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Understanding keloids from bench to market: a review of origin, community impact, treatment economics, existing therapies, and pipeline products

Abstract

Invasive fibroproliferative lesions driven by failures in tissue remodeling after injuries to the skin, keloids are physiological conditions which are becoming increasingly studied and treated. Unlike healthy tissue which terminates inflammation upon wound resolution, keloid scars are propagated by hyperactive dermal fibroblasts that resist apoptosis and overproduce disorganized collagen. The pathogenic process is heavily triggered by elevations in systemic inflammatory markers and via high-tension mechanical forces, disproportionately impacting melanin-rich skin types.

Valued at estimates of several billions, the global keloid scar management market is driven by an urgent demand for non-destructive therapeutics. Though standard treatments such as intralesional corticosteroid injections and silicone sheeting exist, such offerings permit for localized tissue damage and high recurrence. The translational pipeline is currently shifting away from these options, introducing pre-clinical and clinical products such as fibroblast programming techniques and targeted biologics.

Future directions in the field of keloid research and innovations will emphasize personalized combination therapies and digital risk management, as well as other early bioengineered interventions resolving aberrant cellular cascades at their onset.

Keywords: commercial market analysis, extracellular matrix remodeling, health equity, hypertrophic scar, keloid, scarring, tissue engineering, translational therapeutics, regenerative medicine.

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Abbreviations: TGF, transforming growth factor; CAGR, compound annual growth rate; DNA, deoxyribonucleic acid; MSC, mesenchymal stem cell; AT1, angiotensin II type 1 receptor; TAC, triamcinolone acetonide; BMP-4, bone morphogenetic protein 4; BTX-A, botulinum toxin type A; CTGF, connective tissue growth factor; GF, growth factor.

Introduction

Notably, wound healing is a fundamental tissue interaction that serves as a model for immunology, pathology, and regenerative therapeutic development. Understanding the interconnected cascade of healing and skin reconstitution is essential in medicine, enabling professionals to understand pathological deviations, prevent chronic complications arising from clinical techniques, improve interventions, etc.[1]

Specifically, alterations in fibroproliferation can result in hypertrophic or keloid scarring, a disruption to the normal wound healing continuum.[1] Unlike scarring resulting from normal response to injury, keloid cutaneous scar formation involves invasion of the surrounding healthy tissue beyond the original wound boundary. It is currently hypothesized that keloid scarring is driven by the increased deposition of extracellular matrix components (e.g. collagen) due to excessive growth factor and cytokine expression, disregarding the appropriate apoptosis response.[2]

Past research has attempted to identify the specific cellular, genetic, and molecular factors responsible for keloid scarring, leading to several treatment developments. Examples include combination therapies of surgical removal and steroid therapy, as well as inhibition of growth factor β and the recombinant cytokine interleukin-10.[1,2] However, such treatments are not completely effective, with keloids maintaining a high rate of recurrence.[1]

Hence, while the global patient demand for effective keloid scar treatments is large, a critical gap remains in deeper mechanistic research and product validation.[3] Interestingly, the bioengineering and dermatological fields have also historically understudied keloid formation, despite disproportionately high incidence in individuals of African, Asian, and Hispanic descent.[4] An improved understanding of the pathomechanisms leading to keloid formation will enable better targeting of therapies, tissue engineering techniques, and surgical interventions in these communities and beyond.[2]

Thus, in response to the necessity of keloid research advancement, this review article provides critical context by synthesizing the physiology of the skin, contrasting normal versus aberrant wound healing, and exploring systemic risk factors and complications of scarring.[2-4] Additionally, this piece provides a systematic overview of global market trends, noting commercialized developments, mentioning emerging clinical and pre-clinical therapeutics, breaking down mechanistics of product function, and explicitly highlighting connections to biomedical inequities. By accentuating the global burden of disease, commercial profitability, potential for scientific breakthroughs, and direct impacts to patient advocacy, this article attempts to provide a multi-stakeholder justification for innovations responding to keloids.[3]

Physiological etiology and history

Healthy healing of skin tissue

The human skin is complex in composition, made up of the epidermis, dermis, and hypodermis layers. The epidermis acts as a barrier, while the dermis acts as an elastic support via collagen and glycosaminoglycans. The hypodermis serves as an insulating, fat-storing cushion connecting to underlying muscle. Within the healthy variants of these layers, type I and type III collagen fibers

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are organized in a lattice fashion, permitting appropriate mechanical elasticity and downstream signaling for functionalit. In response to skin injuries, the normal wound healing cascade initiates, divided into four regulated phases: hemostasis, inflammation, proliferation, and tissue remodeling. Throughout hemostasis, a temporary fibrin clot is formed to control hemorrhage due to an open wound. During initial inflammation, antigen presenting cells like macrophages capture and process foreign pathogens while neutrophils clear away damaged cellular debris created by injury. Additionally, crucial cytokines such as transforming growth-factor-β-1 (TGF-β-1) and fibroblast growth factors are released to signal for cell proliferation at the site.[1,2] In healthy tissue, TGF-β-1 and fibroblast growth factor signaling induces a transition from the cell proliferation phase into tissue remodeling. Mechanistically, TGF-β-1 binds to a complex of type I and type II receptors that phosphorylate SMAD proteins and drive the transcription of pro-proliferative genes when activated.[29,30] Fibroblast growth factors also drive cell division through the initiation of a phosphorylation cascade pushing cells through the cell cycle, occurring upon heparin-sulfate-proteoglycan-stabilized growth factor binding to receptors The activated complexes recruit adapter proteins and guanine nucleotide exchange factors that further phosphorylation, urging phosphorylated extracellular signal-regulated kinase to enter the skin cell nucleus and activate transcription factors promoting cell division.[31,32]

Diseased healing of skin tissue

During tissue remodeling, fibroblasts undergo programmed apoptosis and matrix metalloproteins break down excessive fibrin clotting to restore structural equilibrium.[1] However, in the case of hypertrophic scar and keloid formation, this transition is disrupted.[5] This unchecked cell signaling causes a massive imbalance between matrix deposition and degradation.[2] Keloids exhibit continuous, aggressive fibroblast proliferation due to excessive growth factor (TGF-β-1 and TGF-β-2) expression and inhibition (TGF-β-3) downregulation, leading to failures in cellular apoptosis and increased extracellular matrix component deposition.[1] Causally, the overactive TGF-β-1 and TGF-β-2 signaling blocks the activities of essential apoptosis-activating molecules such as caspase-3.[33,34] Sustained cytokine signalling can also induce differentiation of typical fibroblasts into hyperactive myofibroblasts, upregulating the production of collagen and overexpressing plasminogen activator-inhibitor–1 (blocking fibrinolysis, which normally restores structural equilibrium).[5,6,34]

Demonstrated in Figure 1, this induction of clot formation and inhibition of fibrinolysis disrupts physiological balance, leading to complications like thrombosis and wound expansion.

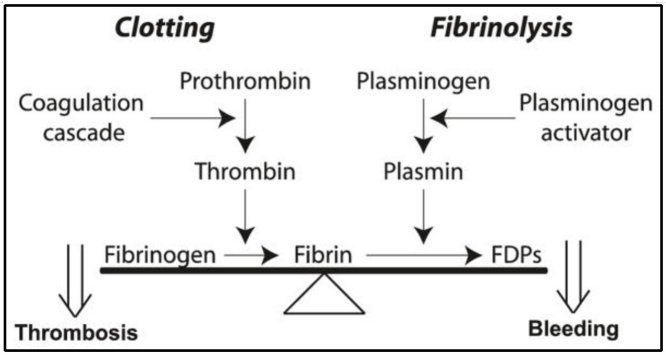


Figure 1 Overview of the general wound healing cascades.[7]

The image demonstrates the balance between fibrin clot formation and fibrinolysis, two opposing biological processes that are involved in the cessation of bleeding when blood vessels are injured and dissolving of a clot during healing. As physiological equilibrium is disrupted in favor of clotting, issues such as thrombosis within vasculature or wound expansion in the skin may arise.

Additionally, the resulting environment of dense, non-functional fibrin networks leads to the expansion of cutaneous scars beyond original injury boundaries, structurally altering the typical dermis architecture.[8]

Keloids may grow in characteristic shapes depending on location, relating to induce mechanical forces on the wound.[9] When a developing wound is repeatedly stretched by underlying muscles, stress is placed on skin cells.[35,36] This stress triggers cellular mechanoreceptors, which in turn signal fibroblasts and immune cells to engage in excessive inflammation. As demonstrated in Figure 2, keloids on the anterior chest grow horizontally in a "crab-like" shape while keloids on the lower abdomen may grow vertically due to rectus abdominis muscle movement.[9]



Figure 2 Typical keloid on the body's anterior chest wall.[9]

The image shows an example of a keloid on the anterior chest wall, shaped in a "crab-like" formation. In this part of the body, keloids may grow horizontally due to tension induced by pectoralis major muscle contraction.

Associated diseases and physiological risk factors for keloids

Keloid formation is heavily triggered by trauma to an injury site, local inflammation, and genetic predisposition.[8] Scarring may manifest on the face, back, and chest following nodulocystic acne rupture which induces chronic dermal inflammation.[4] Standard surgical procedures, like cesarean sections and sternotomies, may also serve as mechanical triggers for keloidogenesis.[3]

Several other risk factors dictate keloid susceptibility, documented in Table 1.[4]

Table 1 Typical risk factors for keloidogenesis, including inheritance, location of injury, and personal demographic characteristics[4,9,10]

Risk factor	Impact on keloidogenesis
Anatomical location of injury	Areas of the body experiencing high tension due to muscle contraction are more uniquely prone to aggressive keloid propagation.[4] Constant mechanical stretch forces can activate mechanosensitive ion channels on dermal fibroblasts and lead to wound expansion.[4,9]
Genetic predominance	Single-nucleotide polymorphisms and gene irregularities can promote fibroblast differentiation and collagen production.[10] Additionally, variable gene expressivity may lead to fluctuating severity of traits such as keloid susceptibility. Different phenotypes may include tiny, unnoticed earlobe scars or severe, large-scale masses.[10]
Age demographics	The peak incidence occurs between ages 10 to 30, coinciding with elevated systemic hormone levels (growth, sex steroids, etc.) and heightened metabolic activity.[10]

Beyond cosmetic appearance, unchecked keloid growth can lead to several diseases. Examples may include chronic localized pain, hyperesthesia (sensory sensitivity), and intractable pruritus (chronic itching), induced due to the entrapment of peripheral nerve endings in dense collagen masses.[8]

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Mechanistically, continuous physical compression of the peripheral nerves leads to the destruction of thick nerve fibers, instead promoting unmyelinated C-fibers to grow at the outer edges of keloid masses. These unmyelinated fibers are extremely sensitive and prone to misfiring, causing chronic itching pains.[37,38] Furthermore, nerve endings traumatized by physical pressure inappropriately secrete neuropeptides like substance P, materials which stimulate nearby mast cells to release histamine that can further irritate tissue.[39]

As keloids extend beyond injuries to the joints, they may also induce severe restriction of range of motion and functional mobility, leading to muscle atrophy (muscle weakening due to minimized stimulation), muscle contractures (ligament shortening due to inactivity), pressure ulcers, and blood clots (reduced healthy blood circulation can lead to thrombosis risks).[11]

Keloid-impacted communities and associated accessibility gaps

Systemic health inequities regarding keloid research and treatment accessibility persist.[12] As shown below in Figure 3, epidemiological data suggests that individuals with melanin-rich skin (Fitzpatrick skin types type IV to VI, often in African, Asian, and Hispanic communities) experience dramatically higher incidence of keloids, ranging from 4.5% to 16%. Comparatively, less than 1% of Caucasian individuals experience keloidogenesis.[13] However, clinical trial design, therapeutic development, and medical school training curricula have historically centered around Caucasian individuals, underrepresenting skin of color in research and development.[3]

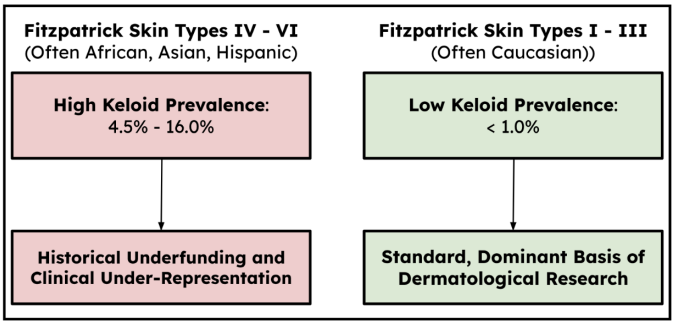


Figure 3 Overview of the onset and response to keloids in specific communities.[13]

The image describes the disparities that exist between communities experiencing high rates of keloid incidence (4.5% to 16.0%) and low keloid incidence rates (less than 1.0%) in regards to respective research, treatment, and medical accessibility. Communities are categorized based on commonly seen Fitzpatrick skin types, a skin classification system with six categories measuring different maintenance of melanin pigment and responses to external conditions.

These disparities introduce critical ethical challenges within research product development.[12] Melanosomes in darker skin are larger and more dispersed, degrading at slower rates compared to fair skin and creating further signaling between melanocytes and fibroblasts (leading to greater keloid incidence).[10] As clinical research and funding overlook these skin-sensitive interactions, minority communities face limited treatment options for keloids.[3] Rather, ineffective interventions such as intralesional steroid injections may be recommended, inducing distressing pigmentary changes like inflammatory hyperpigmentation or hypopigmentation.[14]

Specialized cosmetic dermatology clinics, high-end laser treatment systems, and advanced medical scar therapeutics are also heavily concentrated within Western cities, limiting reach to the communities with greatest demonstrated need.

This mandates a structural realignment of biomedical research, demanding the integration of diverse patient cohorts in pre-clinical modeling and early-stage treatment design to better account for the biological nuances of melanin-rich skin.[3]

Market size, trends, and drivers

Insurance costs, treatment fees, and market dynamic trends

Documented below in Table 2, managing keloids and hypertrophic scars presents substantial economic challenges varying based on clinical modality, incurred out-of-pocket costs, and baseline insurance coverage of treatments.[3]

Market size, growth trends, and segmentation

As seen in Figure 4, the broader global wound care market has been valued at approximately $25.07 billion and is projected to expand to $35.13 billion.[16,17] For pathological scarring, the global scar treatment market has exhibited valuations of $2.9 billion, with a robust compound annual growth rate (CAGR) of 10.6% in areas such as Asia from 2026 to 2033 (3,18). Of this number, hypertrophic scars and keloids contribute to over $1.5 billion of the market.[18]

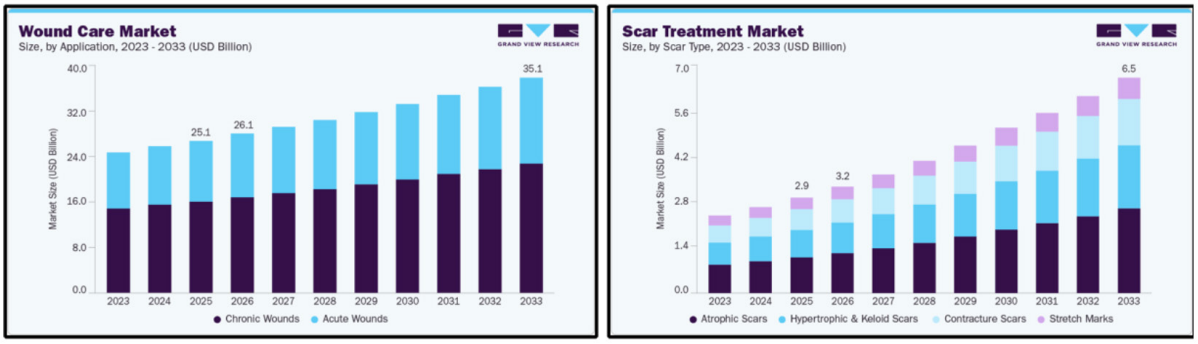


Figure 4 Overview of the 2026 wound care and scar treatment markets.[17-19]

A. This image showcases the 2026 market size and forecasts for global wound care, owed to a growing amount of surgical cases and the increasing prevalence of chronic disorders like keloidogenesis.

B. This image visualizes the 2026 market size and projections for global scar treatments, growing due to aesthetic concerns in clinics, increased incidence of tissue trauma, and technological advancements.

Table 2 Available treatments, fees, and impacts to market dynamics[3,8,14,15]

Treatment type	Average cost per session	Insurance coverage status	Market dynamics
Topical products and silicone gel sheets	$30 - $100 per month.[3,8]	Fully out-of-pocket, provided over-the-counter.[3,8]	In high supply and universally available at clinics, yet fails to meet long-term recurrence Demands.[3,8,14]
Intralesional corticosteroids	$150 – $400.[8]	Covered in-full or mostly covered, if deemed medically necessary for function.[8]	In high supply and universally available at clinics, yet fails to meet long-term recurrence Demands.[8,14]
Laser therapies	$300 – $1,200.[3,14]	Rarely covered due to cosmetic classifications.[3,14]	In high demand, but in restricted supply due to high device cost and limited clinical availability.[14]
Surgical excisions	$3,500 – $10,000+.[15]	Partially covered if documentation of functional impairment is provided.[15]	Limited access, requires multi-disciplinary clinical teams.[15]

As seen in Table 3, North America dominates the wound care and scar markets due to extensive healthcare expenditures, established keloid clinical infrastructure, and the early adoption of keloid-oriented treatment devices.[20] The Asian-Pacific region is growing quickly in impact, however, involving itself extensively by expanding healthcare access, introducing aesthetic medicine techniques, and diversifying patient portfolios.[3]

Table 3 Market size, project growth, demographics, etc. data from 2026[3,16-18,20]

Market metric sector	Current valuation (USD)	Projected valuation (USD)	Estimated CAGR	Regional dominance factors
Global general wound care market	$25.07 Billion.[16,17]	$35.13 Billion.[16,17]	4.33%.[16,17]	Accelerated by rising chronic wound incidence and elective procedures.[16]
Global scar treatment market	$2.9 Billion.[18]	$6.5 Billion.[18]	10.6%.[18]	Driven by non-invasive device innovations and high clinical demand, especially in aesthetic treatments.[3,18]
Hypertrophic scar and keloid market	$1.5 Billion.[18]	$5.6 Billion.[18]	10.6%.[18]	High concentration of advanced aesthetic and dermatological device platforms, scar revision surgeries.[18,20]

In regards to market segmentation, the wound care and scar markets can be broken down based on scar type, treatment type, end-user goals, and region. Surgical scars of the atrophic and keloid scar divisions led the market in recent years, anticipated to contribute even more due to factors such as surgical procedure availability and need.[17]

The global wound care and scar markets can also be divided into therapeutic designations such as topical products versus laser therapies and injectable corticosteroids. Topical products and silicone sheets held the majority share of the market in 2024, favored for their over-the-counter accessibility, cost-effectiveness, and non-invasive nature.[14,17] However, laser therapies are predicted to grow quickly in significance, driven by technological advances and consumer willingness to invest in advanced treatments for aesthetic purposes.[17,18]

In terms of end-users and region, the markets can be categorized into clinics and hospitals, retail and online pharmacies, and countries. Hospitals and clinics dominate the market due to comprehensive diagnosis and treatment, but dermatology clinics are expanding quickly due to the popularity of cosmetic procedures. And, though North America leads scar treatments due to skin disorder prevalence, the Asia-Pacific market is set for rapid growth due to rising populations and evolving beauty standards.[17]

Propellers of market growth

Several economic and clinical drivers propel the sustained expansion of the keloid and hypertrophic scar markets, such as rising injury incidence, biocompatibility concerns in regards to treatments, hospital costs, and changes in pharmaceutical innovations.[3,20,21]

Rising rates of surgical intervention and a growing volume of traumatic injuries have also increased the share of the population that is at risk for keloids and hypertrophic scarring.[3]

Additionally, traditional invasive treatments have experienced failure due to biocompatibility issues, which induce structural graft rejection or keloid recurrence that drives up outpatient hospital costs.[20] The high costs of non-invasive molecular targeted therapies, however, have also led to increased costs.[21]

Products and treatments

Existing products and standard treatment interventions

For keloid management, surgical excision alone is discouraged due to potential induction of new, aggressive wound-healing response and induced recurrence rates of 45% to 100%.[22] Rather, combined surgical removal with post-operative adjuvant therapies is suggested to minimize complications and recurrence.[23]

The gold standard of treatment typically involves surgical excision of keloids followed by radiotherapy, which involves the use of localized external beam radiation over fresh incisions to ablate residual hyperactive dermal fibroblasts that want to expand wound

borders.[15] This suppression of fibro proliferations drives recurrence rates from 45% to 100% down to 10% to 20%, occurring due to the ionizing energy of radiation rays breaking down the DNA strands of overactive skin cells.[15,40] The DNA damage cannot be repaired effectively by fibroblasts due to their engagement in cell division activities, eventually leading to cell apoptosis upon accumulation of genetic errors.[40]

However, even the gold standard has complications due to radiation usage. Applying ionizing radiation to benign keloid conditions carries a small risk of oncogenic transformation and tissue necrosis, limiting the patient pool to which treatment can be applied. As such, much modern research has instead focused on biologics and biomaterials as post-operation treatments.[6]

Tissue-engineering matrices and cell-based therapeutics, for instance, are being designed to actively re-guide the tissue to healthy remodeling. Animal models using mesenchymal stem cells (MSCs) harvested from patient hair follicles have demonstrated significant reductions in clot thickness, showcasing prevention of hypertrophic scarring.[5] The MSCs work to reduce early-stage inflammation by releasing paracrine factors suppressing pro-inflammatory cytokines. Wounds treated with hair-follicle-derived MSCs thus limited overactive cell division and enhanced apoptosis, restoring the balance of extracellular matrix degradation and synthesis for a thinner dermal layer.[41]

Furthermore, targeting of the renin-angiotensin systems in the body has shown promise, with product developers reporting that dermal fibroblasts treated with Losartan (an angiotensin-II-type-1 receptor antagonist) have exhibited decreased migration beyond wound boundaries, extracellular matrix factor deposition, and growth factor inhibition.[5] Functionally, blockading of the angiotensin II type 1 (AT1) receptor inhibits the gene expression of key pro-fibrotic growth factors, controlling cell replication and minimizing tissue inflammation. Additionally, Losartan directly downregulates the genes responsible for the migratory and contractile behaviors of skin cells, stopping fibroblasts from clustering and instead limiting them to native wound boundaries.[42]

The existing arsenal of available, FDA-approved products for keloid and hypertrophic scar management is summarized in Table 4 below, spanning various clinical modalities. The treatments can also be physically visualized, like in Figure 5 below.



Figure 5 Typical products used for keloid management.[24-27]

Pictures of existing products for keloid and hypertrophic scar management, including A,

A. This image shows the Cica-Care silicone gel sheets product, used for keloid and hypertrophic scar management.

B. This image shows an example of the intralesional triamcinolone product, also used for keloid and hypertrophic scar management.

C. This image shows an example of the fluorouracil co-injection product, also used for keloid and hypertrophic scar management.

Table 4 Existing clinical arsenal of treatments for keloids and hypertrophic scars[14,24-28]

Product type	Key manufacturers of products	Mechanism of action	Demonstrated clinical impacts and limitations
Silicone gel sheets (e.g. NewGel+ and Cica-Care Sheets)	Smith & Nephew.[24]	Gel increased hydration in the stratum corneum, downregulating cytokine signalling via occlusion and limiting abnormal cell proliferation.[14-24]	Silicone gel sheets are highly effective at softening early-stage scars, but less effective at treating calcified, long-term keloids.[14,24]
Intralesional triamcinolone (TAC - Kenalog)	Bristol-Myers Squibb.[14,22,25]	Directly arrests fibroblast proliferation, reducing growth factor signaling and restoring healthy apoptosis.[22-24]	Involved in gold standard treatments, yet 50% of keloids relapse or show no response.[14,25]
Fluorouracil co-injections (5-FU)	Various Manufacturers of Generics.[26-28]	Halts DNA synthesis in hyperactive keloid fibroblasts to stop replication, acting as a pyrimidine analog.[26]	Achieves superior reduction in keloid size and pain management.[27,28]

Mechanisms of action in existing therapeutics

To understand where the current clinical paradigm fails, the specific biophysical and cellular mechanisms of action of commercially available scar products must be evaluated.

During the aberrant wound healing process, the newly formed stratum corneum of the skin is structurally immature and cannot regulate moisture properly. This leads to high rates of trans epidermal water loss, triggering the skin's keratinocytes. The keratinocytes rely on a specific level of intracellular hydration to function, so moisture deficits are registered as cellular stress signals that stimulate the CD14 receptor pathway and produce pro-inflammatory cytokines. As these are produced, dermal fibroblasts are activated and synthesize excessive amounts of extracellular matrix proteins for the eventual growth of a keloid mass.[43,44]

As seen in Figure 6, silicone gel sheets like NewGel+ and Cica-Care do not operate via classical pharmacological delivery of medication and instead function by physically occluding the injured wound site.[14,24] By forming a water-impermeable barrier near the keloid region, the sheet reduces trans epidermal water loss and restores hydration to the damaged tissue. Restored hydration signals to the keratinocytes that the skin barrier is intact, halting the production of pro-inflammatory cytokines and decreasing the activation of TGF–β-1-mediated collagen synthesis.[14]

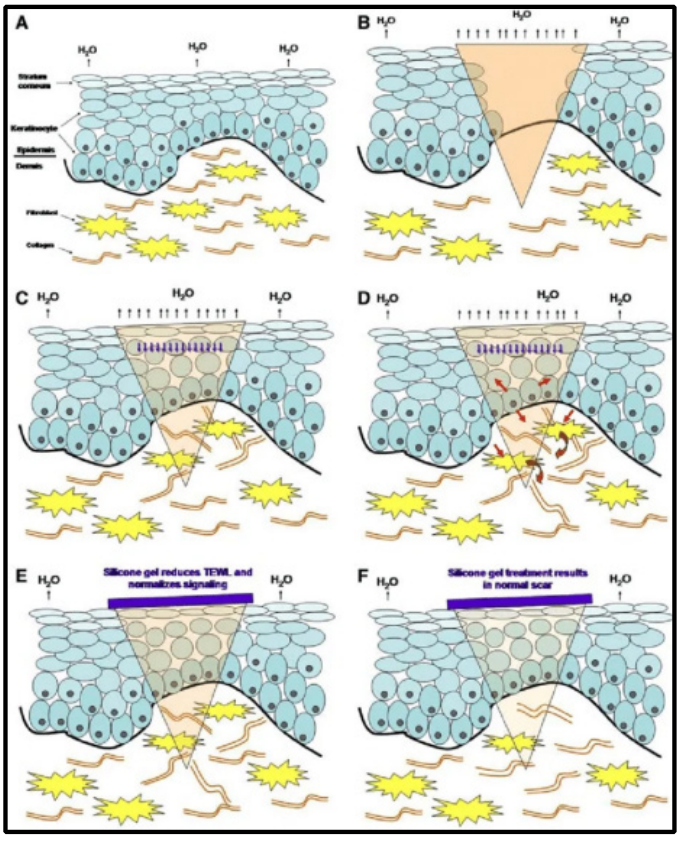


Figure 6 Overview of the mechanisms for keloid healing in silicone sheeting.[45]

This image displays the mechanism for healing of scar tissue and keloids via silicone gel sheet treatment. Treatment of the wound restores the barrier function of the stratum corneum, reducing transepidermal water loss and halting the keratinocyte hyperactivity that would otherwise contribute to keloidogenesis.

Intralesional corticosteroid injections work by suppressing inflammation, reducing collagen production, and breaking down existing keloid scar tissue. Biochemically, the triamcinolone acetonide (TAC) component of the injection binds directly to glucocorticoid receptors within the dermis, translocating to the nucleus to suppress the transcription of pro-inflammatory genes like α-2 type I collagen. This downregulates the expression of vascular endothelial growth factors and reduces the proliferation of fibroblasts, minimizing keloid mass growth. Additionally, TAC restores matrix metalloproteinase expression, breaking down dense collagen networks.[22,46]

Lastly, treatments such as 5-FU fluorouracil co-injection chemotherapy work by blocking DNA replication and cellular proliferation.[47] As a pyrimidine antagonist, 5-FU arrests the cell cycle and selectively halts the proliferation of hyperactive fibroblasts in keloid scar tissue without inducing overall toxicity to the body. As cellular proliferation is inhibited, TGF-β-1-induced type I collagen production is also downregulated, inducing targeted apoptosis within aberrant myofibroblasts.[27]

Pre-clinical trials and pipeline products in clinical development

Molecularly targeted agents and advanced delivery devices are the main products in pre-clinical and clinical trials, involved in several phases.[27]

In pre-clinical testing and in vitro simulations, fibroblast reprogramming and anti-angiogenic interventions are being studied.[5,22]

Bone morphogenetic protein 4 (BMP-4) is currently being added to active myofibroblasts, halting abnormal extracellular matrix assembly and turning the cells into adipocytes (5). The tissue remodeling cascade is triggered by BMP-4, activating peroxisome proliferator-activated receptor-gamma signaling which restores balance between clot formation and fibrinolysis.[5]

Additionally, anti-angiogenic interventions like bevacizumab are being studied in in vitro models for the purpose of disrupting the capillary networks that feed keloids, starving hyperactive scar masses.[22]

In phase II clinical trials, items such as botulinum toxin type A (BTX-A), COX-2 inhibitors (like parecoxib), and anti-tissue-growth-factor biologics are being investigated.[22,27]

BTX-A is currently being studied for its ability to reduce mechanical tension that leads to keloid scar extension, acting by temporarily paralyzing myofibroblasts and reducing their cellular stretch signals. The treatment has demonstrated significant reductions in pain and scar recurrence, but further research must be conducted on diverse patient populations.[27]

COX-2 inhibitors like parecoxib are also being investigated in local administrations, acting to direct keloid minimization and restore physiological balance by inducing scar tissue apoptosis.

And, biologics such as monoclonal antibodies are targeted since they act upon the primary drivers of keloid growth, reducing fibroblast responsiveness to profibrotic growth factor signaling and preventing the differentiation of fibroblasts into aberrant cell types.[22]

Lastly, phase III clinical trials on improved fluorouracil co-injections, laser therapies, and tailored corticosteroid injections are being conducted.[22,27]

Large-scale trials are evaluating the combination of intralesional co-injections, steroids, and ablative lasers for keloid management. The combination has so-far achieved high efficacy compared to stand-alone delivery, significantly reducing keloid volume.[27]

Targeted corticosteroids are being formulated in advanced manners to sustain longer-term drug release, aiming for maintenance of effective localized dosage while reducing the need for frequent delivery.[21]

Mechanisms of action in developing pipeline products

In terms of functionality, bone morphogenetic proteins studied in pre-clinical research heal keloid scars by reinforcing natural tissue remodeling. At a molecular level, BMP-4 activates SMAD-dependent and PPAR-γ signaling pathways, which force myofibroblasts to transdifferentiate into adipocyte fat cells. As the myofibroblasts are induced to convert into adipocytes, they cease the deposition of excessive extracellular matrix components and reverse the buildup of tough, fibrous tissue. Additionally, the mature adipocytes secrete byproducts which further suppress pro-fibrotic activities.[47]

Furthermore, bevacizumab interventions studied at the pre-clinical level act by binding directly to vascular endothelial growth factors (VEGFs) and starving keloid tissue. Keloids are highly vascular, nutrient-rich lesions, so VEGF-binding therapies that reduce new blood vessel formation effectively limit growth (seen in Figure 7). Plus, binding to VEGFs blocks the TGF-β signaling pathway and decreases the synthesis of scar-forming collagen deposits.[48]

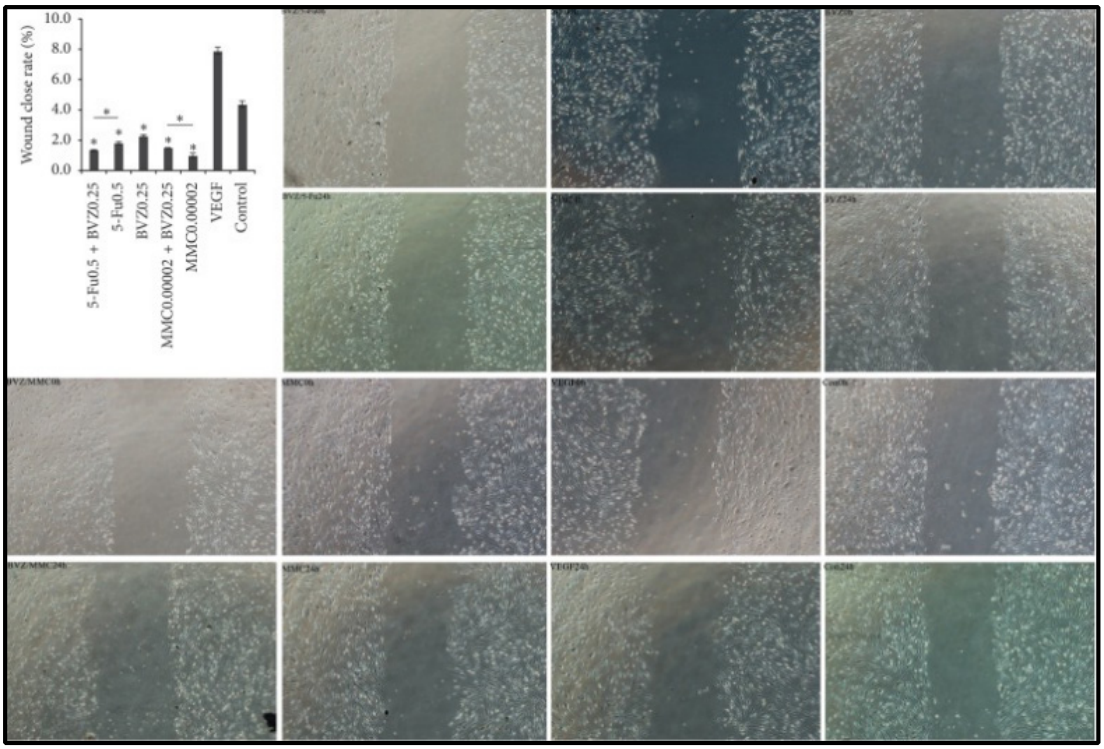


Figure 7 Example of the effects of pipeline drugs on keloids.[48]

This image demonstrates how combined bevacizumab drug interventions show significant inhibitory effects on fibroblast cell migration, leading to limited keloid growth.

In phase II clinical trials, BTX-A suppresses keloid growth by reducing the expression of key pro-fibrotic growth factors such as TGF-β-1 and connective tissue growth factor (CTGF). BTX-A significantly inhibits the growth factors' gene and protein expression, preventing the signaling cascade that otherwise directs cell proliferation and differentiation into myofibroblasts at the wound site.[49]

COX-2 inhibitors and anti-GF biologics work to reduce keloid extension by interrupting chronic inflammation and excessive fibroblast proliferation pathways.[50,51]

COX-2 is typically responsible for synthesizing prostaglandins that recruit inflammatory cells into a wound. As these factors are inhibited, downstream signaling for the release of pro-fibrotic cytokines is stunted.[50]

Anti-TGF-β biologics interrupt the SMAD protein signaling pathway, directly decreasing collagen output and shifting tissue activities from unbridled fibrosis and towards healthier scar degradation. This flattens lesions, limiting scar spread.[51]

Finally, the improved fluorouracil co-injections, laser therapies, and corticosteroid injections which are being studied combinatorially in phase III clinical trials target keloids by suppressing inflammation, blocking cellular proliferation, and reducing collagen deposit formation.[21,22,27]

As mentioned in the discussion of existing treatment options, fluorouracil and corticosteroid injections work by downregulating growth factors contributing to keloid growth while lasers induce DNA damage to hyperactive skin cells. However, while effective individually, corticosteroids can cause adverse side effects like skin thinning and widening of superficial blood vessels. Hence, three-pronged approaches aim to achieve synergistic effects while minimizing complications.[52]

Conclusions and future considerations

Summary of main findings

The management of keloids and hypertrophic scars presents a complex challenge at the intersection of clinical dermatology, material science, and health equity.[3] Pathophysiologically, lesions are induced by disruption to the normal wound healing cascade such as overactive growth factor signaling, inhibited fibrinolysis, and failure of typical cellular apoptosis.[2]

Economically, the keloid and hypertrophic scar markets are large, with the global hypertrophic scar market being valued at over $29.25 billion.[3] However, despite this substantial economic value, imbalances persist in research funding and critical resource allocation, disproportionately impacting melanin-rich communities who face the highest keloid incidence.[12]

As such, work must be done to more robustly include diverse patient populations, focus towards non-invasive clinical interventions that do not further potentiate keloidogesis, and develop smart-sensing treatments that reduce management burden.[3]

The future of keloid research and development

The future of keloid therapeutic research and developments involves a transition from on-specific, invasive interventions (like high-dose steroid injections or excisions) to non-invasive, precise molecular therapies involving biomaterials.[21]

Existing clinical interventions remain restricted by major therapeutic trade-offs. Silicone gel sheets are non-invasive, yet maintain limited efficacy against mature scars. Advanced therapies like intralesional steroids or fluorouracil co-injections carry high recurrence rates and significant tissue side effects due to localization failures.[14,23,24]

To further advance the field, engineers and clinical researchers should focus on the following areas for precise modulation listed in Table 5.[4]

Table 5 Areas of improvement needed in keloid research, therapeutic development, and distribution[3,4,22]

Treatment modifications	Theoretical basis
Mechano transduction modulation	Researchers can develop smart, electrospun scaffolds and tension-shielding polymer dressings to neutralize the mechanical stretch forces which drive keloid growth, especially in high-tension zones of the body.[4]
Targeted molecular delivery	Pairing vascular-related therapies with intracellular signaling blockers can halt fibroblast proliferation at the molecular level.[22]
Inclusive design frameworks	Centering early-stage pre-clinical and clinical trial designs around diverse patient cohorts can assist with development.[3]

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Conflicts of interest

The authors declare that there is no conflict of interest.

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