RESEARCH PAPER

Advanced Drug Delivery Systems and Regenerative Strategies for Burn Wound Healing: A Pharmaceutics Perspective

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ABSTRACT
Burn injuries continue to be a major global health problem associated with high morbidity, mortality, and longterm functional and aesthetic complications. Current wound-healing treatments—including autografts, allografts, and topical antimicrobial agents—primarily aim to achieve rapid wound closure without guaranteeing full re-epithelialization or scar-free healing. Recent developments in pharmaceuticals and drug delivery have given rise to innovative strategies to improve the bioavailability, targeted delivery, and controlled release of therapeutic agents for burn wound healing. This review critically examines how advanced drug delivery systems can be used in conjunction with regenerative medicine strategies in burn wound management. Special focus is given to nanotechnology-based carriers, hydrogel-based scaffolds, and bioadhesive formulations for the sustained and localized delivery of growth factors, antimicrobial agents, and anti-inflammatory compounds. Additionally, stimuli-responsive 'smart' biomaterials, stem cell-based therapies, exosome-mediated delivery, and in situ bioprinting technologies are assessed for their potential to enable personalized and precision-based burn care. This review offers a comprehensive pharmaceutical perspective on existing and emerging technologies for burn treatment, highlighting the shift from passive wound coverage to active, targeted, and regenerative therapies.

Keywords: Burns; Wound healing; 3D bioprinting; Conventional treatments; Nanotechnology; Drug delivery systems; Regenerative medicine

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1. INTRODUCTION

Burns represent one of the oldest and most challenging medical conditions known to humanity,[1] yet they continue to demand the full weight of modern biomedical innovation.[2] Unlike most acute injuries, burn wounds inflict simultaneous damage across multiple tissue layers—from the epidermis and dermis to subcutaneous fat, muscle, and even bone in the most severe cases—triggering a cascade of local and systemic responses that can overwhelm normal physiological homeostasis.[3,4] The immune system, vascular network, and cellular repair machinery are all recruited and, in large burns, often dysregulated, leading to systemic inflammatory response syndrome (SIRS), sepsis, multi-organ dysfunction, and death.[5]

Despite decades of research, the fundamental challenge of burn wound management remains largely unchanged[6]: restoring the critical barrier and functional properties of skin as rapidly, completely, and cosmetically as possible.[7] Skin, the largest organ of the human body, performs indispensable roles in thermoregulation, immunological defence, fluid homeostasis, sensory perception, and social interaction.[8] Its loss, even temporarily, carries lifethreatening consequences.[9] The complexity of achieving true skin regeneration, as opposed to mere scar-based repair, has driven an explosion of interest across fields including cell biology, biomaterials science, nanotechnology, gene editing, and artificial intelligence.[10]

Burn wound healing presents significant challenges for drug delivery due to impaired vascularization, excessive exudate, enzymatic degradation, and altered skin barrier properties. Conventional topical formulations often suffer from poor penetration, rapid drug clearance, and inadequate retention at the wound site, resulting in suboptimal therapeutic outcomes. Advanced drug delivery systems have emerged as promising solutions.

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Nanocarriers such as polymeric nanoparticles, liposomes, and solid lipid nanoparticles enhance drug solubility, stability, and targeted delivery while enabling controlled and sustained release of therapeutic agents.

This review provides a structured, evidence-based overview of the global burden of burn injuries, the biology of wound healing and pathological scarring, current standard treatments, and the most exciting emerging therapies. By synthesizing advances from bench to bedside, this paper aims to illuminate both the progress achieved and the substantial gaps that remain in burn care.

2. GLOBAL BURDEN OF BURN INJURIES

Burn injuries constitute a major global health problem associated with significant morbidity, disability, and socioeconomic burden worldwide.[11,12] According to the Global Burden of Disease (GBD) 2021 study, approximately 248 million burn cases (95% CI: 226.9–272.3 million) were reported globally, with an age-standardized prevalence rate (ASPR) of 2,974 per 100,000 population, reflecting a 0.43% decrease compared with 1990.[14] Regional analysis showed marked disparities: Southern Latin America recorded the highest ASPR (7,898 per 100,000), whereas East Asia had the lowest (2,005 per 100,000).[16]

Unintentional injuries account for approximately 80.68% of burn-related years lived with disability (YLDs), followed by self-harm and interpersonal violence (13.5%) and transport-related injuries (5.82%). Treatment expenses exceed $39,600 per patient, and future projections suggest global burn cases could increase to approximately 613 million by 2050.[14]

Fig. 2 shows age-specific prevalence by sex, illustrating an increasing trend with age, with consistently higher prevalence in males. Fig. 3 presents global distribution and temporal trends showing higher burden in low- and middle-income regions.

3. LIMITATIONS OF CONVENTIONAL BURN CARE

The current gold standard for extensive burns remains the split-thickness skin graft (STSG),[19] which involves harvesting a thin layer of the patient's own skin from an unburned donor site and transplanting it to the burn wound. While autografts offer permanent coverage and eliminate immunological rejection, they are fundamentally limited by:[20]

Donor site morbidity: Harvesting creates a secondary wound that is painful, prone to infection, and may result in scarring.[21]

Limited donor area: In patients with burns covering >40% of total body surface area (TBSA), donor sites are insufficient, necessitating repeated harvesting.[22]

Lack of dermal regeneration: STSGs provide epidermal coverage but do not reconstitute the dermal layer, resulting in fragile skin prone to blistering, contracture, and limited elasticity.[23]

Hypertrophic scarring: Even successfully grafted burns frequently develop raised, thickened scars due to excessive collagen deposition and myofibroblast contraction.[24]

Acellular dermal matrices (ADMs) such as Integra® and AlloDerm® have partially addressed dermal deficiency by providing a collagen-glycosaminoglycan scaffold for neodermis formation.[25] However, ADMs require a two stage procedure, suffer from slow vascularization, and remain susceptible to infection.[26] Cultured epithelial autografts (CEAs) are laboratory-expanded keratinocyte sheets, but are notoriously fragile, exhibit poor take rates

(often <50%), require 2–3 weeks of ex vivo expansion, and lack dermal components.[28]

3.1 The Paradigm Shift: From Wound Closure to Tissue Regeneration

The fundamental limitation of conventional burn therapy is that it prioritises wound closure—preventing infection and fluid loss—rather than tissue regeneration restoring the anatomical, biomechanical, and functional properties of native skin.[29,30] Regenerative medicine seeks to address this gap by harnessing biological principles of embryonic development, stem cell differentiation, and tissue morphogenesis to recreate skin de novo. This paradigm shift is enabled by: (1) iPSCs and MSCs offering inexhaustible cell sources[31]; (2) 3D bioprinting enabling precise deposition of multiple cell types[32]; (3) exosome-based cell-free regenerative signaling[33]; (4) nanotechnology enhanced biomaterials with controlled drug release[34]; and (5) CRISPR-Cas9 gene editing tools.[35]

4. PATHOPHYSIOLOGY OF BURN WOUND HEALING

Thermal burns caused by dry (fire/flame) and wet (scalds) sources account for nearly 80% of reported burn injuries. Severe burns involving ≥20% TBSA can trigger burn shock, characterized by increased capillary permeability, hypovolemia, and reduced cardiac output. Rapid edema forms within the first 8 hours post-injury, requiring prompt fluid resuscitation. Large burns often lead to hypermetabolism, chronic inflammation, and muscle wasting, which impair wound healing and increase susceptibility to infection.

4.1 Classification of Burns

Burn wounds are classified according to severity, which depends on the patient's age, percentage of TBSA burned, depth, and involvement of critical body regions (Table 1).[37,38]

Table 1: Classification of burn injuries based on TBSA and depth.

Burn Severity / Area (TBSA)	Burn Depth / Type	Characteristics / Clinical Features

Minor Burns	First-Degree (Superficial Thickness)	Affect only the epidermis. Skin appears red, dry with mild pain. Usually heal without scarring.
Criteria for Minor Burns	—	<10% TBSA in adults, <5% in children/elderly. Mostly superficial with <2% full-thickness burns.
Major Burns	Second-Degree (Partial Thickness)	Partial damage to dermis with blister formation and significant pain.
Major Burn Criteria	—	>20% TBSA in adults, >10% in children/elderly, >5% full-thickness, or burns on critical areas.
Second-Degree (2A)	Superficial Partial Thickness	Involve epidermis and upper dermis. Blisters, moist surface, severe pain. Usually managed with dressings.
Second-Degree (2B)	Deep Partial Thickness	Affect deeper dermal layers. Drier skin, more blistering, less painful, greater scarring. Often require surgery.
Third-Degree	Full Thickness	Damage entire dermis. Skin may appear white, brown, or charred; usually painless due to nerve damage. Require surgical grafting.
Fourth-Degree	Deep Tissue Burns	Extend beyond skin to muscles, tendons, or bone. Appear blackened with significant tissue loss. Require extensive surgery.

4.1.1 Classification Based on Severity by Burn Size

Burn injuries are commonly classified into minor, moderate, and major categories. Minor burns involve less than

10% TBSA in adults (<5% in children/elderly) with <2% full-thickness involvement. Major burns affect more than 20% TBSA in adults (>10% in children/elderly) or >5% full-thickness. Such classification guides resuscitation and surgical planning.

4.1.2 Classification Based on Depth

First-degree burns involve only the epidermis; second-degree burns (partial-thickness) extend into the dermis (2A: superficial; 2B: deep); third-degree burns (full-thickness) destroy the entire dermis and are typically painless; fourth-degree burns involve deeper structures (muscles, tendons, bone) as illustrated in Fig. 5.

4.2 Zones of Burn Injury

The Jackson burn model describes three concentric zones of tissue damage.[39] The central **zone of coagulation** represents irreversible necrosis.[40] The **zone of stasis** contains potentially salvageable tissue vulnerable to conversion if ischemia, edema, or infection supervenes.[41] The outermost **zone of hyperemia** consists of viable, inflamed tissue that typically recovers within 7–10 days.[42] Prevention of conversion of the zone of stasis into the zone of coagulation is a primary therapeutic objective[43], as illustrated in Fig. 6.

4.3 Phases of Burn Wound Healing

Cutaneous wound healing proceeds through four overlapping phases: hemostasis, inflammation, proliferation, and remodeling[46] (Fig. 7, Fig. 8).

4.3.1 Haemostasis (Immediate to Hours)

Vascular injury leads to platelet aggregation and fibrin clot formation, releasing PDGF, TGF-β, and VEGF. Burns create large areas of coagulative necrosis requiring debridement.[49]

4.3.2 Inflammation (Days 1–7)

Damage-associated molecular patterns (DAMPs) secreted by damaged tissue activate toll-like receptors (TLRs), stimulating the inflammatory cascade. Dysregulated inflammation leads to delayed healing and excessive scarring, particularly in diabetic and elderly patients.[50,51,52]

4.3.3 Proliferation (Days 4–21)

This phase encompasses: (1) Re-epithelialization—keratinocytes migrate across the wound bed via integrinmediated adhesion and MMP-mediated ECM remodeling[54]; (2) Granulation tissue formation—fibroblasts synthesize collagen while endothelial cells form new capillary networks driven by VEGF and HIF-1α[56]; (3) Wound contraction myofibroblasts expressing α-SMA contract wound margins, often causing pathological contracture.[57]

4.3.4 Remodeling (Weeks to Months/Years)

Collagen fibers are reorganized from random to parallel alignment along tension lines, mediated by MMP activity and TIMPs.[58] Hypertrophic scars result from imbalanced collagen synthesis/degradation with persistent TGF-β signaling. Unlike normal skin (collagen I:III ratio ~4:1), hypertrophic scars exhibit ratios of 10:1 or higher.[59]

4.4 Barriers to Regeneration in Burn Wounds

Several factors impede regenerative healing:[60] ischemia and thrombosis causing secondary necrosis[61]; bacterial biofilm formation by Pseudomonas aeruginosa and Staphylococcus aureus[62]; systemic hypermetabolism impairing angiogenesis[63]; loss of dermal appendages (hair

follicles, sweat/sebaceous glands) that are stem cell niches[64]; and chronic M1 macrophage activation causing excessive TGF-β production and hypertrophic scarring.[65]

5. CONVENTIONAL THERAPIES AND THEIR LIMITATIONS

The overall goals of burn wound care are to prevent infection, debride burned tissue, relieve pain, minimize scar formation, and restore functional integrity. Silver sulfadiazine (SSD) cream has been extensively employed as a first-line treatment for minor burns; however, its use is restricted by adverse reactions including neutropenia, erythema multiforme, crystalluria, and methemoglobinemia. For severe second- and third-degree burns, skin grafting may be necessary, but graft failure necessitates repeat procedures and is associated with bleeding, contracture, skin discoloration, lack of sensation, and chronic pain. Conventional dressings require frequent changes, causing bleeding, pain, and patient discomfort, underlining the need for advanced wound dressing systems.

6. MODERN APPROACHES TO PROMOTE BURN WOUND HEALING

6.1 Autologous Skin Grafts

6.1.1 Split-Thickness Skin Grafts (STSGs)

STSGs remain the gold standard for definitive wound closure in deep partial- and full-thickness burns[66] (Fig. 9). Grafts are harvested at 0.008–0.016 inches depth using an oscillating dermatome[67,68] and processed through a mesh carrier at expansion ratios of 1:1.5 or 1:3[71]; Meek micrografting enables 1:6 or 1:9 ratios in resource-limited settings.[72] The biological basis of graft take involves: imbibition (0–48h), inosculation (days 2–3), and neovascularization (days 5–7).[76]

6.1.2 Full-Thickness Skin Grafts (FTSGs)

FTSGs incorporate the entire dermis, providing superior pliability, durability, and cosmetic outcome.[70] They are preferred for functionally critical areas such as eyelid reconstruction, nasal coverage, palmar burns, and facial defects.[84] The fundamental constraint is limited donor availability, as donor sites require primary closure or STSG coverage.[85]

6.1.3 Allografts and Xenografts

Cadaveric allografts and porcine xenografts serve as temporary biological dressings.[89] Allografts temporarily restore barrier function, reducing fluid loss, suppressing bacteria, alleviating pain, and promoting neovascularization[91], but are rejected within 10–21 days[92] (Fig. 10). Porcine xenografts offer lower cost and consistent supply[93] but are rejected more rapidly (7–10 days)[94] (Fig. 11).

6.2 Acellular Dermal Matrices (ADMs)

6.2.1 Integra® Dermal Regeneration Template

Integra® consists of a bilayer: a dermal layer of cross-linked bovine collagen/chondroitin-6-sulfate (pore size 70– 200 μm) promoting fibroblast infiltration and neovascularization, and an outer silicone sheet acting as a temporary epidermal substitute. After 2–3 weeks, the silicone is removed and a thin STSG applied. Limitations include susceptibility to infection during vascularization and high treatment costs.

6.2.2 AlloDerm® and Decellularized Dermal Matrices

AlloDerm® is a decellularized human cadaveric dermal matrix maintaining native ECM architecture (collagen types I, III, IV, V, VII; fibronectin; laminin; elastin; proteoglycans) while eliminating cellular components to reduce immune rejection. It is used as a dermal layer under STSG in one-stage burn reconstruction. Limitations include high cost, cadaveric supply dependency, and variable integration in poorly vascularized wounds.

6.2.3 Bioengineered Skin Substitutes

Apligraf® is a living bilayered substitute comprising neonatal foreskin-derived fibroblasts in bovine type I collagen matrix and a stratified keratinocyte layer, producing growth factors (KGF, EGF, VEGF, PDGF, IGF-1). Its use is limited by high cost, short shelf life, and absence of permanent skin appendages.

6.3 Synthesis: Unifying Limitations of Conventional Approaches

Table 2: Comparative overview of autologous skin grafts and biological/bioengineered skin substitutes.

Modality	Coverage	Persistence	Appendages	Primary Limitation
STSG (Meshed)	Large areas	Permanent	None	Donor morbidity; mesh-pattern scar; no appendages
STSG (Sheet)	Small/facial	Permanent	None	Limited donor supply; failure risk
FTSG	Small cosmetic	Permanent	Partial	Very limited donor area; requires primary closure
Cadaveric Allograft	Temp bridge	10–21 days	None	Immune rejection; disease risk; supply constraints
Porcine Xenograft	Temp bridge	7–10 days	None	Faster rejection; no vascularization; surface-only

Integra® ADM	Large areas	Perm (2stage)	None	Two surgeries; infection lag; high cost
AlloDerm®	Moderate	Perm (1stage)	None	Cost; resorption risk; cadaveric supply dependency
Apligraf®	Moderate	Weeks	None	High cost; 10–15d shelf-life; variable take

STSG = split-thickness skin graft; FTSG = full-thickness skin graft; ADM = acellular dermal matrix.[97,98]

7. STEM CELL THERAPIES FOR BURN HEALING

7.1 Mechanisms of Stem Cell-Mediated Healing

Stem cells promote burn wound healing through multiple mechanisms: (1) **Paracrine signaling**—MSCs secrete >300 bioactive molecules including VEGF, HGF, FGF, and exosomes containing microRNAs that modulate inflammation and fibrosis[99]; (2) **Immunomodulation**—MSCs inhibit T-cell proliferation and stimulate M2 macrophages[100,101]; (3) **Anti-fibrotic effects**—MSCs down-regulate TGF-β1 signaling and decrease α-SMA expression[102]; (4) **Differentiation**—MSCs can differentiate into fibroblasts, endothelial cells, and keratinocyte-like cells[103]; (5) **Homing**—via SDF-1/CXCR4 signaling.[104]

7.2 Stem Cell Sources for Burn Therapy

Table 3: Comparison of major stem cell types for skin regeneration and burn wound therapy (as of 2025).

Stem Cell Type	Source	Key Advantages	Challenges	Clinical Status	Ref.
BM-MSCs	Bone marrow	Well-studied; multipotent; immunomodulatory	Invasive harvest; low yield; age-dependent	Trials ongoing	(105)
ADSCs	Liposuction	Abundant; minimally invasive; high proliferation	Standardization needed; potency varies	Expanding use	(106)
UC-MSCs	Umbilical cord	Non-invasive; young cells; low immunogenicity	Allogeneic; banking needed	FDA-approved (2025)	(107)
iPSCs	Reprogrammed somatic cells	Patient-specific; unlimited differentiation	Tumorigenicity; costly	Preclinical	(108)
Epidermal SCs	Basal epidermis	Direct keratinocyte differentiation	Rare; difficult isolation	Research stage	(109)
Muse Cells	Multiple tissues	Trilineage; low tumorigenicity	Limited clinical data	Preclinical	(110)

7.3 Clinical Evidence and Trials

A landmark 2025 study published in *npj Regenerative Medicine* demonstrated that cord tissue-derived induced MSCs (CT-iMSCs) incorporated into Integra® at 5,000–20,000 cells/cm² accelerated wound healing in a porcine full-thickness burn model, showing faster re-epithelialization, reduced inflammation, and marked reduction in fibrosis markers.[111,112,113] A Phase II trial by Auxocell Laboratories demonstrated that autologous ADSCs sprayed onto STSGs improved graft take rates and reduced healing time by an average of 5.2 days compared to STSG alone.[114] The FDA granted Regenerative Medicine Advanced Therapy (RMAT) designation to several ADSC-based products in 2024.[115]

Table 4: Drug Delivery Systems in Burn Healing.

System	Drug Type	Advantage	Limitation
Nanoparticles	Curcumin, antibiotics	Controlled release, enhanced penetration	Stability issues
Liposomes	Growth factors	Biocompatible, dual drug loading	Leakage
Hydrogels	Proteins, cells	Moist environment, sustained release	Mechanical weakness
Nanofibers	Antimicrobials	ECM mimicry, high surface area	Scale-up issues

7.4 Exosome Therapy: The Cell-Free Revolution

Extracellular vesicles termed exosomes (30–150 nm) secreted by MSCs have become a novel paradigm in cell-free therapy.[118] Key benefits over direct cell therapy include: no tumorigenicity or immune rejection risk; stable lyophilized storage; simplified regulatory pathway; and scalable bioreactor production.[119,120,121] In vivo models show exosome-loaded hydrogels can promote burn wound healing by 30–40% over acellular hydrogels.[122] Challenges include lack of standardized isolation procedures and batch-to-batch variability.

8. 3D BIOPRINTING FOR SKIN REGENERATION

8.1 Bioprinting Modalities

Table 5: Overview of major 3D bioprinting modalities for skin tissue engineering.

Modality	Mechanism	Advantages	Applications in Skin	Ref.
Extrusion-Based	Pneumatic/mechanical nozzle dispensing	High cell density; versatile bioinks	Dermal substitutes; fullthickness skin models	(123)
Inkjet-Based	Droplet via thermal/piezoelectric actuation	High resolution; precise cell placement	Epidermal-dermal bilayer; in situ printing	(124)
Laser-Assisted (LAB)	Laser-induced forward transfer (LIFT)	Nozzle-free; high viability	Vascularized dermal constructs; melanocyte patterning	(125)
SLA/DLP	Photopolymerization of bioink layers	High resolution; complex geometries	Skin appendages; microvasculature	(126)
Volumetric	Tomographic light projection	Ultra-fast (<30 sec); no layering artifacts	Early-stage for skin; demonstrated in bone	(127)
In Situ (LIGO)	Direct printing onto wound bed	Patient-specific; bypasses lab culture	LIGO device (Australia 2025); field medicine	(128)

8.2 Bioink Formulation for Skin Tissue Engineering

Table 6: Comparison of commonly used bioink materials for skin bioprinting.

Bioink Material	Composition	Advantages for Skin Bioprinting	Limitations
GelMA	Photocrosslinkable modified gelatin	RGD motifs; tunable stiffness; MMP-degradable	Requires UV crosslinking; weak alone
Alginate	Polysaccharide; Ca^{2+} crosslinked	Fast gelation; printable; inexpensive	Lacks cell adhesion motifs; limited degradation
Collagen Type I	Native ECM protein; thermal gelation	Biomimetic; promotes cell infiltration	Low mechanical strength; batch variability
Fibrin/Fibrinogen	Coagulation protein; thrombin-activated	Angiogenic; rapid gelation; hemostatic	Poor extrusion; requires blending
Hyaluronic Acid (HA)	GAG; methacrylated or thiolated	Native dermal component; antiinflammatory	Rapid degradation; low viscosity
Chitosan	Deacetylated chitin; pH gelation	Antimicrobial; biodegradable; hemostatic	Acidic dissolution; slow gelation
Silk Fibroin	Bombyx mori-derived protein	High tensile strength; oxygen permeable	Requires blending; immunogenicity concerns
Decellularized ECM	Tissue-derived acellular matrix	Retains native growth factors; low immunogenicity	Batch variation; weak rheology

8.3 Breakthrough: In Situ Bioprinting (LIGO Device)

In May 2025, Inventia Life Science (Australia) initiated a first-in-human clinical trial evaluating the LIGO in situ bioprinting platform for burn treatment at Concord Repatriation General Hospital, Sydney.[129] The LIGO system integrates high-resolution 3D optical scanning, automated wound-bed preparation, and robotic deposition

of patientderived cells into a customized bioink directly onto the burn site.[130,131] Early clinical observations suggest accelerated re-epithelialization with wound closure at approximately 8 weeks, compared with 12–14 weeks typically required with STSG.[132]

9. NANOTECHNOLOGY-ENHANCED BIOMATERIALS

9.1 Nanofiber Scaffolds

Electrospinning produces polymer fibers of 50–500 nm diameter, closely resembling the fibrillar architecture of the ECM.[133] This structural similarity provides favorable topographical cues supporting fibroblast, keratinocyte, and endothelial cell adhesion, migration, and tissue organization.[134] The high surface-area-to-volume ratio and interconnected porous structure enhance oxygen diffusion, nutrient transport, and exudate absorption.[135] Nanofiber scaffolds also serve as controlled-release drug delivery systems for antimicrobial substances, growth factors, and anti-inflammatory agents.[136]

9.2 Nanoparticle Drug Delivery

9.2.1 Chitosan Nanoparticles in GelMA Bioinks

3D bioprinted bioinks comprising curcumin-loaded chitosan nanoparticles and GelMA exhibited greater antimicrobial efficacy against *S. aureus* and improved cell proliferation compared to curcumin-free controls.[140,141]

9.2.2 Liposomal Nanoparticle Systems

Liposomes are ideally suited for simultaneous delivery of multiple drugs, including hydrophobic drugs partitioned into the lipid bilayer (NSAIDs, vitamin E) and hydrophilic drugs in the aqueous lumen (vancomycin, growth factors such as PDGF). PEGylation of the liposomal surface minimizes nonspecific protein adsorption and increases tissue residence.[143,144]

9.2.3 Gold Nanoparticles (AuNPs) and Photothermal Therapy

Gold nanoparticles exploit localized surface plasmon resonance (LSPR). When exposed to NIR light (650–900 nm), AuNPs convert absorbed energy to heat, reaching 50–80°C at the nanoparticle surface within seconds—above the thermal tolerance of bacteria (~45–50°C)—enabling ablation of necrotic tissue.[145,146,147,148]

9.3 Smart Hydrogels with Stimuli-Responsive Release

9.3.1 The 4D Bioprinting Paradigm

4D bioprinting extends conventional 3D bioprinting by incorporating stimuli-responsive biomaterials that undergo programmable changes in shape, stiffness, or therapeutic function in response to environmental triggers postimplantation.[149,150,151] Exploitable triggers include pH, temperature, enzymatic activity, reactive oxygen species (ROS) concentration, and electrical signals.[152]

9.3.2 Toward Autonomous Wound Management

Integrated platforms combining nanofiber scaffolds, nanoparticle drug delivery systems, and stimuli-responsive hydrogels represent a fundamental shift from passive wound coverage to active, adaptive wound management.[153,154,155] Such systems simultaneously provide structural ECM mimicry, self-regulating antimicrobial delivery triggered by infection, temperature-driven in situ gelation, and oxygen supplementation for hypoxic wound beds.

10. GENE EDITING AND MOLECULAR THERAPIES

10.1 CRISPR-Cas9 for Inherited Skin Diseases

A proof-of-concept study in 2017 used CRISPR-Cas9 to correct COL7A1 mutations in patient-derived keratinocytes ex vivo, which were expanded into epidermal sheets and transplanted back, leading to successful long-term functional skin regeneration.[159] Targeted deletion of pro-fibrotic mediators (TGF-β1, Smad3) in dermal fibroblasts can decrease collagen overproduction. Significant hurdles remain: off-target editing, Cas9 immunogenicity, in vivo delivery to deep wound areas, and ethical concerns.[161,162]

10.2 RNA Interference (RNAi) and MicroRNA Therapy

Small interfering RNAs (siRNAs) targeting pro-fibrotic genes (COL1A1, CTGF, PAI-1) delivered via lipid nanoparticles reduce hypertrophic scarring in preclinical models. MicroRNA-29 family members (miR-29a/b/c) suppress collagen synthesis and have been explored encapsulated in exosomes or synthetic nanocarriers.[163]

10.3 Platelet-Rich Plasma (PRP) and Growth Factor Augmentation

Platelet-rich plasma (PRP) contains supraphysiologic levels of PDGF, TGF-β, VEGF, EGF, and IGF-1. A 2024 meta-analysis of 18 RCTs (n=1,247 burn patients) concluded that PRP supplementation reduces healing time by an average of 4.7 days (95% CI: 3.2–6.1) compared to standard care.[164,165] Nanofat (NF) combined with PRP has demonstrated synergistic effects significantly accelerating tissue regeneration.[166]

11. EMERGING AND FUTURE TECHNOLOGIES

Table 7: Emerging and future technologies in skin regeneration and burn care.

Technology	Mechanism	Potential Impact	Timeline	Key Challenges
CRISPR Gene Editing	Correction of genetic defects	Curative for inherited skin diseases	Clinical trials 2027–2030	Off-target effects; delivery; ethics
4D Bioprinting	Shape-morphing stimuli-responsive bioinks	Self-assembling vasculature; adaptive ECM	Preclinical 2025– 2028	Stimulus control; bioink design; stability

Exosome-Loaded Bioinks	MSC-derived exosomes in 3D constructs	Cell-free regeneration; reduced rejection	Research 2025–2027	Isolation standardization; release kinetics
VCA	Composite tissue transplantation	Full-scale restoration; facial/hand transplants	Clinical (limited centers)	Lifelong immunosuppression; donor shortage
AI-Guided Treatment	ML models for personalized therapy	Precision medicine; improved outcomes	Emerging 2025–2026	Data scarcity; algorithm validation
Organoid-Derived Skin	3D mini-organs from pluripotent stem cells	Includes appendages, immune cells, nerves	Preclinical 2026– 2030	Maturation time; scalability; vascularization
Smart Dressings	Biosensors + ondemand drug release	Real-time infection detection; telemedicine	FDA clearance 2026–2028	Power source; biocompatibility; cost

11.1 Vascularized Composite Allotransplantation (VCA)

VCA involves transplanting composite tissues skin, muscle, bone, nerves, and blood vessels as a single vascularized unit.[167] Over 50 face transplants and 100+ hand transplants have been performed at specialized centers worldwide as of 2025. While VCA offers unparalleled functional and aesthetic restoration, it requires lifelong immunosuppression with attendant risks of infection, malignancy, and metabolic complications.

11.2 Organoid Technology

Skin organoids self-organizing 3D structures derived from pluripotent stem cells recapitulate key features of native skin including stratified epidermis, basement membrane, and dermal-epidermal junction.[168] Advanced organoids incorporate hair follicles, sebaceous glands, and neural/immune components. Challenges include prolonged maturation (4–6 months), variable reproducibility, and host vascularization upon transplantation.[169]

11.3 Artificial Intelligence in Burn Care

Machine learning algorithms are being developed to: (1) predict burn depth and healing potential from multispectral imaging; (2) optimize bioink composition and cell density for patient-specific bioprinted skin; (3) predict hypertrophic scarring risk from genomic/proteomic variables; and (4) guide personalized immunosuppression regimens. Pilot studies show improved AUC >0.85 for burn depth classification, versus ~0.75 for average clinicians.[170]

12. FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

12.1 The Road to Scarless Healing

Fetal wounds (<24 weeks' gestation) and adult oral mucosa share scarless healing characteristics: rapid reepithelialization, minimal inflammation, and organized collagen deposition. Strategies to replicate this include: (1) TGF-β3 supplementation to block TGF-β1; (2) scaffolds mimicking fetal ECM with hyaluronic acid; (3) gene delivery of FGF-7 (keratinocyte growth factor); and (4) macrophage polarization to the M2 phenotype via IL-4/IL-13.

12.2 Integrating Multi-Omics for Precision Medicine

Single-cell RNA sequencing (scRNA-seq) has uncovered novel heterogeneous cell types in burns, including profibrotic and pro-regenerative fibroblast subsets. Proteomics and metabolomics of wound exudates allow real-time monitoring of healing and early complication identification. Integration of patient-specific cellular phenotypes and genomic risk scores will enable optimal selection of stem cell sources, bioink formulations, and adjuvant therapies.

12.3 Global Health Equity and Access

Most burn mortality occurs in low- and middle-income countries (LMICs) that lack access to advanced therapies. Portable bioprinting devices (e.g., LIGO), freeze-dried allogeneic cell sheets, and low-cost nanofiber dressings provide pathways toward making regenerative medicine more accessible. Capacity building, regulatory harmonization, and tiered pricing models are needed for sustainable implementation.

12.4 Ethical Considerations

Rapid innovation raises profound ethical issues: (1) informed consent for acutely injured patients regarding experimental therapies; (2) equity concerns regarding access to regenerative therapies; (3) the distinction between therapeutic and cosmetic enhancement; and (4) restrictions on embryonic stem cell research in some jurisdictions. Multistakeholder dialogue engaging clinicians, ethicists, patients, policymakers, and industry is urgently needed.

NOVEL CONTRIBUTIONS OF THIS REVIEW

This review offers a pharmaceutics perspective on burn wound healing combining advanced drug delivery systems with regenerative medicine approaches. It emphasizes the potential of nanocarriers, bioadhesive systems, and stimuli-responsive biomaterials for enhancing therapeutic outcomes. New developments in 3D bioprinting and exosome-mediated delivery are examined in depth with their translational potential highlighted. This review is

distinguished by inclusion of the latest developments through 2025.

CONCLUSION

Burn wound healing is on the brink of a regenerative revolution. The integration of stem cell biology, tissue engineering, nanotechnology, 3D bioprinting, and gene editing is shifting burn care from palliative wound closure to true tissue regeneration. Clinical milestones in 2025 including the LIGO in situ bioprinting trial and CT-iMSCenhanced dermal matrices—mark significant progress. Substantial obstacles remain: vascularisation of thick constructs, regeneration of functional skin appendages, prevention of hypertrophic scarring, and cost-effectiveness. The ultimate goal is to restore anatomically correct, mechanically strong, and aesthetically natural tissue indistinguishable from normal skin—a vision that will benefit the 11 million people affected by burns each year.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that supports the findings of this study are available within the article.

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