustrated the effectiveness of tFNAs in managing diabetic wounds [75]. In glucose-rich environments, tFNAs markedly improved the proliferation and migration of keratinocytes, fibroblasts, and endothelial cells. They also enhanced the release of growth factors like vascular endothelial growth factor A (VEGF-A) and increased the levels of β-catenin, LEF1, and TCF1 by stimulating the Wnt signaling pathway. In diabetic rat models, tFNA treatment accelerated WH and enhanced the renewal of epithelial cells, capillaries, and collagen. The findings suggest that tFNAs promote diabetic WH *via* modulation of the Wnt signaling route (Fig. S1D in Supporting information).

(3) Burn wounds

For the treatment of burn wounds, tFNAs also demonstrate considerable therapeutic efficacy. Burns often induce mitochondrial dysfunction and excessive reactive oxygen species (ROS). To address this, researchers developed a novel tFNA-based nanozyme capable of penetrating skin and mucosal barriers within 24 h, reaching depths of up to 450 μm [76]. This high permeability is vital for preserving mitochondrial structure and function. During the repair process, tFNA-based nanozymes effectively reduced ROS levels *via* the extracellular signal-regulated kinase 1/2–nuclear factor erythroid 2-related factor 2–heme oxygenase-1 (ERK1/2–Nrf2–HO-1) signaling route, thereby restoring redox balance. Both *in vitro* and *in vivo* experiments confirmed that these nanozymes facilitated re-entry of skin cells into the proliferative phase after burn injury, enhanced cell migration, and accelerated the early stages of WH (Fig. S1C in Supporting information). tFNAs exert their therapeutic effects through intrinsic mechanisms, promoting cell growth, diversification, and movement, eliminating surplus ROS, and curbing inflammatory reactions. Leveraging their antioxidant and anti-inflammatory effects, tFNAs regulate endoplasmic reticulum (ER) and mitochondrial functions, inhibit the overexpression of dynamin-related protein 1 (Drp1), and restore cellular homeostasis, thereby accelerating WH. Additionally, tFNAs activate the Akt/Nrf2/HO-1 signaling route to strengthen antioxidant defenses, protect endothelial cells, attenuate inflammatory cascades, and stimulate angiogenesis, collectively enhancing tissue regeneration. The experimental results show that the healing area on the side treated with tFNAs is larger than that of the diabetic control group. The average epidermal thickness of the samples treated with tFNAs reached 2.19-fold that of the diabetic control group. The combination of these mechanisms and properties offers promising therapeutic strategies for chronic wounds and ischemic diseases by addressing both oxidative damage and vascular deficiency (Fig. S2A in Supporting information) [77].

In summary, tFNAs significantly promote the healing of both acute and chronic wounds by regulating multiple signaling pathways and cellular mechanisms, demonstrating particular promise in the treatment of diabetic wounds. Their multifunctionality, pro-

moting angiogenesis, enhancing antibacterial effects, regulating immune responses, and repairing dysfunctional cells, provides both theoretical foundations and practical guidance for future clinical applications.

2.1.2. Application of tFNA-based drug delivery systems in wound repair

(1) Infection wounds

While the biological functions of tFNAs notably enhance the local microenvironment for WH, their standalone therapeutic efficacy remains limited in certain clinical contexts. To address this, researchers have developed tFNA-based drug-loaded delivery systems that synergize the biological advantages of tFNAs and the cargoes to achieve enhanced therapeutic outcomes. For example, Zhang *et al.* engineered a novel p-TDN system by incorporating antisense peptide nucleic acids (asPNAs) into Tetrahedral DNA nanostructure (TDNs). This system specifically targets the filamentous temperature-sensitive Z (ftsZ) gene in bacteria, facilitating asPNA delivery into methicillin-resistant *Staphylococcus aureus* (MRSA) *via* TDNs. The results showed a concentration-related suppression in ftsZ expression, thereby hindering bacterial proliferation (Fig. S2B in Supporting information) [78]. Additionally, the combination of antimicrobial peptides (AMPs) with tFNAs has been shown to enhance antibacterial effects. Research has also verified that tFNAs can serve as efficient carriers for small-molecule antibiotics including erythromycin and methicillin. Sun *et al.* introduced the concept of, and experimental evidence revealed that tFNA-antibiotic compound (TAC) could enhance bacterial uptake and improve antibacterial efficacy (Fig. S2C in Supporting information) [79,80]. In a 2023 study, the same research group set up a mouse model for localized wound infections to evaluate the efficacy of TAC treatments. Mice treated with TACs exhibited significantly reduced white blood cell and neutrophil counts, indicating an alleviation of infection. Compared to the control group, the TAC group showed diminished inflammatory cell infiltration, increased neovascularization, and improved epithelial cell organization during the healing process. Moreover, TAC treatment controlled macrophage phenotype transition from M1 to M2, effectively modulating the inflammatory microenvironment at the infection site. These results underscore the considerable efficacy of tFNAs in combating antibiotic resistance (Fig. S2D in Supporting information) [81].

(2) Chronic wounds

Beyond antibacterial applications, tFNA-based systems have also shown promise in vascular regeneration for chronic wound management. Lin *et al.* constructed a functional tFNA-based delivery mechanism incorporating the REGRT healing peptide-tFNAs, which boosted matrix metalloproteinases (MMPs) activity by activating the ERK signaling route, thereby facilitating cell migration. Under advanced glycation end-product (AGE)-induced diabetic conditions, p@tFNAs markedly improved crucial angiogenic activities such as endothelial cell migration, growth, and tubule development and increased vascular growth factor levels. *In vivo* studies further confirmed that p@tFNAs notably improve skin renewal, blood vessel formation, and collagen accumulation at injury locations (Fig. S3A in Supporting information) [82].

To enhance the efficiency of FNA distribution, theoretically, attaching 1–4 FNAs to the top of tFNAs is feasible. However, studies have shown that with an increase in cationic loading at the top, the intracellular uptake of tFNAs through clathrin-mediated endocytosis weakens. To address this, Ge *et al.* proposed an innovative approach using a template-based click chemistry reaction to link Apt02 (a DNA aptamer mimicking VEGF-A activity) to the non-apex sites of tFNAs, generating the tFNA-Apt02 complex (TAC). Additionally, the research group employed DNA double-helix groove docking technology to load the small-molecule drug dimethyloxallyl glycine (DMOG) onto the TAC complex, forming the tFNA-Apt02-DMOG complex (TACD). This design significantly improved cellular uptake efficiency, surpassing traditional FNA conjugation methods. Furthermore, their study demonstrated that TACD promoted the release of VEGF, blood vessel formation, and the expansion and movement of human umbilical vein endothelial cells (HUVECs). In particular, TACD enhanced angiogenesis by upregulating the VEGF/VEGFR and hypoxia-inducible factor (HIF) signaling routes. In a mouse model with diabetic skin wounds, TACD markedly improved angiogenesis and collagen accumulation, thereby hastening the healing process (Fig. S3B in Supporting information) [83]. These findings demonstrate that drug-loaded tFNAs play a crucial role in wound treatment as they provide precise and efficient delivery.

2.1.3. Upgraded delivery by tFNAs in wound repair

Beyond their use as standalone therapeutic agents or drug carriers, tFNAs have been increasingly integrated with other biomaterials to further optimize WH outcomes. Hydrogels, commonly used as wound dressings, offer excellent moisture retention, biocompatibility, and wide applicability in trauma treatment [84]. The combination of tFNAs with hydrogels not only accelerates WH but also improves the wound microenvironment by promoting cell proliferation, migration, and angiogenesis. tFNAs, serving as optimal platforms for administering drugs, enhance the steadiness and efficacy of antimicrobial peptides such as GL13K and exhibit robust biological activities, including cell migration enhancement, immune regulation, and anti-inflammatory effects [85]. Researchers successfully developed HAMA/tFNA-GL13K composite nanogel hydrogels, demonstrating the broad-spectrum antimicrobial effects of tFNA-GL13K, its ability to promote cell movement, and its efficacy in preventing scar development both *in vitro* and *in vivo* (Fig. S3C in Supporting information) [86]. Further studies revealed that the HAMA/tFNA-GL13K hydrogel significantly enhanced the healing of infected full-thickness skin wounds by exerting antimicrobial effects, inhibiting ROS production, promoting cell migration, and suppressing the overexpression of inflammatory factors. This strategy presents an effective approach for treating bacterial infections. Moreover, tFNA-based delivery systems can be integrated with other protease-sensitive materials, such as aptamers and small molecules like miRNAs, to further enhance angiogenesis and anti-inflammatory properties [87]. Furthermore, tFNA-based hydrogels are suitable for fabricating organoid tissue engineering scaffolds, and these applications underscore their broad translational potential. Given their capacity for miRNA delivery, tFNAs have been recognized as ideal carriers [88,89]. Recently, researchers developed a bio-switchable miRNA delivery system (BiRDS) based on tFNAs, which comprises three miRNAs and a core of nucleic acids. This design aimed to optimize loading capacity while preserving the inherent properties of tFNAs (Fig. S3D in Supporting information) [90,91]. BiRDS showed remarkable stability, efficient tissue and cellular penetration, and high biocompatibility [92]. By selectively downregulating heparin-binding epidermal growth factor (HB-EGF), BiRDS inhibits the NF-κB route and alters the PTEN/Akt pathway, thereby promoting the shift from inflammation to cell growth in the course of wound recovery. As a transdermal miRNA therapeutic, BiRDS exhibits excellent stability and efficient cellular uptake and enhances the migration and growth of HaCaT cells. These combined effects reduce inflammation and accelerate WH, providing new therapeutic strategies for inflammatory skin disorders, skin cancer, and allergic dermatoses.

On that basis, the research team further designed a multifunctional tFNA-based nanocomposite, BiRDS/LEV (B/L) [93]. This innovative platform, for the first time, achieved co-loading of small-molecule drugs and miRNAs. B/L offers numerous advantages, including simple synthesis, high stability, excellent biocompatibility,

efficient transdermal and cellular uptake, and good biosafety. Additionally, it demonstrates potent antibacterial effects on both Gram-positive and Gram-negative bacteria by disturbing their cellular membranes. Notably, B/L demonstrates superior antibacterial efficacy compared to antibiotics alone. Its topical application reduces antibiotic dosage and frequency and minimizes potential adverse side effects. Moreover, by inhibiting the expression of key inflammatory factors, B/L significantly reduces inflammation both *in vitro* and *in vivo*, thereby promoting the healing of infected wounds.

Importantly, this tFNA-based nanoplatform exhibits broad versatility. Owing to their DNA nature and unique tetrahedral structure, tFNAs can carry a variety of therapeutic agents, such as oligonucleotides, peptides, and small-molecule drugs, making them well-suited for personalized and combination therapies. In future research, such multifunctional nanocomposites are expected to play pivotal roles in treating complex and refractory diseases, representing a promising therapeutic strategy.

In conclusion, tFNAs demonstrate multifaceted roles in the field of WH. By intervening in specific genes or signaling pathways, tFNAs promote cell proliferation, migration, and differentiation, thereby accelerating wound repair and the formation of new tissue. They also inhibit inflammatory responses, reduce the risk of infection, and enhance wound cleanliness. Acting as a three-dimensional structural framework, tFNAs facilitate cell proliferation and movement, stimulate neovascularization and tissue regeneration, improve healing outcomes, and reduce the risk of scarring. Furthermore, tFNAs stimulate the proliferation of endothelial cells and the expression of angiogenic factors, increasing the supply of oxygen and nutrients, which further accelerates WH (Table S1 in Supporting information).

The tunability and customizability of tFNAs allow for personalized treatment plans tailored to different wounds, achieving precision therapy and enhancing therapeutic efficacy and personalized treatment outcomes. In therapeutic settings, tFNAs exhibit the capacity to transport a variety of bioactive substances. Their excellent biocompatibility and resistance to enzymatic degradation ensure effective cellular delivery and stability within physiological environments. Systems based on tFNAs increase drug bioavailability, enable precise targeting, and promote controlled release, which is highly advantageous for precision medicine.

2.2. Suppression of skin fibrosis

Skin fibrosis is a common pathological phenomenon during tissue repair, widely associated with local and systemic disorders [94–97]. It is typically characterized by tissue injury and the emission of inflammatory agents like IL-1, TNF-α, and interferon gamma (IFN-γ), which activate the pathway of transforming growth factor-β (TGF-β) signaling route. This activation subsequently triggers epithelial-mesenchymal transition (EMT) and ECM deposition, thereby driving the fibrosis process [98,99]. Furthermore, the alteration of cellular metabolism is crucial in fibrosis progression, particularly in promoting fibroblast proliferation and collagen synthesis, where enhanced glycolytic pathways further exacerbate fibrosis [98].

Activation of inflammasomes and pyroptosis further intensifies local inflammation, leading to the release of pro-inflammatory cytokines such as IL-1β and IL-18. These factors establish a vicious cycle of inflammation and fibrosis that accelerates the fibrotic process in skin damage [100–102]. Although treatment strategies have been developed to alleviate skin fibrosis, many carry side effects, particularly those targeting immune modulation, apoptosis, or pyroptosis [102]. As a result, cutting-edge drug delivery systems need to be developed that are capable of more effectively hindering the fibrosis process and minimizing adverse effects. tFNAs have demonstrated potential in mitigating skin fibrosis attributed their antioxidant and anti-inflammatory effects, as well as their low immunogenicity. Notably, tFNAs can attenuate skin fibrosis by inhibiting EMT and decreasing the expression of related inflammatory cytokines. Furthermore, when used as nanocarriers for therapeutic agents, tFNAs can significantly enhance treatment efficacy (Fig. S4A in Supporting information) [103]. To further optimize therapeutic outcomes, Jiang *et al.* developed a novel BiRDS carrying miR mimics miR-27a for targeting skin fibrosis and pyroptosis-related pathways [104]. This system achieved bio-switchable drug release by incorporating an oligonucleotide sequence responsive to RNase H activity. *In vitro*, BiRDS demonstrated effective cellular uptake and markedly suppressed the expression of fibrosis-related genes and ECM deposition. Moreover, by inhibiting pyroptosis-related pathways, BiRDS reduced the release of inflammatory factors and protected cells from inflammatory damage. Animal model experiments confirmed its robust anti-fibrotic effects and biosafety without causing significant systemic toxicity. These findings underscore the potential of tFNAs as versatile nanoplatforms for the treatment of fibrotic skin diseases.

2.3. Anti-aging effects on the skin

Aging is a complex biological process characterized by a decline in cellular functions and tissue degeneration. Among various contributing factors, ultraviolet (UV) radiation is a major driver of skin aging, as it induces direct DNA damage and exacerbates oxidative stress, thereby accelerating the aging process of the skin. Aged cells exhibit permanent cell cycle exit, resistance to apoptosis, and secretion of pro-inflammatory factors known as the senescence-associated secretory phenotype (SASP). The release of these factors not only exacerbates local inflammation but also further drives the aging process [105,106]. Current anti-aging treatments are often invasive or minimally invasive, with a risk of adverse effects [107]. Therefore, developing non-invasive and low-risk treatment methods is crucial for improving skin health and delaying aging. tFNAs, as novel platforms for anti-aging therapy, have shown unique advantages. Studies have indicated that tFNAs can regulate apoptosis-related signaling pathways, promote cytochrome C expression, and selectively remove senescent skin fibroblasts. The anti-aging effects of tFNAs are primarily attributed to their antioxidant and anti-inflammatory properties. Specifically, tFNAs enhance cellular antioxidant capacity by upregulating heme oxygenase-1 gene expression and simultaneously inhibit the secretion of inflammatory cytokines, thereby mitigating senescence-related cellular damage [108].

Building on these benefits, Xie *et al.* developed a transdermal drug delivery system combining tFNAs with lipoic acid (LA) to treat UV-induced skin damage. This system significantly improved both cellular uptake of LA and skin penetration depth, thereby achieving enhanced antioxidant and anti-inflammatory effects. Topical application of this system accelerated WH, reduced inflammation, and promoted collagen synthesis in mice, showcasing tFNAs' effectiveness in treating skin ailments (Fig. S4B in Supporting information) [109].

In another study, Lin *et al.* designed a novel BiRDS system for UV-induced skin aging. Their system effectively delivered miR-31 inhibitors to aging skin, markedly improving anti-aging outcomes, particularly in the protection of hair follicle stem cells. This study highlights BiRDS's excellent RNA delivery performance and provides valuable insights for developing stable framework nucleic acid-based delivery systems (Fig. S4C in Supporting information) [110].

Moreover, TDNs have recently gained considerable attention as promising drug carriers. Researchers designed a tetrahedral nanocage, termed siR-TDNbox, which encapsulated a specific siRNA. Research conducted both *in vitro* and *in vivo* suggested that

the nanocage effectively inhibited the mTORC1/S6 signaling pathway, reduced the expression of aging markers, alleviated chronic inflammation during aging, and improved overall physiological function. This dual-action approach offers a compelling strategy for anti-aging therapy and demonstrates the potential of tFNAs in drug delivery system construction (Fig. S4D in Supporting information) [111].

2.4. Application in psoriasis treatment

Psoriasis, a persistent and repetitive inflammatory skin disorder, impacts not just the skin but can also affect the joints. This condition manifests through a variety of physical symptoms. This condition impacts about 2%–3% of the world's populace, affecting over 125 million people globally. The pathogenesis of psoriasis is intricate, mainly characterized by dysregulated T-cell activity and abnormal proliferation and differentiation of keratinocytes. However, the precise etiology and underlying mechanisms remain incompletely understood [112]. Current therapeutic approaches mainly focus on inhibiting T-helper cell activity or managing keratinocytes growth. Options include immunosuppressive medications such as cyclosporine and methotrexate, as well as monoclonal antibodies targeting TNF-α and IL-17. While these treatments can alleviate symptoms, a definitive cure remains elusive [112,113]. Therefore, developing groundbreaking therapeutic drugs is essential, especially those that can provide extended symptom relief or possibly cure the disease.

Targeting miRNAs represents a promising therapeutic strategy for psoriasis management. miR-125b, which is significantly downregulated in psoriatic skin, can inhibit proliferation and promote differentiation when overexpressed in primary human keratinocytes [114]. However, the clinical application of miR-125b is impeded by its poor stability and limited ability to penetrate the skin [115–118].

In recent years, FNA technology has demonstrated unique advantages in the treatment of psoriasis. Studies have shown that FNAs can serve as carriers to deliver miRNA-125b effectively, thereby regulating keratinocytes proliferation. The FNA-miR-125b complex exhibits higher stability and greater cellular internalization compared to free miR-125b mimics [119]. In a mouse model of psoriasis, delivery of miRNA-125b *via* FNAs significantly mitigated skin lesions, as evidenced by reduced epidermal thickening, lower psoriasis area and severity index (PASI) scores, and alleviated local inflammatory responses. The results underscore the capability of FNA-miRNA systems in the topical treatment of psoriasis *via* precise regulation of keratinocytes function and inflammatory factor expression (Fig. S5A in Supporting information).

In addition to FNA-based strategies, RNA interference (RNAi) technology has also provided new avenues for psoriasis treatment. A novel transdermal RNAi drug system, termed STT, has been developed by integrating pH-sensitive tannic acid (TA), RNase H-reactive sequences, siRNA, and tFNAs. STT distinctly hinders the NF-κB signaling pathway, suppresses the development of dendritic cells (DCs), and reduces the generation of proinflammatory cytokines such as TNF-α, IL-23, and IL-17, thereby curbing the growth of keratinocytes [120]. This system improves RNAi efficiency *via* a lysosomal escape mechanism and exhibits superior anti-inflammatory effects compared to free siRNAs. Research results indicate that STT can effectively modulate skin immune responses and the transmission of inflammatory signals, thereby alleviating the pathology caused by psoriasis and offering a targeted immunotherapeutic approach for the disease (Fig. S5B in Supporting information).

In summary, merging FNA with RNAi techniques has paved the way for novel methods in treating psoriasis topically. By precisely regulating immune cell functions, the expression of inflammatory factor expression, and keratinocytes proliferation, these novel delivery systems may overcome the limitations of conventional therapies, offering more effective and durable therapeutic outcomes.

2.5. Skin cancer therapy

Malignant melanoma is an aggressive and highly lethal form of skin cancer [121], with approximately 60% of cases associated with mutations in the *Braf* gene [122,123], which activate the rat sarcoma virus/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase/extracellular signal-regulated kinase (Ras/Raf/MEK/ERK) signaling pathway and leading to cell growth, spread, and resistance to apoptosis [124]. RNAi technology, which specifically degrades mRNAs to silence gene expression, is a potential therapeutic approach for cancer treatment [125]. However, the poor *in vivo* stability of siRNAs requires efficient systems for delivery aimed at boosting treatment effectiveness [126]. A research team has designed a tFNA-based nanostructure by modifying siRNA targeting *Braf* (siBraf) with sticky ends and incorporating the DNA aptamer AS1411. The final nanocomplex is termed tFNAs-AS1411-siBraf [127]. In A375 melanoma cells, this complex demonstrated high cellular uptake efficiency, robust silencing of the *Braf* gene, and marked inhibition of cell proliferation and migration. Mouse model experiments showed that tFNAs-AS1411-siBraf significantly suppressed tumor growth without noticeable toxicity. Mechanistically, inhibiting *Braf* gene expression blocked the RAS/RAF/MEK/ERK signaling pathway, reduced cell proliferation and metastasis, and enhanced apoptosis. This innovative system efficiently delivers siRNAs and effectively inhibits the growth and metastasis of malignant melanoma, representing a promising strategy for RNAi-based melanoma therapy.

Traditional melanoma treatments, such as surgical removal, radiotherapy, and chemotherapy, prove more efficacious in cases where the tumor has not metastasized [128,129]. However, for advanced melanoma, the efficacy is limited [130–132]. In recent years, immunotherapy, particularly immune checkpoint blockade (ICB), has been extensively studied and applied in the clinical treatment of melanoma. Nevertheless, a lack of highly tumor-specific immune responses limits therapeutic outcomes in some patients [133–135]. Consequently, creating methods that are both more accurate and highly targeted is vital for enhancing melanoma treatment results. Transdermal drug delivery (TDD) systems have been extensively applied in the management of dermatological diseases and skin cancer due to ease of administration and reduced systemic toxicity [136,137]. However, traditional TDD systems are primarily designed for small-molecule drugs and are often ill-suited for large-molecule agents [138–140]. To address this, researchers have explored DNA self-assembled nanostructures, especially tetrahedral DNA frameworks such as TH21, for transdermal delivery [92]. These structures possess good biocompatibility, as well as controllable size and shape, and can effectively facilitate the transdermal delivery of large-molecule drugs (such as NADs), providing new ideas for non-invasive local therapy.

For instance, a research team has loaded glabridin, a flavonoid compound with antioxidant, anti-inflammatory, and whitening properties but limited transdermal ability, onto tFNAs to construct tFNAs-glabridin nanocomplexes. This strategy significantly enhanced the transdermal penetration and cellular uptake efficiency of glabridin. *In vitro* experiments demonstrated that tFNAs-glabridin outperformed free glabridin and achieved effective inhibition of melanin production and reduced pigmentation. This highlights the promise of tFNA-based TDDs as effective, non-invasive drug administration strategies in the treatment of superficial skin diseases [89]. Moreover, Shen *et al.* developed a nucleic acid-based immune adjuvant (FNAIA) framework for transdermal administration in the chemo-immunotherapy for malignant melanoma (Fig.

S6A in Supporting information) [141]. By incorporating doxorubicin (DOX), which induces immunogenic cell death, this system not only exhibited excellent skin penetration but also effectively activated DCs and enhanced the immune response. When combined with anti-PD-1 antibodies, the FNAIA/DOX complex achieved remarkable tumor suppression and extended survival in animal models. This therapeutic strategy not only significantly boosts local immune responses but also reduces drug exposure to normal tissues, thereby minimizing systemic side effects, especially hepatotoxicity. This study provides an innovative approach to treating malignant melanoma, highlights the great potential of FNAs in transdermal delivery and immunotherapy, and offers new insights into personalized treatment of skin cancer.

3. Potential application of tFNAs in mucosal disease management

Mucosal tissues, found in the oral cavity and eyes, serve as important immune barriers in the human body. Damage to these tissues can lead to conditions such as oral mucositis and corneal epithelial defects. Traditional treatment methods (*e.g.*, local drug delivery, anti-inflammatory drugs, and immunomodulators) are limited by poor bioavailability, local toxicity, and imprecise targeting, often yielding suboptimal outcomes and risk of side effects or drug resistance with prolonged use [142]. tFNAs can serve as precise drug delivery platforms capable of transporting anti-inflammatory agents, antimicrobial drugs, or immunomodulatory molecules directly to mucosal lesions. By improving the local immune environment, enhancing tissue repair, and accelerating the healing process, tFNAs elevate the effectiveness of current treatments and pave the way for tailored approaches to mucosal diseases, holding significant potential for clinical applications in the future.

3.1. Prevention of radiation-induced oral mucositis (RIOM)

RIOM, a prevalent form of oral mucositis, often arises as a complication following radiotherapy, especially in patients with head and neck cancer, exhibiting incidence rates surpassing 80%. While ionizing radiation effectively eradicates tumor cells, it can also damage normal tissues [143], leading to complications such as oral mucositis (OM), manifesting as mucosal epithelial cell damage, with patients often experiencing oral pain, dysphagia, and an increased risk of systemic infection. This severely impacts quality of life and ultimately affects prognosis [142–144]. Current RIOM treatment strategies, oral hygiene management, local pain relief, nutritional support, epidermal growth factors, anti-inflammatory drugs, natural remedies, and laser therapy, exhibit limited effectiveness, lack widespread acceptance, and have not substantially altered disease severity or duration. Therefore, the treatment of RIOM remains a significant challenge in treating head and neck cancer, highlighting the critical demand for innovative medications and treatment strategies [145].

Curcumin (Cur), a natural anti-inflammatory and anticancer compound, has shown potential in RIOM treatment. Nonetheless, the clinical use of this method is hindered by its limited bioavailability and instability. In the past, researchers have engineered a delivery platform for Cur utilizing DNA nanostructures, referred to as Cur-tFNAs, with the goal of creating an innovative nanomaterial characterized by its superior solubility in water, efficient encapsulation, prolonged release of the drug, and stable pharmaceutical properties. When contrasted with unbound Cur, the Cur-tFNA system has demonstrated enhanced stability of the medication, compatibility with biological systems, an increased propensity for cellular internalization, and a more pronounced utilization within tissues [146]. Furthermore, Cur-tFNAs also demonstrates superior anti-inflammatory effects. Consequently, Zhang *et al.* have combined Cur with tFNAs to form a Cur-tFNAs complex [50]. *In vitro* experiments showed that Cur-tFNAs significantly improved the antioxidant capacity of human oral keratinocytes (HOKs) compared to Cur or tFNAs alone, and effectively reduced DNA damage caused by radiation. Furthermore, *in vivo* experiments confirmed the potential of this complex in preventing and treating RIOM. This study not only validates the potential of tFNAs as an effective Cur delivery platform and suggests that Cur-tFNAs may offer a precise and efficient approach to treating RIOM and related mucosal injuries (Fig. S6B in Supporting information).

3.2. Promotion of corneal epithelial healing

The cornea, as the transparent barrier of the eye, plays a dual role, focusing incoming light and protecting against external insults. While not categorized under the mucosa, the cornea is crucial for protective and sensory functions, mirroring the importance of mucosa [147,148]. Corneal damage, particularly to the stromal layer, can result in vision loss. Fortunately, the corneal epithelium (CE) has self-renewing capabilities, and after injury, it can restore its integrity through reepithelialization, a process crucial for vision preservation involving complex mechanisms such as cell migration, proliferation, differentiation, and matrix remodeling [149–151]. Consequently, rapid and effective re-epithelialization after corneal injury is vital for maintaining the homeostasis of the corneal epithelium.

Considering the complexity and importance of corneal WH, researchers have conducted numerous related experiments [152,153]. Despite significant progress in recent years, there are still limited therapeutic drugs that can promote corneal healing [154]. In summary, effective treatment for corneal injuries remains a significant challenge.

Recent advances have highlighted the promising role of tFNAs in the management of corneal injuries. Liu *et al.* established a mouse model of corneal alkali burns and discovered that tFNAs enhanced the growth and migration of corneal epithelial cells and fibroblasts by activating the p38 and ERK1/2 signaling pathways. Additionally, tFNA treatment increased the release of pro-angiogenic cytokines VEGF and bFGF and reduced the generation of inflammatory factors TNF-α and IL-1β. These effects collectively accelerated reepithelialization after corneal burns and helped preserve corneal transparency [21]. These findings laid a scientific foundation for the application of tFNAs in corneal repair and provided new perspectives for broader skin, mucosal, and barrier tissue WH applications (Fig. S7A in Supporting information).

In another study, Li *et al.* developed a tFNA-based gene delivery system termed tFNA-miR-21 complex (T-21). This system protected miR-21 from degradation and after being delivered to corneal epithelial cells *via* endocytosis, promoted cell proliferation and migration. *In vivo* studies showed that T-21 significantly accelerated WH in a mouse corneal scratch model and exhibited high biocompatibility [155]. These findings further demonstrate the enormous potential of tFNAs as efficient carriers in miRNA delivery and corneal injury repair, facilitating their broader applications in skin/mucosal/barrier tissue WH (Fig. S7B in Supporting information).

Dry eye disease (DE), a complex condition caused by hyperosmolarity and instability of the tear film, often leads to ocular discomfort and potential visual impairment, severely affecting the quality of life of patients. Approximately 4.1% to 23.7% of the global population is affected by this condition [156,157]. Inflammation is recognized as a central mechanism in the progression of DE, making the development of efficient and safe anti-inflammatory treatment methods critically important. Studies showed that tFNAs significantly alleviated DE-associated damage by promoting

corneal epithelial healing, restoring goblet cell function, and enhancing tear secretion [158]. RNA-seq analysis revealed that tFNA treatment normalized the expression of a wide range of genes. Further investigation demonstrated that tFNA reduced excessive ROS and modulated the inflammatory microenvironment, particularly through the suppression of inflammatory cytokines, such as matrix metalloproteinase 9 (MMP9) and IL-6, *via* the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway. Importantly, tFNAs exhibit excellent safety, with no detectable toxicity. These findings strongly support the promise of nucleic acid-based nanomaterials in DE treatment and highlight their broader clinical applicability (Fig. S7C in Supporting information).

3.3. Treatment of oral mucosal cancer

Oral squamous cell carcinoma (OSCC), a malignant tumor primarily occurring in the oral mucosa, is characterized by aggressive invasion and a high rate of metastasis [159]. While surgical resection remains the major treatment method for early-stage OSCC, patients with advanced disease often require radiotherapy and chemotherapy [160]. However, these strategies face challenges due to drug resistance and side effects, highlighting critical necessity for more efficacious treatment strategies [161]. miRNAs, as important gene regulators, are crucial in the onset, development, and therapy of tumors [162,163]. Among them, microRNA-149–3p (miR-149) acts as a miRNA that suppresses tumors, effectively hindering the growth of tumor cells through the suppression of the Pi3k/Akt pathway, indicating its potential as an effective gene-based cancer treatment [164,165]. However, its clinical application is limited by low cellular uptake efficiency and poor stability [166].

To address these limitations, researchers developed a tFNA-based delivery system for miR-149, termed T-miR-149 [167]. tFNAs represent an innovative category of nucleic acid nanomaterials, renowned for their outstanding biocompatibility, robust stability, and the ability to efficiently deliver miRNAs and enhance cellular uptake and targeting performance. *In vitro* experiments showed that T-miR-149 significantly reduced the expression of Pi3k and Akt, inhibited the invasion and migration of OSCC cells (such as Cal27), and enhanced tumor cell apoptosis [168]. Furthermore, T-miR-149 activated the Pi3k/Akt and Akt/Bcl-2 signaling pathways, thereby boosting pro-apoptotic activity (Fig. S7D in Supporting information) [169].

In vivo studies further validated the anti-tumor effects of T-miR-149, as evidenced by a significant increase in survival rates in mouse models [170]. Compared to traditional chemotherapeutic agents, T-miR-149 offered better precision when targeting tumor cells and effectively reduced side effects, underscoring its favorable biocompatibility and therapeutic potential. These findings strongly support the promise of tFNAs in OSCC treatment and open new research directions for the development of tFNA-based miRNA delivery systems [171].

In summary, the use of tFNAs miR-149 carriers enhances the stability and targeting precision of miR-149, thereby boosting its anti-tumor effects. Utilizing tFNAs in treating OSCC is highly promising, offering fresh avenues for creating secure, specific, and efficacious treatment approaches.

4. Summary and outlook

NADs such as siRNA, miRNA, and ASO typically possess linear or simply branched nucleic acid molecular structures [172]. During the delivery process, to protect these nucleic acid molecules from degradation by endogenous nucleases, enhance their stability, and improve cellular uptake efficiency, specific delivery systems are often required, such as liposomes or nanoparticles [173–177]. tFNAs, as a novel drug delivery platform, exhibit significant potential in the biomedical field due to their excellent cellular biocompatibility, low toxicity, and intrinsic bio-regulatory functions [170]. tFNAs are capable of crossing biological obstructions like the cell membrane and blood-brain barrier, aiding in accurate and effective medication administration. The distinct three-dimensional configuration and ease of editing of these systems enable the logical creation of tailored drug delivery systems across diverse areas, especially for preventing and managing skin, mucosal, and barrier tissue conditions.

In the prevention and treatment of skin, mucosal, and barrier tissue diseases, tFNAs demonstrate significant advantages. tFNAs can deliver therapeutic agents to the affected areas with high efficiency and specificity, minimizing the impact on surrounding healthy cells. This precise delivery strategy not only enhances therapeutic efficacy but also reduces adverse reactions to the greatest extent, making tFNAs an effective means for combating these diseases. Furthermore, tFNAs can accurately deliver growth factors and other healing-promoting agents, accelerating and improving the efficiency of healing. The ability of tFNAs to target specific sites ensures that therapeutic agents reach optimal concentrations at the site of injury, thereby maximizing therapeutic effects. This targeted delivery system is highly effective, minimally invasive, and can significantly enhance patient treatment outcomes, showing great potential for application. Through this innovative drug delivery method, tFNAs offer a new possibility for the treatment of skin, mucosal, and barrier tissue diseases.

Although most studies on tFNAs and their complexes remain at the preclinical stage, considerable advances have been made in several therapeutic domains, including the treatment of radiation-induced oral mucositis, promotion of skin healing, and anti-aging interventions, paving the way for broader therapeutic applications. Nevertheless, the clinical translation of tFNAs continues to face challenges, particularly in terms of biosafety, pharmacokinetics, structural stability, and cost-effectiveness. Overcoming these challenges will be critical for their eventual clinical implementation.

In terms of stability, despite progress achieved *via* structural optimization and crosslinking strategies to enhance resistance to enzymatic degradation, tFNAs still exhibit limited persistence *in vivo*, requiring frequent administration. To address this issue, various modification methods have been employed. For instance, the incorporation of i-motif and other acid-responsive elements enables tFNAs and their complexes to escape from lysosomal degradation. Moreover, the integration of tFNA-based NADs with hydrogel systems offers sustained-release properties, which can reduce systemic clearance and prolong therapeutic efficacy [178,179]. Additionally, to improve therapeutic outcomes, it is crucial to optimize its targeting mechanisms and enhance its tissue penetration capabilities. At the same time, delving deeper into stimulus-responsive designs can also help to increase the precision of drug delivery [180].

Furthermore, the clinical safety and efficacy of tFNAs require validation through well-designed clinical trials. Close collaboration with regulatory agencies will be essential to advance their clinical application. To obtain regulatory approval for clinical use, strict quality control must be implemented in the production process. Establishing standardized procedures and adhering to Good Manufacturing Practices (GMP) are key measures to ensure patient safety and product efficacy [177]. Simultaneously, establishing an appropriate regulatory framework and collecting comprehensive data on pharmacokinetics, toxicity profiles, and therapeutic effects are essential prerequisites for translating laboratory findings into viable treatment methods. Rigorous preclinical and clinical evaluations are key steps in achieving this transformation. Interindividual variability also presents a challenge; thus, precision medicine approaches that consider genetic and metabolic characteristics among patients could optimize therapeutic outcomes.

While the current manufacturing cost of tFNAs remains relatively high, ongoing advancements in synthesis and production technologies are expected to reduce these costs over time, ultimately enabling large-scale production and widespread application.

In conclusion, tFNAs represent a highly promising and innovative drug delivery strategy for the prevention and treatment of diseases affecting the skin, mucosal, and barrier tissue surfaces. As research continues to evolve, tFNA-based drugs are expected to open new frontiers in disease prevention and treatment, offering transformative opportunities for clinical interventions and contributing significantly to the advancement of the medical sector.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Yuge Zhang: Formal analysis, Data curation, Conceptualization. **Siqi Xu:** Data curation. **Chenpeng Chen:** Formal analysis. **Haiyu Xian:** Formal analysis. **Qitao Wen:** Data curation. **Yunfeng Lin:** Writing – review & editing, Supervision, Conceptualization. **Tao Wang:** Data curation, Conceptualization.

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Supplementary materials

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