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Polydeoxyribonucleotide as a Regenerative Agent in Dermatology and Wound Healing: Mechanisms, Clinical Applications, and Safety

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Polydeoxyribonucleotide (PDRN), a highly purified salmon-sperm–derived DNA polymer, exhibits potent regenerative and anti-inflammatory effects. This review critically explores the dual mechanisms of PDRN—namely, adenosine A2A receptor activation and nucleotide provision via the salvage pathway—and synthesizes the current clinical evidence regarding its applications in dermatology and wound healing. Preclinical and clinical studies have shown that PDRN enhances angiogenesis, modulates cytokine profiles, and accelerates tissue repair processes, resulting in improved healing rates in chronic diabetic foot ulcers, pressure ulcers, and venous leg ulcers as well as faster epithelial regeneration in surgical donor sites and corneal wounds. Adjunctive benefits have also been reported in lichen sclerosis, osteoarthritis, and aesthetic dermatology. Furthermore, PDRN demonstrates excellent safety profile, with minimal adverse events reported across multiple trials and real-world applications. Emerging delivery platforms and combination therapies have further expanded the therapeutic potential. This review highlights the potential of PDRN as a versatile and safe regenerative agent by integrating mechanistic insights with robust clinical data.

Keywords: Adenosine A_2A receptor, Anti-inflammation, Polydeoxyribonucleotide, Regenerative medicine, Wound healing

Introduction

Polydeoxyribonucleotide (PDRN) is a highly purified DNA polymer derived from the sperm of salmon species, such as *Oncorhynchus mykiss* and *Oncorhynchus keta*, and is composed of fragments ranging from 50 to 1,500 kDa. Through high-temperature extraction and rigorous purification, PDRN achieves > 95% DNA content, with proteins and peptides being effectively inactivated to minimize immunogenic risk [1,2]. Decades ago, PDRN was initially employed to enhance healing in radiodermatitis and skin graft donor sites [3]; subsequently, its safety profile and purity have been investigated for a wide range of regenerative applications.

Mechanistically, PDRN supports tissue repair through two synergistic pathways. First, extracellular degradation of PDRN by ectonucleases, including ectonucleoside triphosphate diphosphohydrolase-1 (CD39) and ecto-5'-nucleotidase (CD73), generates adenosine, which activates the adenosine A2A receptor (A2AR), thereby elevating intracellular cyclic adenosine monophosphate (cAMP) and initiating pro-angiogenic and anti-inflammatory signaling cascades. Second, PDRN fragments enter the cells through equilibrative nucleoside transporters, which supply nucleotide precursors that bolster the salvage path-

way for DNA repair and cell proliferation [1]. Together, these processes promote vascular endothelial growth factor (VEGF) expression, modulate cytokine profiles, and accelerate fibroblast and endothelial cell activities in injured tissues.

Clinically, PDRN has demonstrated significant benefits in chronic wound management, including diabetic foot ulcers, pressure ulcers, and venous leg ulcers. Of note, randomized trials have reported substantially higher healing rates with PDRN treatment than with standard care [4,5]. Beyond dermatological wounds, PDRN shows promise in lichen sclerosis, osteoarthritis, tendon injuries, and epithelial regeneration at burn and surgical donor sites [6,7]. This review explores the molecular mechanisms of PDRN, synthesizes key clinical evidence, and assesses its safety and tolerability to provide a comprehensive overview of its therapeutic potential in dermatology, wound healing, and regenerative medicine.

Mechanisms of action

Adenosine A2A receptor activation

As previously mentioned and shown in Fig. 1 herein, PDRN is degraded by extracellular ectonucleases (CD39 and CD73) into nucleosides, predominantly adenosine [4]. The elevated adenosine binds to A2AR on endothelial cells, fibroblasts, and immune cells [8], activating G_s-protein–coupled adenylate cyclase and increasing intracellular cAMP levels. This triggers

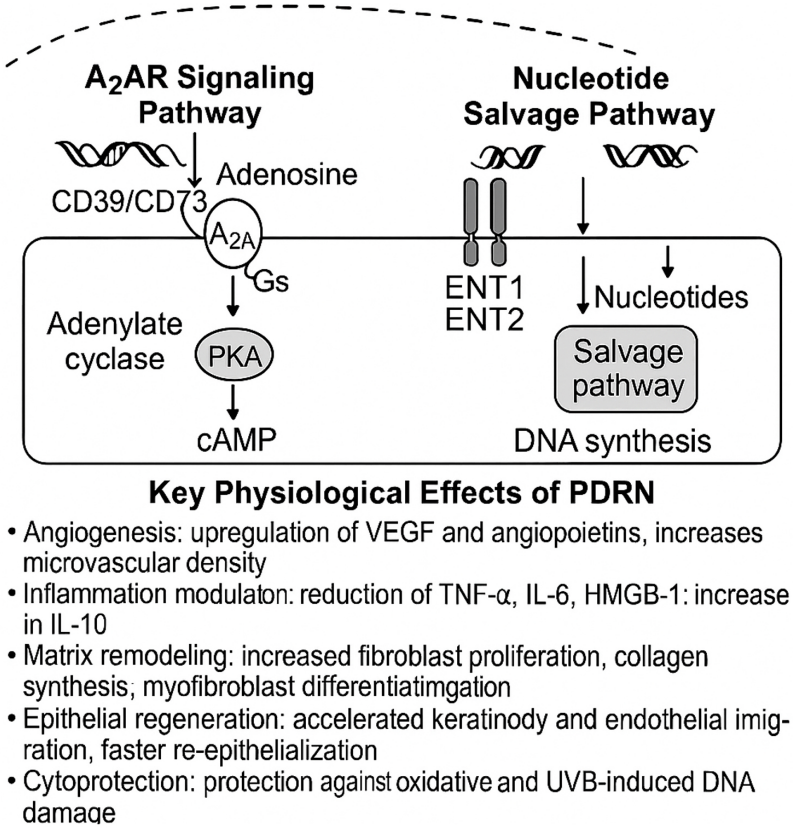

Fig. 1. Schematic representation of PDRN's mechanisms of action in cells. A2AR signaling pathway (left): PDRN is first cleaved by ectonucleases into adenosine, which then docks onto A2AR on the cell surface, activating the G_s protein. G_s, in turn, stimulates adenylate cyclase to increase the intracellular cAMP levels. Elevated cAMP levels activate CREB, a transcriptional switch that drives the production of anti-inflammatory molecules and pro-angiogenic factors, helping to resolve inflammation and promote new blood vessel growth. Nucleotide salvage pathway (right): Outside the cell, ectonucleases chop PDRN into their nucleotide building blocks. These nucleotides are imported through ENT1 and ENT2 transporters. Once inside, they replenish the cell's nucleotide pool and are incorporated into DNA, supporting the repair of damaged DNA strands and fueling cell division and tissue regeneration. A2AR, adenosine A2A receptor; CD39, ectonucleoside triphosphate diphosphohydrolase-1; CD73, ecto-5'-nucleotidase; ENT, equilibrative nucleoside transporter; PKA, protein kinase A; cAMP, cyclic adenosine monophosphate; PDRN, polydeoxyribonucleotide; VEGF, vascular endothelial growth factor; TNF-α, tumor necrosis factor-alpha; IL, interleukin; HMGB, high-mobility group box; UVB, ultraviolet B; CREB, cAMP response element-binding protein.

protein kinase A signaling, which upregulates hypoxia-inducible factor-1 and cAMP response element-binding protein while inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells, thereby shifting the tissue milieu toward anti-inflammatory and pro-angiogenic states: VEGF and angiopoietins are upregulated [12,13], whereas the pro-inflammatory cytokines (tumor necrosis factor-alpha, interleukin-6 [IL-6], and high-mobility group box-1) are suppressed and the anti-inflammatory cytokine IL-10 is enhanced. In rodent models of inflammatory arthritis, the reduction of joint inflammation and cartilage damage by PDRN is reversed by A2AR antagonists, confirming receptor-mediated immunomodulation [14,15]. Furthermore, A2AR signaling promotes tissue regeneration by enhancing fibroblast proliferation, collagen synthesis, and migration; stimulating endothelial cell proliferation and neovessel formation; and activating osteoblast and chondrocyte functions. In vitro, PDRN increases human osteoblast proliferation and alkaline phosphatase activity—markers of bone formation—and augments aggrecan and type II collagen deposition in chondrocytes while reducing matrix metalloproteinase-2 (MMP-2) and MMP-9 activities [16,17]. These combined actions limit apoptosis, reduce inflammatory stress, and prepare the injured tissues for effective repair.

Salvage pathway and nucleotide provision

A unique aspect of PDRN is its role in providing building blocks for DNA synthesis in healing cells. Under conditions of tissue injury, especially hypoxia or nutrient deprivation, cells often cannot efficiently synthesize de novo nucleotides. Instead, they rely on salvage pathways to recycle nucleotides for DNA repair and replication [4]. PDRN, a DNA polymer, is a direct source of purines and pyrimidines when broken down [1]. Experimental studies have demonstrated that radiolabeled PDRN fragments are taken up by proliferating fibroblasts and are incorporated into the DNA of dividing cells, indicating that PDRN supplies nucleotides for DNA synthesis. By enhancing the salvage pathway, PDRN accelerates the proliferation of cells required for tissue regeneration [18]. This mechanism complements A2AR activation, while adenosine signaling provides pro-growth and pro-angiogenic signals. The salvage pathway ensures that cells have the raw materials to respond to those signals by synthesizing DNA and dividing. This results in an overall increase in wound closure and tissue repair. For instance, the activation of the salvage pathway via PDRN has been linked to faster re-epithelialization in skin wounds. This may increase granulation tissue formation in PDRN-treated ulcers [19].

Synergistic effects and other mechanisms

Through pathways, PDRN influences multiple aspects of wound healing. It stimulates the release of growth factors such as fibroblast growth factor, insulin-like growth factor, and epidermal growth factor indirectly via A2AR-mediated signaling [20], which in turn encourages fibroblast migration and differentiation into myofibroblasts for wound contraction. It promotes endothelial cell proliferation and new vessel sprouting (angiogenesis) to supply the regenerating tissues. It also appears to protect cells from stress-induced damage; for example, treating human dermal fibroblasts with PDRN after ultraviolet B irradiation led to activation of p53 and enhanced DNA repair, suggesting potential anti-photoaging benefits [21]. Additionally, PDRN may aid adipose tissue-derived stem cell niches, as one study noted the increased proliferation of preadipocytes with PDRN exposure, potentially expanding the pool of progenitor cells available for repair [22,23]. All of these effects converge to create a more regenerative environment. The "dual action" of PDRN via cell signaling and substrate provision is thought to underlie the improved healing outcomes observed in experimental models. In diabetic murine models of impaired wound healing, PDRN treatment restored normal wound closure rates with histological evidence of higher vascular density and better-organized collagen deposition relative to untreated controls [24]. These benefits were largely lost when an A2AR antagonist was co-administered, underscoring the centrality of this receptor in the effects of PDRN.

In summary, PDRN's mechanism of action are mainly twofold: it not only activates pro-healing signaling via A2AR stimulation, leading to angiogenesis and reduced inflammation, but also supplies the necessary nucleotides for cell proliferation through the salvage pathway. This combination results in accelerated and effective tissue regeneration across various cell types (endothelial cells, fibroblasts, keratinocytes, and osteoblasts), which explains its broad utility in regenerative medicine and wound management.

Clinical applications

PDRN has been investigated in various clinical conditions that require enhanced tissue repair or anti-inflammatory modulation. This section reviews the evidence for the therapeutic applications of PDRN, with subdivisions by medical domain, focusing on dermatology, wound healing (including chronic ulcers and other skin conditions), and other regenerative medicine contexts. Key clinical studies and outcomes are summarized, highlighting the efficacy and limitations of PDRN.

Dermatology and wound healing

1) Chronic wounds and ulcers

One of the most prominent uses of PDRN is the treatment of chronic skin ulcers and difficult-to-heal wounds. Diabetic foot ulcers have received special attention because of their prevalence and refractory nature. In a landmark multicenter randomized controlled trial (RCT), Squadrito et al. [25] evaluated PDRN in patients with diabetic foot ulcers (Wagner grades 1–2) over an 8-week treatment period. Patients received PDRN both intramuscularly (5.625 mg daily, 5 days/week) and via perilesional injections (twice weekly), in addition to standard wound care. The results were dramatic; by 8 weeks, 37.3% of PDRN-treated patients achieved complete wound closure compared with 18.9% in the placebo group (p = 0.003). The median percentage of ulcer re-epithelialization was significantly higher in the PDRN group than in the placebo group (82.2% vs. 49.3 %, $p < 0.001$). Importantly, this benefit was achieved without any significant drug-related adverse events and the time to complete wound healing (for those that did heal) did not differ between the groups, indicating that PDRN primarily increased the proportion of wounds that could heal rather than merely accelerating healing [25]. This is one of the largest trials on chronic diabetic ulcers and provides strong evidence that PDRN can rescue otherwise "hard-to-heal" wounds. The proposed mechanism for these ulcers is enhanced angiogenesis in ischemic diabetic tissues and stimulation of tissue repair processes, as discussed earlier.

Supporting this finding, several smaller studies reported improved healing of various ulcers in patients with PDRN. In a randomized trial on pressure ulcers (bedsores) in immobilized patients, weekly PDRN injections (combined Intramuscular and perilesional, similar dosing as in the diabetic study) for four weeks led to significant reductions in wound size compared with standard care alone. By the end of the survey, PDRN-treated pressure ulcers showed greater re-epithelialization and improvement in the Pressure Ulcer Scale for Healing, which is consistent with previous evidence in models of diabetic foot ulcers and burn wounds. Notably, no complications or delays in healing were observed with PDRN treatment, and the authors highlighted that PDRN-treated wounds consistently progressed through typical healing phases, whereas some control wounds remained stalled [26]. Another study examined venous leg ulcers by comparing a topical gel containing PDRN plus hyaluronic acid (HA) with an HA-only gel. After 45 days, 67% of the patients treated with PDRN gel achieved complete wound closure, which was significantly higher than the 22% achieved with HA alone. This suggests a synergistic effect when PDRN is combined with other wound-healing agents such as HA, possibly providing both biochemical stimulation (from PDRN) and an optimal moist healing environment (from HA) [27].

Acute wound settings were also explored. A pilot study in Italy on split-thickness skin graft donor sites found that dressings soaked in a PDRN solution led to faster re-epithelialization of the donor site than standard dressings. By the time of suture removal, wounds treated with PDRN were more likely to be fully epithelialized, indicating a potential benefit in surgical wound recovery [28]. Similarly, the ophthalmologic use of PDRN has shown efficacy in mucosal/epithelial healing, and one trial reported that PDRN eye drops significantly accelerated corneal epithelium regeneration after photorefractive keratectomy (laser eye surgery) in treated patients experiencing faster closure of corneal defects with no adverse effects [29]. Collectively, these studies demonstrate the broad ability of PDRN to enhance the healing of epidermal and epithelial injuries spanning from the skin to the cornea.

Chronic wound healing is often impaired by underlying pathologies, such as diabetes, peripheral arterial disease, or prolonged pressure, which results in hypoxia and inflammation. PDRN directly addresses these issues by promoting angiogenesis and resolving inflammation. Thus, jump initiation is a typical healing cascade. For example, in diabetic mouse models, PDRN treatment restored wound healing to near-normal levels, accompanied by increased microvessel density in the wound bed and increased VEGF expression [30]. These mechanistic findings are mirrored in human histopathology; biopsies from PDRN-treated ulcers showed greater granulation tissue and better organization of collagen fibers than those from untreated ulcers. Clinicians have further noted that PDRN can convert a chronic nonhealing ulcer into one that progresses to closure, thus fulfilling an unmet need for wound management. Given the positive results in diabetes and pressure ulcers, PDRN is currently employed as a standard adjunct therapy for chronic wounds in some countries (e.g., Italy, South Korea). PDRN has been officially approved in Italy for injectable and topical use in wound healing, reflecting its established therapeutic value [26,31].

2) Dermatologic conditions and skin regeneration

Beyond chronic ulcers, PDRN has shown promise for other dermatological conditions characterized by inflammation or tissue degeneration. One such condition is lichen sclerosis, a chronic inflammatory disease that causes atrophic and sclerotic lesions (often on the genital skin). The standard therapy relies on topical corticosteroids. In 2013, Laino et al. [32] added

subdermal PDRN injections around the lesions (5.625 mg weekly) to steroid treatment and observed marked improvements in clinical signs (reduced sclerosis, itching, and lesions) compared with steroids alone. A subsequent controlled trial by Zucchi et al. [33] confirmed that intradermal PDRN as an adjunct lead to greater symptom relief and lesion regression in lichen sclerosis patients. This suggests that the anti-inflammatory and tissue-reparative actions of PDRN can benefit autoimmune skin disorders by improving tissue remodeling in chronically inflamed skin.

Aesthetic and regenerative dermatology is another growing area in PDRN applications. There is increasing use of PDRN (also referred to as "polynucleotide [PN]" injections) as a skin rejuvenation treatment to improve signs of aging such as fine wrinkles, elasticity loss, and skin dryness. Although many aesthetic claims are anecdotal, emerging clinical studies support some benefits. For instance, a recent study on aging neck skin found that injectable PNs significantly improved skin elasticity and firmness and reduced wrinkle depth throughout the treatments. Patients who received PDRN-based injections had measurably better skin turgor and collagen density than those who did not, indicating genuine dermal remodeling. In a cellular study, PDRN activated dermal fibroblasts and promoted the synthesis of collagen, elastin, and other matrix components, while exerting anti-inflammatory effects that could mitigate photoaging damage [34]. PDRN may also play a role in pigment modulation and has been reported to inhibit melanogenesis *in vitro*, suggesting its potential to improve hyperpigmentation or melasma. However, clinical evidence for this is limited [35].

Hair restoration is another novel dermatological application. A pilot study by Lee et al. [36] evaluated a topical PDRN-based solution for female pattern hair loss and reported that it improved hair density and thickness in the areas of alopecia. Although the exact mechanism is unclear, it has been postulated that PDRN improves perifollicular vascularization and reduces inflammation around hair follicles, creating a better environment for hair growth. Similarly, clinicians have reported the anecdotal use of PDRN injections in scalp mesotherapy to strengthen the hair in patients with androgenetic alopecia, although more rigorous trials are needed.

Finally, the wound-healing process of PDRN was applied to minimize scar formation. A recent randomized trial investigated the effect of early postoperative PDRN injections on surgical scar quality in patients undergoing dermatological surgery. Although detailed results are pending, we hypothesize that by accelerating organized healing and modulating inflammation, PDRN may lead to softer, pliable scars with better cosmetic appearance. This is consistent with previous observations that graft donor sites and burns healed with PDRN tend to have improved tissue quality and less fibrosis. This could expand the use into preventative scar therapy in surgical practice [20].

In conclusion, PDRN has robust evidence in the dermatological field, particularly for enhancing wound healing in patients with chronic ulcers and injuries. Diabetic foot and pressure ulcers showed significantly improved healing rates after PDRN therapy. Adjunctive benefits have been noted in inflammatory skin diseases (lichen sclerosis), and PDRN is increasingly utilized in aesthetic medicine for skin rejuvenation, and possibly scar and hair loss treatments. These applications leverage the core actions of PDRN: promoting angiogenesis, collagen production, and healthy tissue remodeling while tempering chronic inflammation. Thus, PDRN represents a valuable tool in dermatology that may address both the medical and cosmetic aspects of skin health.

Safety and adverse effects

A critical aspect of any therapeutic agent, especially a biological agent such as PDRN, is its safety profile. PDRN has consistently demonstrated excellent safety and tolerability in both preclinical and clinical studies. This section summarizes findings on PDRN's adverse effects, or lack thereof, and discusses any precautions.

Preclinical toxicology

PDRN has shown no significant toxicity in animal studies, even at high doses. Acute and chronic toxicity tests in rodents revealed that repeated systemic administration of PDRN did not cause organ damage or mortality [37]. For example, Galeano et al. [38] reported that PDRN at a dose of 8 mg/kg (a dose much higher on a weight basis than typical human doses) showed no toxic effects on mice's brain, liver, lungs, muscle, or heart on histological examination. Similarly, long-term administration did not induce blood test or organ function abnormalities. These findings are attributed to the nature of PDRN as a polymer of nucleotides, which are normal cellular constituents. Once broken down, its metabolites can be integrated or excreted without causing harm. Furthermore, as the extraction process removes proteins, the risk of immune reactions (such as anaphylaxis or serum sickness) is minimal [39].

Clinical trial safety data

Human trials on PDRN have uniformly reported a low incidence of adverse events. In a large diabetic foot ulcer trial (216

patients), there were no differences in adverse effects between the PDRN and placebo groups over 8 weeks [25]. The investigators noted excellent safety and tolerability with no systemic side effects or wound complications attributable to PDRN [25]. Injection-site reactions are rare and mild. Similarly, trials on pressure and venous ulcers have not reported any significant adverse outcomes of PDRN injections or topical application [26]. In osteoarthritis studies, intra-articular PDRN was as safe as HA injections. A meta-analysis found no significant difference in adverse event rates (and overall very low event numbers in both groups) [40]. Some patients experience transient injection-related pain or swelling, which is common with any joint injection; however, there have been no reports of inflammatory flares or joint infections attributable to PDRN. Even when PDRN was combined with other substances (such as HA or used in a gel with HA), no new safety issues emerged [41].

Immunogenicity and allergic reactions

Immune reactions are a theoretical concern for biological agents derived from animal sources. However, the manufacturing of PDRN yields highly pure DNA fragments, removes immunogenic proteins, and produces a product that is not associated with allergic reactions. Antibody formation against PDRN or diminishing efficacy with repeated use has also been not reported. Clinical practice in chronic conditions often involves repeated courses of PDRN (e.g., serial injections for chronic ulcers or a series of joint injections over months), and no loss of efficacy or adverse immune events have been observed. The origin of DNA from fish sperm raises the question as to whether patients with fish allergies are at risk. Nevertheless, because proteins are the usual allergens and PDRN contains negligible amounts of protein, it is generally considered safe even in these individuals, although caution and monitoring are prudent. No cases of allergic anaphylaxis due to PDRN have been documented in the literature.

Adverse effect profile

The adverse effect profile of PDRN is immature. No significant side effects have been consistently noted across clinical trials and no dose-limiting toxicities have been identified. Mild effects that have been observed infrequently include transient pain at the injection sites, minor bruising, and mild redness when injected intradermally (similar to mesotherapy reactions). These symptoms are self-limiting and do not require intervention. There is no evidence of systemic side effects, such as alterations in blood pressure, blood glucose, or renal or hepatic function, attributable to PDRN in controlled studies. This safety profile allows PDRN to be used even in vulnerable populations, such as people with diabetes and ulcers (where many other drugs are contraindicated owing to poor circulation) or elderly patients with osteoarthritis (who may not tolerate nonsteroidal anti-inflammatory drugs or other medications). Without immunosuppressive or procoagulant effects, PDRN can be layered into standard care without added risk. For example, PDRN has been safely administered alongside antibiotics, compression therapy for ulcers, and oral analgesics without interactions.

Precautions

Although no serious adverse events have been associated with PDRN, standard precautions include using an aseptic technique for injections to avoid infection and monitoring wound patients for any signs of local infection (since they are inherently at risk, although PDRN itself does not increase that risk). As a DNA-derived product, theoretical concerns about transmissible agents have been allayed by rigorous purification and sourcing from controlled environments; PDRN is not a blood product and has no risk of viral transmission. Some PDRN formulations are combined with other components (e.g., PDRN + HA gel); therefore, one should refer to those specific components for any additional precautions (for instance, HA is also very safe, but if lidocaine is included for pain relief, lidocaine precautions are applied). The safety profile of PDRN allows it to be a versatile therapy that can be confidently added to patient regimens with minimal monitoring beyond usual care.

Future directions

PDRN has been established as a valuable regenerative medicine agent; however, research continues to explore new frontiers for its use. Future directions for PDRN are envisaged in the following domains.

Expanded clinical indications

Current evidence supports the use of PDRN in wounds and osteoarthritis; however, future large-scale trials may extend its use. Potential areas of research include rheumatoid arthritis (leveraging the anti-inflammatory effect observed in animal models) and other autoimmune conditions in which tissue damage is a concern. Chronic inflammatory diseases, such as inflammatory bowel disease and chronic periodontitis, may also benefit from the dual action of PDRN in promoting repair and modulating inflammation [42]. High-quality clinical trials

under these conditions would clarify the role of PDRN and pave the way for new therapies (e.g., a trial of PDRN enemas or injections in ulcerative colitis for mucosal healing could be envisioned based on preclinical data).

Combination therapies

Future use of PDRN will likely involve combining it with other regenerative strategies for achieving additive or synergistic effects. The first is a combination of growth factors and cell therapies. For instance, PDRN can be co-delivered with platelet-rich plasma or stem cell injections to boost the extracellular matrix (via PDRN effects) and cellular repair engines. Another promising combination is PDRN + HA, as already tested in knee osteoarthritis, which showed improved outcomes compared to HA alone [41]. A similar combination has been tested in dermal fillers (to enhance longevity and tissue integration) and ophthalmology (PDRN + artificial tears for severe dry eye healing). Additionally, PDRN with phototherapy or lasers is being explored (for example, applying PDRN after fractional laser resurfacing to enhance healing and collagen remodeling in aesthetic treatments) [43].

Tissue engineering and drug delivery innovations

In the bioengineering sphere, PDRN is believed to act as a bioactive scaffold. To create scaffolds that actively stimulate regeneration, research is ongoing to incorporate PDRN into novel biomaterials such as electrospun nanofiber mats for skin wounds or 3D-printed bone grafts [44]. One challenge is controlling the release kinetics of PDRN; too fast a release might shorten its effect. Therefore, future biomaterials should aim for sustained or stimuli-responsive release. Hydrogels that respond to pH or temperature to release PDRN when needed have been studied [45]. Microneedle patches loaded with PDRN offer a minimally invasive way to deliver PDRN to chronic wounds or aging skin for rejuvenation. Moreover, the production of synthetic or recombinant PDRN (e.g., microbially derived PDRN) is an area of interest [46]. If PDRN chains could be produced via engineered bacteria or enzyme systems, it might allow for specific size ranges or modifications and alleviate the dependency on fish sources. A recent report successfully produced PDRN fragments using a microbial system and showed that they retained their efficacy in wound healing assays [45]. This could lead to more standardized products and reduced costs.

Mechanistic research and optimization

Future research will also delve deeper into the mechanisms of PDRN at the molecular level. For instance, the relative contributions of the A2AR vs. salvage pathway in different contexts (wound vs. cartilage vs. muscle) have not been fully elucidated, and understanding this could optimize the use of PDRN (e.g., pairing it with an adenosine uptake inhibitor such as dipyridamole may prolong its A2AR-mediated action [47], which could be tested in therapy). In addition, investigations into whether PDRN affects other adenosine receptors (such as A2BR in muscle differentiation) could broaden its scope [47]. If the PDRN components engage A2BR and promote myogenesis, they may also be used in muscle injury rehabilitation or sarcopenia (age-related muscle loss) [8]. The optimal dosing and route for each indication is another area for refinement. For example, could oral PDRN (if formulated to survive digestion) provide systemic benefits for conditions such as peripheral artery disease? Alternatively, is the future focused on localized delivery systems? However, these questions remain to be answered.

Long-term outcomes and surveillance

As PDRN use has become more common, accumulating data on long-term outcomes is essential. Do chronic wounds healed with PDRN have lower recurrence rates? Are scars more pliable? Do repeated PDRN injections delay the need for joint replacement over the years? Such long-term benefits, if demonstrated, will solidify the place of PDRN in standard treatment algorithms. Additionally, with the expansion of PDRN use geographically and into new patient populations, continued pharmacovigilance is needed to ensure that its safety profile remains favorable. Thus far, all evidence has been reassuring; nevertheless, vigilance is prudent.

Regulatory approvals and guidelines

Finally, future directions include achieving broader regulatory approval and incorporation into clinical guidelines. It is ongoing, and future trials could support approval by agencies such as the Food and Drug Administration or European Medicines Agency for indications such as diabetic foot ulcers or knee osteoarthritis. With formal approval, usage would increase, and more practitioners would gain experience with PDRN. Professional society guidelines (for wound care or osteoarthritis management) may begin to include PDRN as more Level I evidence emerges (e.g., if another large RCT corroborates the diabetic ulcer trial, wound care guidelines may list PDRN injections as a recommended adjunct for non-healing ulcers). In South Korea and Italy, PDRN has already been integrated into practice; the hope is that other regions will follow as data and experience grow.

In conclusion, the future of PDRN is bright, with multiple exciting avenues for expanding its therapeutic impact. This unique dual mechanism provides a platform that can be constructed using new technologies and combined approaches. As research continues, PDRN may evolve from a niche regenerative therapy to a mainstream component of healing-focused medical care used in engineering tissues for the everyday management of chronic diseases.

Discussion

PDRN has emerged as a multifaceted therapeutic agent in pharmacology and regenerative medicine. Its dual mechanism of action—namely, stimulating A2AR and supplying DNA building blocks—enables it to orchestrate a robust pro-healing response in tissues. The evidence reviewed herein highlights the efficacy of PDRN in various applications; it accelerates wound closure in chronic skin ulcers, improves tissue quality and angiogenesis in ischemic conditions, and reduces pain and inflammation in degenerative joint diseases. In dermatology, PDRN has proven valuable for hard-to-heal wounds, such as diabetic foot ulcers [48], and shows potential for cosmetic rejuvenation and scar modulation. PDRN is appealing because of its safety profile across trials and real-world use and has demonstrated excellent tolerability with no significant adverse effects [49]. This allows clinicians to apply it to elderly patients or to those with comorbidities without concern.

The therapeutic impact of PDRN can be attributed to its ability to address both sides of the regeneration coin, which boosts intrinsic repair processes (cell proliferation, collagen deposition, and new vessel growth) and concurrently tempers destructive processes (inflammation and matrix breakdown). This holistic approach helps tip chronic, nonhealing states back towards healing, as evidenced in chronic ulcer studies, where PDRN nearly doubled the healing rate [4]. Moreover, PDRN versatility means that it does not target a single organ or disease, but is a fundamental aspect of biology, tissue repair, and remodeling, making its potential applications diverse. A review of the current literature indicates that PDRN has already secured a role in specific fields (such as wound care in Italy and Korea), and with growing evidence, its adoption is likely to widen internationally.

Nevertheless, it is essential to acknowledge that PDRN are not a panacea. Wound healing and tissue regeneration are complex processes. PDRN provides a significant boost, but optimal outcomes still require good overall care (e.g., pressure offloading in ulcers and rehabilitation in orthopedic injuries). Although promising results exist for many indications, some are based on limited studies; thus, further research is vital. Future studies should aim to clarify the long-term benefits of PDRN, optimal dosing regimens, and effectiveness in broader patient populations. As new delivery methods and combination strategies are developed, they should be rigorously tested to ensure that they translate into clinical improvements.

In conclusion, PDRN represents a novel and valuable addition to therapeutic toolkits for dermatologists, wound specialists, and regenerative medicine practitioners. It embodies the concept of a pro-healing drug that works with the body's natural repair mechanisms to restore the form and function of damaged tissues. Clinical evidence, supported by a strong mechanistic foundation, posits that PDRN is an effective treatment for enhancing wound healing, promoting tissue regeneration in chronic degenerative conditions, and improving patient outcomes in areas that are traditionally challenging to manage. As our understanding and utilization of PDRN continue to evolve, it promises to enhance the quality of life of patients suffering from chronic wounds, osteoarthritis pain, and other conditions, while maintaining a high safety standard. The story of PDRN is a testament to the progress in regenerative therapeutics, turning fundamental scientific insights into tangible healing for patients, and we will likely see its role expand as a standard of care in the years to come [50].

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