

Dynamic Mechanical Stimulation of Fibroblasts in Aligned Scaffolds: Inhibiting the YAP/TAZ Pathway to Reduce Wound Contraction

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Abstract

Pathological scarring and wound contraction remain significant medical challenges, often resulting in functional impairment, loss of mobility, and aesthetic distress (1,2). Adult wound healing usually ends with fibrotic scars and disorganized collagen. In contrast, fetal healing happens without scarring. Why? Because fetal skin has a low-tension environment and special fibroblast lineages (3,4). Central to this biophysical regulation is the YAP/TAZ signaling pathway, a mechanosensitive molecular rheostat that senses matrix stiffness and tension to drive the myofibroblast phenotype (5,6,7). This review examines recent advancements in the synergistic use of aligned scaffold architectures and dynamic mechanical stimulation to guide cellular recruitment and maturation (8,9,10). Furthermore, we explore therapeutic strategies to inhibit the YAP/TAZ pathway ranging from pharmacological agents like Verteporfin to "smart" drug-delivery nanogels to interrupt the fibrotic feedback loop and steer the healing process toward functional skin regeneration (11,12,13).

Keywords: Fibroblasts, Aligned Scaffolds, YAP/TAZ Pathway, Wound Contraction

1. Introduction: The Clinical and Mechanobiological Burden of Scarring

Skin wounds, particularly those involving substantial tissue loss, often exceed the body's natural capacity for orderly restoration (1). In adult mammals, the standard response to injury is a highly coordinated multi-stage process hemostasis, inflammation, proliferation, and remodeling—that generally culminates in a fibrotic scar (2,4). Pathological scarring, such as keloids and hypertrophic scars (HTS), leads to long-term pain, infection, and functional defects (1,2). A critical outcome of this process is wound contraction, driven by the differentiation of fibroblasts into myofibroblasts (6,7). These cells express alpha-smooth muscle actin (α -SMA) and generate significant contractile forces, which are necessary for rapid wound closure but, when persistent, lead to debilitating contractures (6,7).

Recent advancements have highlighted that the mechanical environment of the wound is a primary determinant of healing quality (1,2). Mechanotransduction the process by which cells convert physical forces into biochemical signals allows

fibroblasts to perceive the increased tension and substrate rigidity of adult wounds (4,6). This perception triggers pro-fibrotic pathways, primarily through the activation of the Hippo pathway effectors YAP and TAZ (5,6,7). Engineering strategies that utilize biomimetic scaffolds to modulate these mechanical cues are now a cornerstone of regenerative medicine (1,2).

2. Materials and Methods

2.1. Search Strategy

A systematic literature search was conducted in three electronic databases: PubMed/MEDLINE, Scopus, and Web of Science. The search period covered January 1, 2015, to June 1, 2026, to include both foundational and recent advances. The following search string was adapted for each database syntax:

("YAP/TAZ" OR "Yes-associated protein" OR "TAZ" OR "Hippo pathway") AND ("scarless healing" OR "scarless regeneration" OR "wound contraction" OR "fibrotic scar" OR "myofibroblast") AND ("aligned scaffold" OR "nanofiber alignment" OR "topographical guidance" OR "contact

guidance") AND ("mechanical stimulation" OR "cyclic stretch" OR "bioreactor" OR "dynamic loading") AND ("Verteporfin" OR "mechanotransduction inhibitor" OR "FAK inhibitor").

2.2. Inclusion and Exclusion Criteria

Articles were included if they met the following criteria: (i) peer-reviewed original research or review articles published in English; (ii) studies investigating YAP/TAZ signaling in skin wound healing, scarring, or fibroblast mechanotransduction; (iii) research on aligned scaffolds, dynamic mechanical stimulation, or pharmacological inhibition (e.g., Verteporfin) for dermal regeneration; (iv) in vitro, in vivo, or ex vivo models relevant to human skin repair. Conference abstracts, book chapters, editorials, preprints, and non-English articles were excluded. Studies focusing solely on non-dermal fibrosis (e.g., lung, liver, cardiac) were considered only when they provided mechanistic insights directly applicable to skin.

2.3. PRISMA 2020 Study Selection Process and Data Extraction

This review followed the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting framework for the identification, screening, and inclusion of

eligible studies (Figure 1). Identification: A total of 98 records were identified through database searching (PubMed/MEDLINE, Scopus, Web of Science), and an additional 5 records were identified through manual searching of reference lists, giving 103 records in total.

Screening: After removal of 20 duplicate records, 83 unique records were screened by title and abstract against the eligibility criteria in Section 2.2. Of these, 51 records were excluded at this stage for not meeting the inclusion criteria (e.g., wrong tissue type, wrong outcome, wrong publication type).

Eligibility: The remaining 32 full-text articles were retrieved and assessed for eligibility. Twenty-four were excluded at the full-text stage, for the following reasons: non-dermal fibrosis model without a translatable mechanistic insight ($n = 8$); conference abstract only ($n = 6$); insufficient outcome data ($n = 5$); other reasons, e.g., non-English full text or duplicate dataset ($n = 5$).

Inclusion: Eight studies met all eligibility criteria after full-text review and were included in the narrative synthesis and summarized in Table 2.

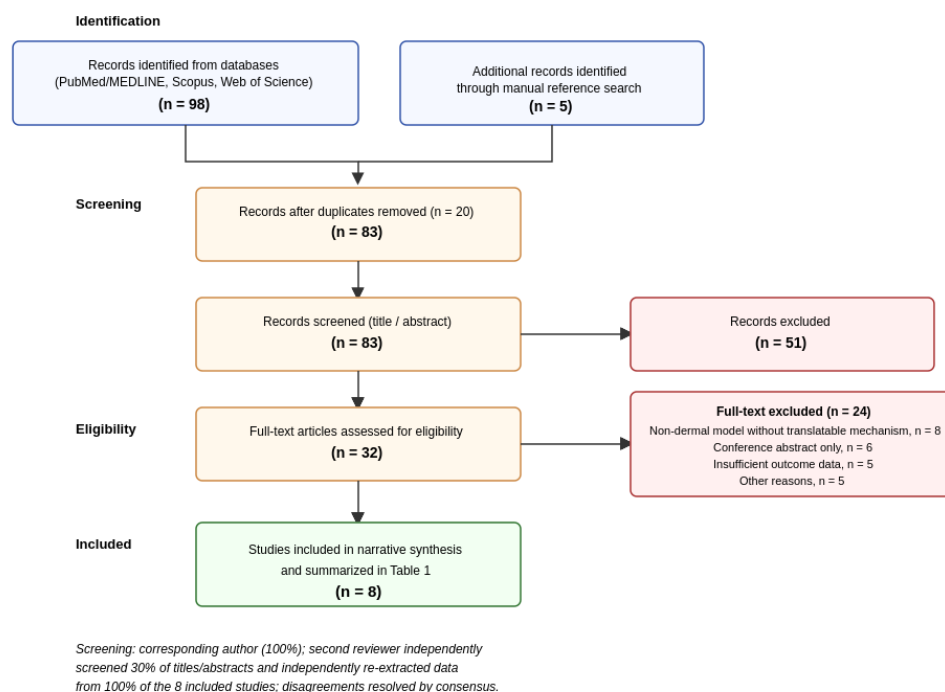


Figure 1. PRISMA 2020 flow diagram summarizing the identification, screening, eligibility, and inclusion of studies ($n = 8$ included).

To minimize selection bias and errors in data extraction, an independent second researcher (second reviewer)

independently screened a random 30% sample of titles/abstracts and independently re-extracted data from all

eight included studies, blinded to the corresponding author's initial decisions. Disagreements in study selection or data extraction were resolved by discussion, and full agreement was reached on the final set of included studies.

2.4. Quality Assessment

We assessed the methodological quality of included original studies using tools appropriate to each study design: SYRCLE's Risk of Bias tool for in vivo animal studies, and the NIH Quality Assessment Tool for in vitro and computational/in

silico studies. Quality assessment was performed independently by the corresponding author and ambiguities were resolved through re-examination and, where necessary, consultation with a methodological expert. Of the eight included studies, five were rated low risk of bias (Sohutskay et al., Sharmin et al., Mascharak et al., Chen et al., Tang et al.), two were rated as having some/moderate concerns (Fan et al., Patten et al.), and one was rated high risk of bias (Jenkins, 2023 reflecting its status as an unpublished doctoral dissertation without full independent peer review).

Study	Risk-of-bias/ Quality Rating	Tool
Sohutskay et al. (2021) (1)	Low risk	NIH QA Tool (computational/in vitro)
Fan et al. (2024) (5)	Some concerns (moderate)	NIH QA Tool (in vitro)
Sharmin et al. (2026) (6)	Low risk	NIH QA Tool (in vitro)
Jenkins (2023) (8)	High risk	NIH QA Tool (in vitro / dissertation)
Mascharak et al. (2025) (11)	Low risk	SYRCLE (in vivo, pig)
Chen et al. (2023) (12)	Low risk	SYRCLE (in vivo, rat/rabbit)
Tang et al. (2025) (14)	Low risk	SYRCLE (in vivo, mouse)
Patten et al. (2025) (16)	Some concerns (moderate)	NIH QA Tool (in vitro)

Table 1. Risk-of-bias / quality assessment summary for the eight included studies.

2.5. Data Synthesis

Due to heterogeneity in study designs, models, and outcome measures, a meta-analysis was not feasible. A narrative synthesis was conducted, organized thematically around three main domains: (i) aligned scaffold architectures; (ii)

dynamic mechanical stimulation; (iii) YAP/TAZ pathway inhibition. Findings were integrated to propose a synergistic model for scarless skin regeneration. The main characteristic and finding of the most relevant studies are summarized in table 2.

Reference	Model	Intervention	Main Finding Related to Reduced Wound Contraction/ YAP/TAZ Inhibition
Sohutskay et al. (2021) (1)	Computational mechanobiological model	Collagen scaffold with different density & alignment	High-density aligned scaffolds prevent permanent 80% contraction; predictably control wound contraction
Fan et al. (2024) (5)	In vitro (cell migration)	Nanofiber scaffold with dual growth factor gradients	Increased migration speed and distance vs. random fibers (reduces contraction time)
Sharmin et al. (2026) (6)	In vitro (3D PCL scaffold in bioreactor)	Perfusion + cyclic stretch (0-5%)	29 µg DNA/g sample vs. 7.52 µg DNA/g sample (3.9× higher); elongated morphology (reduced contractile phenotype)
Jenkins (2023) (8)	Finite element model/ dynamic loading protocol	Fiber alignment & density	High density + high alignment resist severe contraction; 5,000 cycles/day optimal; 10,000 cycles/day induces overuse phenotype
Mascharak et al. (2025) (11)	In vivo (Duroc pig)	Verteporfin, 10 mg/kg IV, single dose, immediately post-wounding	Complete scar prevention; hair follicle & gland regeneration – direct YAP/TAZ inhibition
Chen et al. (2023) (12)	In vitro / in vivo (rat, rabbit)	HA-modified PLA nanogels + Verteporfin (16 µg VP / 40 mg PLA), topical, daily × 14 days	Selective nuclear YAP inhibition; sustained anti-fibrotic release; scarless healing
Tang et al. (2025) (14)	In vivo (mouse)	CuATSM (Hippo/YAP modulator)	Reduced nuclear YAP translocation; decreased α-SMA & collagen I; scarless regeneration
Patten et al. (2025) (16)	In vitro (human fibroblasts)	Actin microarchitecture + FAK inhibitor (Defactinib)	Prevented YAP nuclear targeting; reduced contraction

Table 2: Summary of key studies on aligned scaffolds, mechanical stimulation, and YAP/TAZ inhibition for scarless skin regeneration

3. Aligned Scaffolds: Engineering "Highways" for Regenerative Healing

The physical architecture of a scaffold dictates the spatial organization of the regenerating tissue (1). While disorganized collagen fibers characterize scar tissue, healthy dermis contains structured patterns that influence cell behavior through contact guidance (1,4).

3.1. Directed Cell Recruitment and Migration

Engineered scaffolds with aligned nanofibrous architectures act as "highways" for cell migration, accelerating the

recruitment of dermal fibroblasts and keratinocytes into the wound void (8,5). For example, radially aligned scaffolds (RAS) guide cells from the wound periphery toward the center, promoting efficient coverage and more uniform contraction than randomly oriented fibers (8). Studies show that oriented nanofibers can significantly increase migration distance and velocity compared to random fibers (5). This topographical guidance is achieved as cells physically adapt to the underlying fibers, elongating their cytoskeleton parallel to the longitudinal axis of the fibers (5).

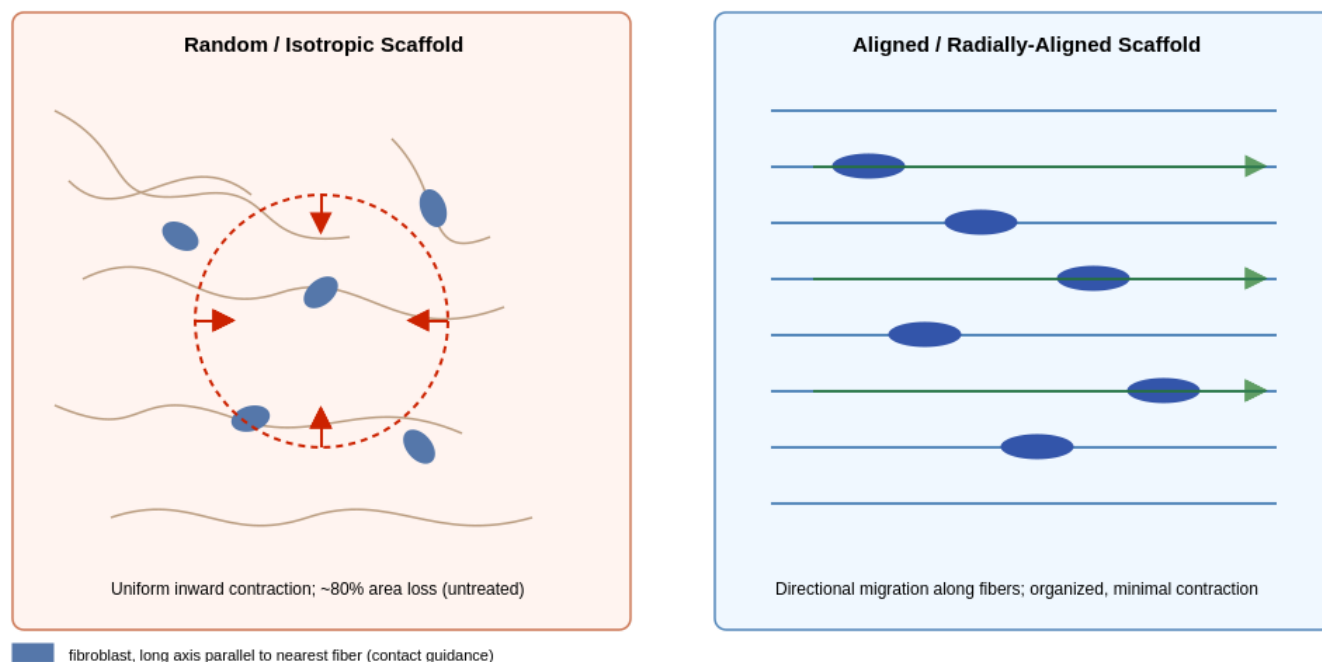


Figure 2. Effect of scaffold fiber alignment on cell orientation and wound contraction: random/isotropic scaffolds (left) versus aligned/radially-aligned scaffolds (right).

3.2. Predicting and Controlling Contraction

Computational models have demonstrated that scaffold fiber alignment and density are paramount design features for predictably controlling wound contraction (1,8). Mechanobiological finite element models indicate that high-density, aligned architectures provide the necessary mechanical resistance to prevent the severe permanent contraction (often reaching 80% area reduction) observed in untreated wounds (1). Furthermore, scaffolds with increased fiber dispersion (isotropy) may exhibit more uniform contraction while still supporting cell infiltration (1,8).

3.3. Immune Modulation via Topography

Beyond guiding fibroblasts, aligned topographies actively modulate the localized immune microenvironment (1,4). Aligned electrospun nanofibers physically force macrophages into an elongated shape, which downregulates the pro-

inflammatory M1 phenotype and upregulates the pro-healing M2 phenotype (1,2,4). This phenotypic switch is driven by the physical inhibition of the JAK-STAT and NF- κ B signaling pathways (1,4). The resulting M2-rich environment is rich in anti-inflammatory cytokines like IL-10, which suppress pathological fibroblast activation and guide scar-free tissue remodeling (4).

4. Dynamic Mechanical Stimulation: Mimicking the Physiological Niche

While static topographical cues provide initial guidance, cutaneous tissues are naturally subjected to dynamic, time-varying mechanical forces (9,10). Dynamic mechanical stimulation (DMS), delivered via bioreactors or smart materials, is essential for the maturation of engineered skin substitutes (9,16).

4.1. Synergistic Effects of Perfusion and Cyclic Stretch

Advanced multi-modal bioreactor systems have been developed to apply simultaneous perfusion and cyclic tensile stimulation to 3D scaffolds (6). Perfusion mimics the in vivo nutrient and waste exchange, while cyclic stretch provides the mechanical cues necessary for functional maturation (6). Validated models using polycaprolactone (PCL) auxetic scaffolds show that the combination of these stimuli leads to significantly improved fibroblast proliferation and collagen production (6). Specifically, cells under perfusion and 0-5% cyclic strain exhibited elongated morphologies indicative of healthy cellular function and 3.9 times higher DNA content than static controls (29 μg DNA/g sample vs. 7.52 μg DNA/g sample) (6,9).

4.2. Finding the Loading "Sweet Spot"

Research into engineered connective tissues, such as tendons, suggests that there is an optimal threshold for mechanical loading (8). Loading protocols of approximately 5,000 cycles per session have been found to promote the greatest matrix synthesis and improved mechanical function (8). However, increasing the load to 10,000 cycles can induce

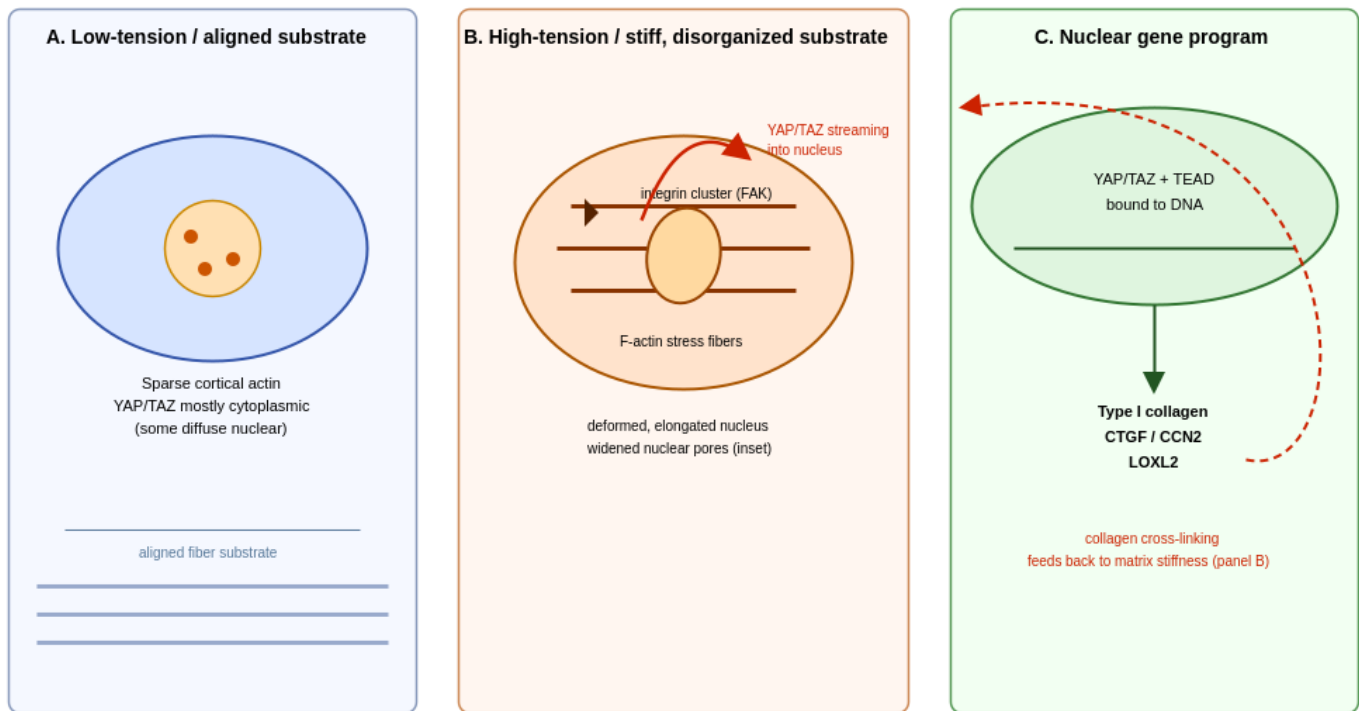
an "overuse" phenotype, characterized by collagen disorganization, premature scaffold fatigue, and diminished mechanical properties (8). This "sweet spot" is critical for tissue engineers to avoid inducing a fibrotic, hyper-proliferative response (8).

4.3. Induced Anisotropy and Maturation

Dynamic stimulation induces anisotropy and improves the tensile properties of engineered tissues even without exogenous scaffolding (4). In human skin substitutes, mechanical stimulation induces rapid fibroblast proliferation and accelerates early maturation, leading to the production of oriented collagen fibers that more closely resemble native dermis (4).

5. The YAP/TAZ Pathway: The Molecular Sensor of Mechanical Stress

The ability of fibroblasts to translate the physical cues from aligned scaffolds and cyclic stretch into biochemical signals is mediated primarily by Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) (5,6,7,18).



Panels A – B – C illustrate how cyclic mechanical tension drives YAP/TAZ nuclear import and a feed-forward pro-fibrotic gene program.

Figure 3. Mechanotransduction of cyclic stretch into nuclear YAP/TAZ import and the downstream pro-fibrotic gene program.

5.1. Mechanotransduction and Nuclear Shuttling

YAP and TAZ act as molecular sensors of matrix stiffness and cell spreading (5,6,7,18). Dermal fibroblasts perceive mechanical cues via transmembrane interfaces like integrins,

which couple the ECM to the intracellular actin cytoskeleton (4,7,18). In high-tension environments, integrin clustering activates focal adhesion kinase (FAK) and Rho GTPases, promoting the assembly of F-actin stress fibers (4,6,7,18).

This cytoskeletal tension transmits force to the cell nucleus, deforming the nuclear membrane and physically expanding nuclear pore complexes (7,18). This expansion facilitates the rapid nuclear translocation of YAP/TAZ (7,18).

5.2. Driving the Fibrotic Feedback Loop

Once inside the nucleus, YAP/TAZ associate with TEAD transcription factors to initiate a pro-fibrotic gene program (5,6,7). This program upregulates the production of Type I collagen and connective tissue growth factor (CTGF/CCN2) (6,7). Additionally, YAP/TAZ drive the expression of structural remodeling enzymes like LOXL2, which increase collagen cross-linking and further elevate matrix stiffness (7,18). This establishes a pathological feed-forward mechanotransductive loop where stiffening ECM drives further YAP activation, leading to progressive fibrosis and wound contraction (4,7,18).

5.3. Lineage Switching: ENF vs. EPF

Recent research has identified that mechanical tension applied to adult wounds activates Engrailed-1 (En1) via the YAP/TAZ-TEAD complex (3). This mechanosensitive transcriptional program converts lineage-negative dermal fibroblasts (ENF, En1-negative fibroblasts) into pro-fibrotic, contractile En1-lineage-positive fibroblasts (EPF, Engrailed-1-positive fibroblasts) (3,11). In contrast, fetal fibroblasts and adult fibroblasts in low-tension environments do not undergo this activation and instead maintain a regenerative, ENF-like phenotype (3,4,11). Disrupting this ENF-to-EPF lineage switch — whether through mechanical unloading (aligned scaffolds, dynamic stimulation) or YAP/TAZ inhibition — is a primary goal for achieving scarless repair (3,11).

6. Therapeutic Inhibition of the YAP/TAZ Axis

Pharmacological and biomaterial-based strategies to inhibit YAP/TAZ signaling have emerged as potent tools for reducing wound contraction and promoting regeneration (11,12,19).

6.1. Verteporfin: A Potent Pharmacological Inhibitor

Verteporfin (VP), an FDA-approved drug for macular degeneration, is a highly selective inhibitor of YAP/TAZ–TEAD interactions (11,12,13). By binding directly to YAP, Verteporfin disrupts its association with TEAD, thereby repressing mechanosensitive gene programs (11,12,13). Preclinical animal studies, notably in red Duroc pigs — the most human-like model of scarring — have demonstrated that a single intravenous dose of Verteporfin (10 mg/kg), administered once, immediately after wounding, is sufficient to prevent scarring and to drive functional wound regeneration, including the regrowth of hair follicles and

glands (11). In the nanogel delivery system reported by Chen et al., each HA/VP-PLA nanoparticle batch was formulated using 16 µg of Verteporfin per 40 mg of PLA (molecular weight 47 kDa), and the resulting nanogel was applied topically once daily for 14 days, yielding sustained anti-fibrotic release over the wound bed (12). Human Phase 2 clinical trials (SCARFREE-001, NCT07488988) are currently investigating intradermal Verteporfin for scar prevention in surgical wounds (13).

6.2. Nanotechnology and Stage-Adaptive Delivery

Complete systemic inhibition of YAP is undesirable as transient activation is required for early cell survival and re-epithelialization (12). To solve this, researchers have engineered hyaluronic acid (HA)-modified and Verteporfin-loaded polylactic acid (PLA) nanogels (12). These sophisticated delivery systems target fibroblasts via CD44 receptors, releasing HA and lactic acid to stimulate healthy migration while providing a sustained release of Verteporfin to selectively inhibit YAP nuclear localization and suppress fibrosis (12).

6.3. Novel Chemical Modulators

Other chemical agents, such as CuATSM, have shown promise in enhancing wound repair without scarring (19). CuATSM modulates the Hippo/YAP signaling pathway by reducing ferroptosis and regulating macrophage polarization, which reduces nuclear YAP levels and downregulates pro-fibrotic markers like collagen Type I (19). Similarly, Fisetin and FAK inhibitors (Defactinib) are being explored for their ability to break the mechanosensitive feedback loop and facilitate compliant dermal remodeling (4,16).

7. Synergistic Regulation: Integrating Alignment, Loading, and Inhibition

The future of scarless healing lies in the coordination of these biophysical and biochemical cues (1,2). Aligned scaffolds provide the uniaxial spatial restriction necessary to limit multi-directional nuclear tension, thereby restricting passive YAP import (7). Superimposing physiological cyclic stretching detunes the static isometric tension of the wound, preventing the assembly of stable actin stress fibers and myofibroblast differentiation (4,9).

Research into mechanosensitive ion channels like TRPV4 has revealed complex regulatory hierarchies (8). While YAP inhibition can block the formation of aligned collagen, simultaneous stimulation of TRPV4 can partially "rescue" aligned collagen formation and the actin cytoskeleton (8). This suggests that targeting multiple nodes in the mechanotransduction network may be necessary to achieve

the anabolic effects required for true tissue regeneration (8,18).

7.1. Proposed Temporal Sequencing of Combined Therapy

A key open question for translating this synergistic model is the temporal sequencing of pharmacological and mechanical interventions: should Verteporfin be administered before mechanical stimulation begins, applied simultaneously with dynamic loading, or introduced only after an initial period of mechanically-guided cell alignment? We propose that the optimal sequencing is stage-dependent, mirroring the three phases of wound healing.

Early phase (mechanical priming before pharmacological inhibition): During the first 24–72 hours after injury, transient YAP/TAZ activity is required for fibroblast survival, migration into the wound bed, and initial re-epithelialization (12). Administering Verteporfin during this window — particularly at systemic or high local concentrations — risks impairing cell viability and delaying closure. We therefore propose that aligned scaffolds and low-amplitude dynamic stimulation should be applied first, without pharmacological inhibition, to establish directional cell recruitment and an initial anisotropic matrix architecture while YAP/TAZ signaling remains permissive for survival and migration.

Mid phase (simultaneous, stage-adaptive delivery): Once initial re-epithelialization is underway (typically once

granulation tissue begins to form), the risk shifts from insufficient cell survival to excessive myofibroblast differentiation and contraction. This is the rationale behind stage-adaptive nanogel systems such as HA/VP-PLA (12): sustained, locally-restricted Verteporfin release can be combined with ongoing cyclic mechanical stimulation, so that the mechanical environment (aligned, cyclically unloaded) and the biochemical environment (YAP/TAZ-restricted) act on the same time axis to prevent the fibrotic feed-forward loop described in Section 5.2 from consolidating.

Late phase (mechanical maintenance, tapering inhibition): As remodeling progresses, complete and prolonged YAP/TAZ suppression is undesirable, since some baseline mechanotransductive signaling is required for matrix maturation and long-term tissue integrity (12). We propose tapering pharmacological inhibition while maintaining aligned scaffold architecture and physiological cyclic loading as the primary long-term regulators of fibroblast phenotype, consistent with the loading "sweet spot" described in Section 4.2 (8).

This staged, sequence-dependent model is, at present, a synthesis of mechanistic reasoning across the reviewed literature rather than a directly tested clinical protocol; we flag it explicitly as a proposed framework requiring dedicated experimental validation, and we return to this point in the Clinical Translation paragraph (Section 8.1).

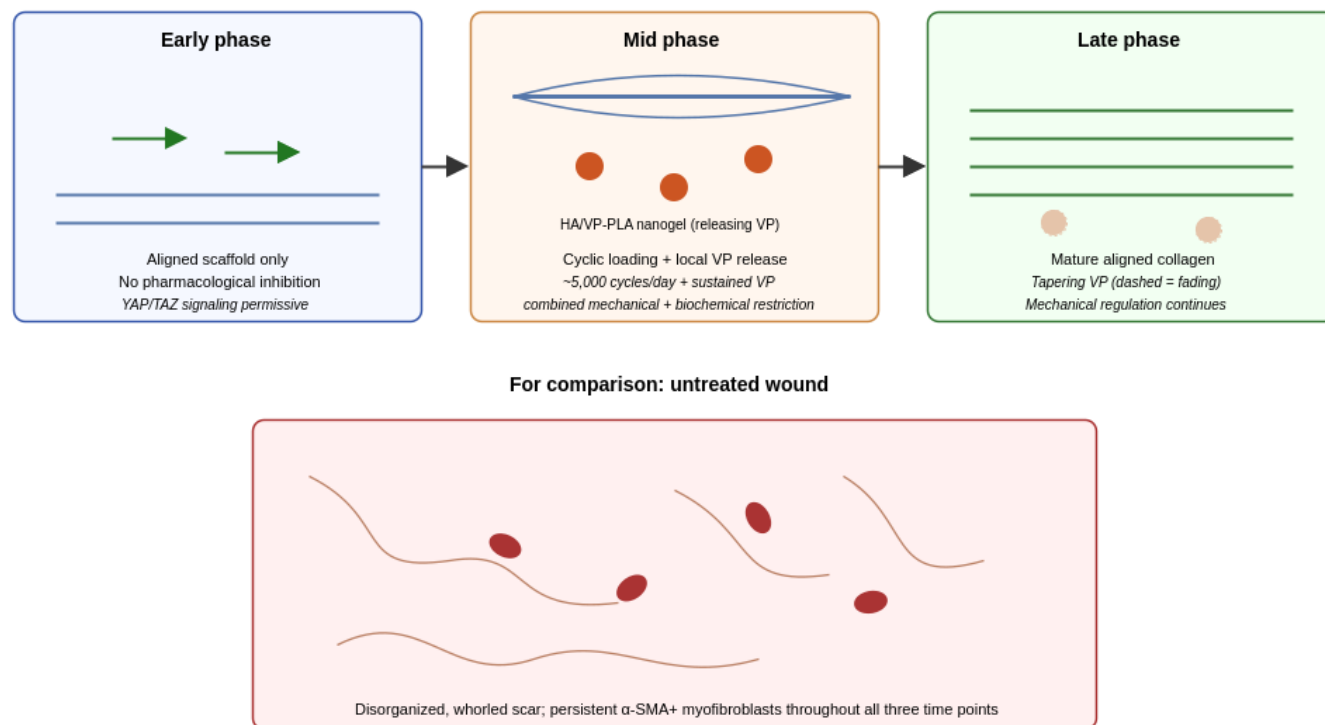


Figure 4. Proposed synergistic model integrating aligned-scaffold architecture, dynamic cyclic loading, and staged Verteporfin delivery across the early, mid, and late phases of wound healing, compared against an untreated wound.

8. Conclusion and Future Directions

To turn a scarring wound into a regenerated one, we need to change the environment around the wound cells not just patch it (1,2,4). By combining aligned scaffold designs that serve as structural guides with dynamic mechanical stimulation that mimics the developmental niche, tissue engineers can steer fibroblast behavior away from the contractile myofibroblast phenotype (4,8,9). The downregulation of the YAP/TAZ signaling axis whether through compliant, biomimetic materials or targeted pharmacological agents like Verteporfin is essential to breaking the cycle of tension-driven fibrosis (7,11,12,18).

To translate these advanced biomaterial systems successfully, several challenges remain (1,8):

Optimization of Loading Protocols: Systematically determining the strain amplitude and frequency (the "sweet spot") that maximizes matrix synthesis without causing damage (8).

Precision Release Kinetics: Synchronizing drug release from scaffolds with the specific stages of cutaneous healing to ensure YAP activity is only inhibited when necessary (12).

Scalable Manufacturing: Utilizing advanced technologies like 3D and 4D bioprinting and AI-guided design to create personalized, high-precision scaffolds (2).

By addressing these clinical and engineering roadblocks, the integration of physical and chemical regulation will redefine the standard of care, transforming pathological adult wound repair into scarless, functional skin regeneration (1,2,11).

8.1. Clinical Translation: Practical Challenges and Pathways Forward

Beyond the mechanistic and preclinical advances described above, several practical hurdles must be addressed before aligned-scaffold and dynamic-stimulation strategies combined with YAP/TAZ inhibition can reach routine clinical use. Scalability is a primary concern: laboratory-scale bioreactors capable of delivering precise, spatially uniform perfusion and cyclic strain (Section 4.1) are difficult to translate into wound-conforming devices for irregular, full-thickness human wounds; a shift toward wearable or dressing-integrated actuators, rather than benchtop bioreactor hardware, will likely be required for bedside application. Manufacturing at clinically relevant scale and cost, while preserving the fiber-scale alignment shown to control contraction (Section 3), will also require moving beyond small-batch electrospinning toward more reproducible, quality-controlled production methods (2).

Regarding Verteporfin safety in humans, the drug's long-standing FDA approval for photodynamic therapy in macular degeneration provides a favorable existing safety record for

the compound itself; however, this experience is based on intravenous administration with light activation, not on the local, un-activated intradermal or topical delivery proposed for scar prevention. The ongoing SCARFREE-001 Phase 2 trial (13) is expected to generate the first controlled human safety and dosing data for this specific indication and route, and its outcome will be a key determinant of whether the pharmacological arm of the synergistic model proposed in Section 7 is clinically viable, as opposed to remaining reliant on mechanical/scaffold-based approaches alone.

Finally, the choice of bioreactor or delivery platform is not a purely engineering decision—it must match the intended clinical workflow. A closed, single-use, disposable dressing-bioreactor suitable for outpatient or bedside use is more realistic for widespread adoption than a reusable, sterilizable benchtop system requiring specialized clinical engineering support. We suggest that future translational work explicitly report device cost, sterilization requirements, and compatibility with standard wound-care workflows alongside biological outcome data, so that efficacy findings can be interpreted against practical deployability from the outset.

9. Declaration of AI-assisted image generation

The schematic illustrations presented in Figures 1, 2, 3, and the PRISMA flow diagram were initially conceptualized and generated using Claude (Anthropic) for primary structural design, scientific layout planning, and initial SVG code generation to visualize the mechanistic concepts and study selection workflow. All AI-generated drafts were subsequently reviewed, rigorously edited, and validated by the authors to ensure scientific accuracy, correct labeling, and full consistency with the cited literature and the manuscript's narrative. The final versions of all figures were refined using standard graphic design software (Canva, Microsoft Word) for professional publication quality.

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