

Review Article

Therapeutic Potential of Immunomodulatory Hydrogels in Infected and Non-Infected Wounds: A Comprehensive Review

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Abstract

Wound healing is a precisely orchestrated cascade involving coordinated interactions among immune cells, cytokines, growth factors, and extracellular matrix (ECM). Although acute wounds heal through orderly phases, infected and chronic wounds exhibit dysregulation with persistent inflammation, impaired immune resolution, and compromised regeneration. Conventional dressings provide passive barrier functions but limited therapeutic intervention. Immunomodulatory hydrogels represent sophisticated platforms that actively reprogram the wound immune microenvironment. These three-dimensional hydrophilic networks deliver bioactive agents, modulate immune responses, provide antimicrobial protection, and mimic native ECM. By controlling inflammation, promoting macrophage polarization toward pro-regenerative phenotypes, and stimulating angiogenesis and re-epithelialization, these materials address fundamental healing barriers. In infected wounds, they integrate antimicrobial and biofilm-disruptive mechanisms while preserving immune homeostasis. In non-infected lesions, they facilitate inflammatory resolution and promote regenerative repair. This review critically examines immunomodulatory hydrogel design, mechanisms, preclinical evidence, clinical translation, and future directions.

INTRODUCTION

Wound healing restores tissue integrity through four overlapping phases: hemostasis, inflammation, proliferation, and remodeling, coordinated by immune cells, growth factors, and ECM [1,2]. Despite skin's regenerative capacity, many wounds become chronic—diabetic foot ulcers, venous leg ulcers, and pressure injuries impose significant global burdens [3]. These wounds exhibit persistent inflammation, impaired angiogenesis, excessive protease activity, and diminished cellular responsiveness. Infected wounds add microbial colonization and biofilm formation that subvert host immunity and prolong healing [4,5].

The immune system coordinates healing. Innate immune cells—neutrophils and macrophages—eliminate pathogens and secrete cytokines that activate fibroblasts, endothelial cells, and epithelial cells [6]. Macrophages are pivotal due to their phenotypic plasticity: pro-inflammatory (M1) macrophages orchestrate early defense, while pro-regenerative (M2) macrophages facilitate angiogenesis, ECM deposition, and remodeling. Non-healing wounds show dysregulated M1 predominance [7,8].

Traditional wound care relies on passive dressings (gauze, foams, films) that maintain moisture but inadequately address biological dysfunctions. Advanced therapies (antimicrobials, growth factors, negative pressure) have benefits but are constrained by narrow therapeutic indices and delivery challenges [9,10]. Hydrogels have emerged as promising biomaterial platforms. These hydrophilic networks absorb water, provide moist environments, conform to wound geometries, and mimic ECM [11]. Their versatility enables precise tuning of mechanical properties, degradation, and bioactivity [12].

Hydrogels now serve as active therapeutic platforms for localized delivery of growth factors, anti-inflammatory drugs, antimicrobials, nucleic acids, and cells [10]. Immunomodulatory hydrogels represent a paradigm shift—they actively control immune cell activity and inflammatory milieu. Rather than suppressing inflammation, they normalize immune balance by regulating macrophage polarization [9]. In infected wounds, they incorporate antimicrobial effects alongside immune control [13,14]. In non-infected wounds, they

recreate regenerative microenvironments [15]. Stimuli-responsive “smart” hydrogels react to pH, ROS, enzymes, or temperature changes, enabling dynamic treatment adjustment [16].

Despite promise, obstacles remain: biocompatibility, manufacturing scalability, regulatory pathways, and understanding hydrogel-immune interactions [17]. This review comprehensively examines therapeutic prospects of immunomodulatory hydrogels for infected and non-infected wounds (Figure 1).

BIOLOGY OF WOUND HEALING AND IMMUNE REGULATION

Following injury, hemostasis begins with vasoconstriction and platelet aggregation, forming a fibrin clot. Platelets release PDGF and TGF- β , recruiting immune cells [18,19]. The inflammatory phase dominates the first days: neutrophils clear pathogens via phagocytosis and ROS. Macrophages then become master regulators, transitioning from M1 (TNF- α , IL-1 β) to M2 (VEGF, FGF, IL-10, TGF- β), promoting angiogenesis, fibroblast activation, and ECM deposition [6,7,20]. The proliferative

phase involves granulation tissue, angiogenesis, and re-epithelialization. Remodeling involves collagen reorganization over weeks to months [21,22].

DAMPs and PAMPs activate PRRs including TLRs, triggering NF- κ B and pro-inflammatory cytokine transcription [20,23]. Macrophage polarization is regulated by interconnected pathways: M1 via IFN- γ /LPS through JAK/STAT1 and NF- κ B; M2 via IL-4/IL-13 through STAT6 or IL-10 through STAT3. Chronic wounds show M1 predominance with impaired M2 transition [7,8].

Pathological wounds show sustained inflammation, failed macrophage polarization, diminished growth factor responsiveness, and biofilm formation. Elevated pro-inflammatory cytokines, ROS, and MMP activity create unfavorable microenvironments [24,25]. Biofilms protect bacteria and sustain TLR activation, causing frustrated phagocytosis and chronic inflammation [26,27] (Figure 2).

PATHOPHYSIOLOGY OF CHRONIC AND INFECTED WOUNDS

Chronic wounds are arrested in inflammation with

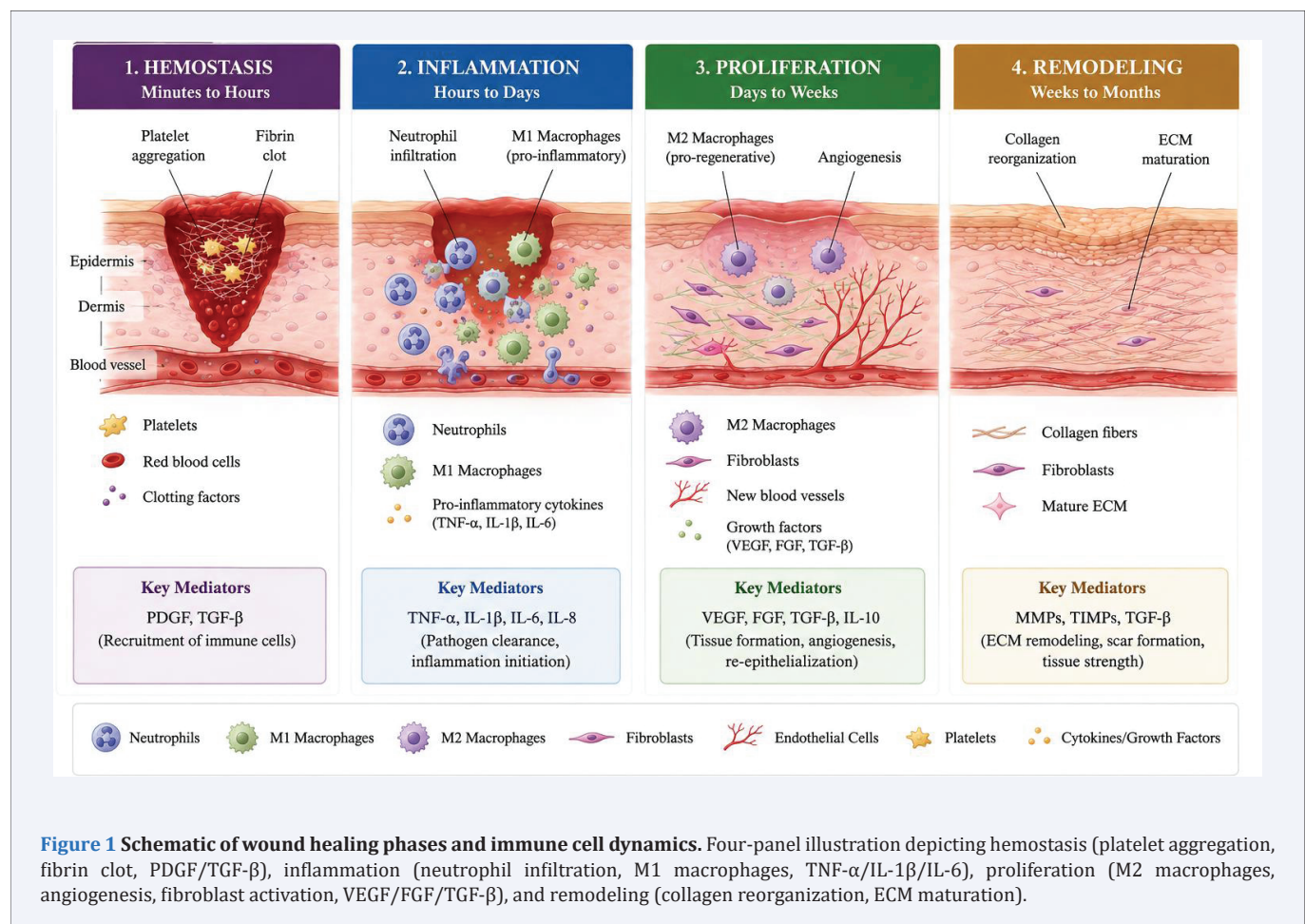


Figure 1 Schematic of wound healing phases and immune cell dynamics. Four-panel illustration depicting hemostasis (platelet aggregation, fibrin clot, PDGF/TGF- β), inflammation (neutrophil infiltration, M1 macrophages, TNF- α /IL-1 β /IL-6), proliferation (M2 macrophages, angiogenesis, fibroblast activation, VEGF/FGF/TGF- β), and remodeling (collagen reorganization, ECM maturation).

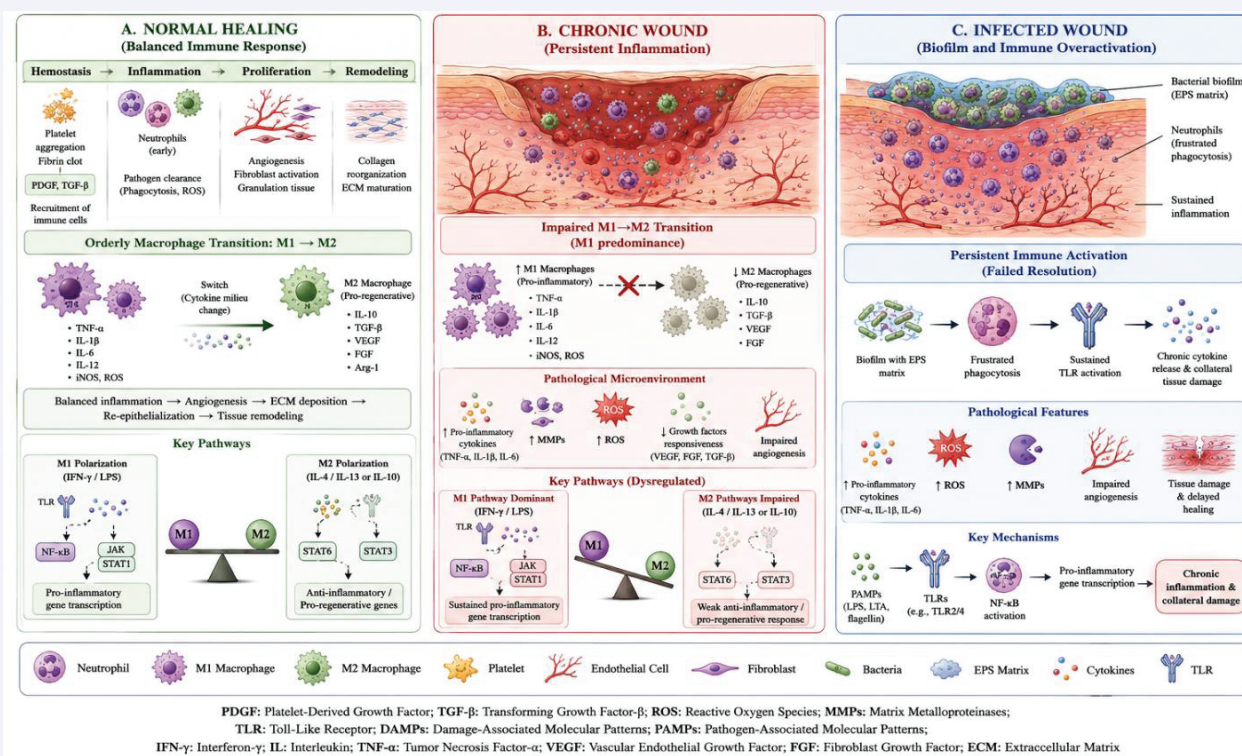


Figure 2 Immune dysregulation in chronic and infected wounds. (A) Normal healing: orderly M1→M2 transition with balanced inflammation. (B) Chronic wound: persistent M1, elevated cytokines/MMP/ROS, impaired angiogenesis. (C) Infected wound: biofilm with EPS matrix, frustrated phagocytosis, sustained TLR activation, collateral damage.

persistent cytokines (TNF-α, IL-1β, IL-6), excessive ROS, elevated MMP activity, reduced growth factors, impaired angiogenesis, and cellular senescence [24,25]. Diabetic wounds involve AGE-RAGE activation of NF-κB, impaired neutrophil function, and reduced growth factor responsiveness [28,29].

Biofilms (present in ~80% chronic wounds) provide physical protection and create microenvironments promoting bacterial persistence [5,4]. Continuous PAMP release sustains inflammation without bacterial clearance, causing frustrated phagocytosis and chronic inflammation [26,27].

HYDROGELS AS ADVANCED BIOMATERIALS

Hydrogels absorb water, maintain moist environments, conform to wounds, and provide barriers. Their porous structure enables exudate management and oxygen/nutrient diffusion [10-13] (Table 1).

Natural polymers (collagen, chitosan, HA, alginate) offer bioactivity but have batch variability and weak mechanics [11,30]. Synthetic polymers (PEG, PVA, PLGA) provide tunable properties but lack bioactivity [10,31].

Hybrid systems (GelMA, HAMA) combine advantages [30,31]. Hydrogels now encapsulate and release growth factors, antimicrobials, anti-inflammatory agents, nucleic acids, and cells in controlled fashion [10,13]. Release kinetics are tuned via crosslinking density, degradation rate, and architecture [10,11].

IMMUNOMODULATORY HYDROGELS: CONCEPTS AND MECHANISMS

Immunomodulatory hydrogels actively regulate immune cell activities, inflammatory signals, and tissue repair pathways, promoting transition from pro-inflammatory to pro-regenerative milieu [9,32].

Macrophage polarization is a key design goal [7,23]. Approaches include sustained cytokine delivery (IL-4, IL-13), ECM-derived peptides, small molecule immunomodulators, physical property manipulation, and MSC-derived secretome [13,14]. IL-4/IL-13 activate STAT6; some hydrogel compositions directly interact with macrophage receptors [15,33] (Table 2).

Hydrogels regulate neutrophil, dendritic cell, and lymphocyte migration and function via chemoattractants

Table 1: Classification and Physicochemical Properties of Hydrogel Systems

Hydrogel Type	Representative Polymers	Crosslinking	Modulus (kPa)	Pore Size (μm)	Degradation	Advantages	Limitations
Natural	Collagen, chitosan, HA, alginate	Physical/chemical	1-50	50-300	Days-weeks	Biocompatible, bioactive	Batch variability, weak mechanics
Synthetic	PEG, PVA, PCL, PLGA	Chemical	5-200	10-200	Weeks-months	Tunable, reproducible	Biologically inert
Hybrid	GelMA, HAMA, PEG-collagen	Photo/enzymatic	10-150	20-250	Weeks	Bioactive + tunable	Complex synthesis
Injectable	Pluronic, PNIPAAm, alginate	Thermo/ionic	0.1-50	50-200	Days-weeks	Minimally invasive	Premature gelation
Self-healing	Schiff base, disulfide	Dynamic covalent	1-50	50-300	Weeks-months	Autonomous repair	Complex synthesis
Conductive	PEDOT:PSS, polypyrrole	Oxidative	10-200	50-250	Weeks-months	Electrical stimulation	Toxicity concerns

Table 2: Immunomodulatory Agents Incorporated into Hydrogels

Agent Class	Examples	Mechanism	Pathways	Preclinical Outcomes	Clinical Status
Growth Factors	VEGF, PDGF, FGF, EGF, TGF-β	Angiogenesis, proliferation	PI3K/Akt, MAPK/ERK	↑Angiogenesis 2-3×, ↑Closure 40-70%	FDA-approved PDGF
Anti-inflammatory Cytokines	IL-4, IL-10, IL-13	M2 polarization	JAK/STAT, NF-κB	↑M2/M1 3-5×, ↓TNF-α 50-80%	Preclinical-Phase II
Small Molecules	Curcumin, resveratrol	NF-κB inhibition, ROS scavenging	NF-κB, Nrf2	↓ROS 50-70%, ↑Closure 30-50%	Preclinical
Immunomodulatory Peptides	RGD, YIGSR	Cell adhesion, integrin signaling	FAK/Src, PI3K/Akt	↑M2 polarization 2-3×	Preclinical
Nucleic Acids	siRNA, miRNA	Gene silencing	RNAi, RISC	↓Target genes 70-90%	Preclinical
Extracellular Vesicles	MSC exosomes	Paracrine signaling	Multiple	↑M2 3-5×, ↑Closure 50-80%	Preclinical-Phase I
Living Cells	MSCs, macrophages	Paracrine secretion	Multiple	↑Closure 50-80%	Clinical trials

and adhesion ligands [20,23]. Neutrophil modulation prevents excessive activation and tissue damage [23,34]. Agents are incorporated via physical entrapment, covalent conjugation, nanoparticle encapsulation, or affinity binding [10,11]. Stimuli-responsive systems enable dynamic adaptation [14,12]. Hydrogels modulate NF-κB (via inhibitors or ROS scavenging), JAK/STAT (via cytokine release), and TGF-β/Smad pathways. Inflammasome (NLRP3) is another target [7,20,23,35].

STIMULI-RESPONSIVE SMART HYDROGEL SYSTEMS

ROS-cleavable linkers (thioetal, boronate ester) release antioxidants in oxidative stress. Preclinical studies show 60-80% ROS reduction, 50-70% cytokine reduction, and 30-50% accelerated closure [16,17,36].

Infected wounds are acidic (pH 5.0-6.0). Polymers with ionizable groups enable selective antimicrobial release. Bacterial burden reduced by 3-5 log [12,14,26,27].

MMP-cleavable peptides release payloads in high-protease environments. MMP-2/9 are elevated 10-100× in chronic wounds. Wound closure improves 40-60% [24-27].

Phenylboronic acid or glucose oxidase systems release insulin/growth factors in diabetic wounds [15]. pH/ROS dual-responsive systems target infected chronic wounds [14,31] (Table 3).

ANTIMICROBIAL AND ANTI-BIOFILM STRATEGIES

Agents include metal nanoparticles (silver, gold), antimicrobial peptides (LL-37), antibiotics, NO donors, and natural compounds [26,27]. Localized release achieves high concentrations with minimal systemic exposure. Silver nanoparticles reduce bacterial burden by 4-7 log [17,36].

Strategies include EPS degradation (dispersin B, DNase), NO release, iron chelation, quorum sensing inhibition, and photothermal approaches [5,26]. Combination hydrogels show synergistic biofilm eradication (>90% reduction) [17,33]. Optimal systems achieve pathogen clearance (4-6 log reduction) while maintaining IL-10/TNF-α ratios >1.0, improving closure 2-3 fold [15,33] (Table 4).

THERAPEUTIC APPLICATIONS

Hydrogels address pathogen elimination and inflammation control in infected wounds. Applications include diabetic foot infections, surgical site infections, burn infections, and *P. aeruginosa* biofilms [26,27,15,36]. In chronic non-infected wounds, hydrogels deliver growth factors and anti-inflammatory cytokines to address sterile inflammation, impaired angiogenesis, and cellular dysfunction [13,14]. Wound closure improves 2-4 fold in diabetic models [37,38]. For acute wounds and surgical incisions, hydrogels fine-tune inflammation and accelerate proliferation via pro-resolving mediators [19,21]. Applications include anti-adhesion, antimicrobial/immunomodulatory dressings, and burn care [17,36].

Table 3: Stimuli-Responsive Hydrogel Systems

Type	Chemical Mechanism	Trigger	Payloads	Release Profile	Preclinical Efficacy	Status
pH-Responsive	Ionizable groups, acid-labile bonds	pH 5.0-6.0	Antimicrobials, anti-inflammatories	10-20% burst, 70-90% over 5-14 days	↑Bacterial reduction 3-5 log	Clinical trials
ROS-Responsive	Thioketal, boronate ester	H ₂ O ₂ 50-200 μM	Antioxidants, anti-inflammatories	5-15% burst, ROS-triggered over 3-10 days	↓ROS 60-80%, ↑Closure 50-70%	Preclinical-Phase I
MMP-Responsive	MMP-cleavable peptides	MMP-2/9 10-100×	Growth factors, anti-inflammatories	Minimal burst, MMP-dependent over 7-21 days	↑Closure 40-60%	Preclinical
Bacterial Enzyme	Bacterial protease peptides	Infection	Antimicrobials	Infection-triggered over 1-7 days	↓Bacteria 4-6 log	Preclinical
Glucose-Responsive	Phenylboronic acid, glucose oxidase	Glucose >200 mg/dL	Insulin, growth factors	Pulsatile over 7-28 days	↑Angiogenesis 2-3×	Preclinical
Temperature-Responsive	LCST polymers	37-39°C	Multiple	Temperature-modulated over 3-14 days	↑Closure 30-50%	Some clinical use

Table 4: Antimicrobial and Anti-Biofilm Hydrogel Strategies

Strategy	Active Agent	Mechanism	Spectrum	Biofilm Efficacy (Log)	Immune Modulation	Status
Metal Nanoparticles	AgNPs, AuNPs, ZnO	ROS, membrane disruption	Broad	2-5 log	AgNPs: M1	FDA-approved some
Antimicrobial Peptides	LL-37, Defensins	Membrane disruption	Broad, including MRSA/VRE	3-5 log	LL-37: M2	Preclinical-Phase II
Antibiotics	Vancomycin, Gentamicin	Cell wall/protein synthesis	Narrow	1-3 log	Minimal	Clinical use
Nitric Oxide	NO donors	Biofilm dispersion, killing	Broad	4-6 log	M2 polarization	Preclinical-Phase I
Biofilm Enzymes	Dispersin B, DNase	EPS degradation	Broad	3-5 log	Minimal	Preclinical
Quorum Sensing Inhibitors	Furanones, AHL analogs	QS antagonism	Gram-specific	2-4 log	May reduce inflammation	Preclinical
Natural Antimicrobials	Chitosan, Honey	Multiple	Broad	2-4 log	Chitosan: M2	Some clinically approved

PRECLINICAL EVIDENCE

In vitro studies show hydrogels improve viability, proliferation, and migration of fibroblasts, keratinocytes, and endothelial cells. IL-4/IL-10 systems induce M2 shift within 24-72 hours [13,14]. Antimicrobial hydrogels show 15-30 mm inhibition zones and 3-6 log bacterial reduction [26,27].

In diabetic models, hydrogels show accelerated closure (40-70%), enhanced granulation (2-3×), angiogenesis (1.5-2.5×), collagen (1.5-2×), and re-epithelialization (50-80%) [15,37]. M1 markers reduced 50-80%; M2 markers increased 3-5× [17,33]. Infected models show bacterial reduction 3-6 log with combination systems; biofilm reduction 70-95% [5,26,27]. Burn and pressure ulcer models show reduced systemic inflammation (30-50%) and infection rates (60-80%) with faster re-epithelialization [25,37]. Porcine models confirm accelerated healing (30-50%), reduced scarring, and improved biomechanical properties [11,39] (Table 5).

CLINICAL TRANSLATION

Conventional moisture-retentive hydrogels (alginate, PVA, polyacrylamide, gelatin) and antimicrobial hydrogels (silver, PHMB) have FDA clearance. Few have active immunomodulatory functionality [10,11,13,30].

Chronic wound trials: PDGF-eluting hydrogel in DFU (n=120) showed 65% closure vs 32% at 12 weeks; amputation 5% vs 15% [28,29]. IL-10 hydrogel in VLU (n=85) showed 58% closure vs 29%; MMP-9 decreased 60-70% [24,25]. Infected wound trials: Silver/curcumin hydrogel in infected DFU (n=95) showed bacterial reduction 3.2 log vs 1.1 log; closure 58% vs 31% [17,36] (Table 6).

Translational barriers include manufacturing (batch variability, sterilization degradation, GMP complexity) [11,30], stability (cold chain required for growth factors/cytokines) [10,13], regulatory (combination product classification increases timeline 3-7 years and cost >\$50M) [10,30], and reimbursement (high cost \$50-500/dressing requires cost-effectiveness demonstration) [28,29] (Table 7).

DESIGN STRATEGIES AND MATERIAL ENGINEERING

Natural polymers (collagen, chitosan, HA, alginate) offer bioactivity [11,30]. Synthetic polymers (PEG, PVA) provide tenability [10,31]. Hybrid systems (GelMA, HAMA) combine advantages [30,31]. Physical entrapment (20-50% burst), covalent conjugation (5-15% burst), nanoparticle encapsulation, or affinity binding enable controlled release [10,11]. Carriers include liposomes, polymeric nanoparticles, and MSNs [10,13].

Table 5: Representative Preclinical Studies

Hydrogel System	Model	Agents	Key Outcomes	Reference
GelMA-IL4/IL13	db/db mouse	IL-4, IL-13	Closure 85% vs 45%; ↑M2/M1 4.2×	[15]
Chitosan/AgNP/IL-10	Rat <i>S. aureus</i>	AgNP, IL-10	Bacterial reduction 4.8 log; Closure 72% vs 28%	[13]
PEG-MMP/PDGF	Mouse pressure ulcer	PDGF-BB	Closure 92% vs 48%; ↑Tensile strength 2.1×	[25]
Alginate/MSC-EV	Rat burn	MSC exosomes	Closure 68% vs 32%; ↑M2/M1 3.5×	[38]
PVA/Curcumin/NO	Mouse <i>P. aeruginosa</i> biofilm	Curcumin, NO	Biofilm reduction 4.2 log; ↓ROS 71%	[17]
Pluronic/AgNP/IL-4	Rabbit surgical infection	AgNP, IL-4	Infection 8% vs 42%; ↓Bacteria 5.2 log	[36]
HAMA/VEGF/PDGF	Pig diabetic	VEGF, PDGF	Closure 82% vs 41%; ↑Vessel density 3.1×	[40]
Collagen/miR-146a	Aged mouse	miR-146a	Closure 88% vs 54%; ↓NF-κB 72%	[14]

Table 6: Clinical Studies and Translational Outcomes

Product	Wound Type	Design	n	Key Outcomes	Limitations
PDGF-BB/HA hydrogel	DFU	RCT	120	Closure 65% vs 32%; Amputation 5% vs 15%	High cost (\$300); Variable stability
IL-10/Chitosan hydrogel	VLU	Double-blind RCT	85	Closure 58% vs 29%; Pain reduction 4.2 vs 1.8	Short half-life; Cold chain
AgNP/Curcumin hydrogel	Infected DFU	Open-label RCT	95	Bacterial reduction 3.2 vs 1.1 log; Closure 58% vs 31%	Silver accumulation; Variable stability
MSC-embedded hydrogel	Chronic DFU	Phase I	15	Closure 67% at 12 weeks	High cost (\$10,000+); Variable potency
LL-37/PEG hydrogel	Infected surgical	Phase I/II	30	Infection 3% vs 17%; Hospital stay 8.2 vs 12.5 days	Peptide degradation; High cost
Exosome-loaded hydrogel	DFU	Phase I	20	Closure 55% at 8 weeks (highest dose)	Scalability; Regulatory undefined

Table 7: Critical Comparison of Hydrogel Systems

Category	Advantages	Limitations	Scalability*	Regulatory	Future Directions
Natural	Biocompatible, bioactive	Batch variability, weak mechanics	4	510(k)	Blends, crosslinking
Synthetic	Tunable, reproducible	Biologically inert	5	510(k)/PMA	Bioactive functionalization
Growth Factor	Potent efficacy	High cost, stability	2-3	Combination	Controlled release
Cell-Based	Regenerative potential	High complexity	1-2	Biologic + device	Off-the-shelf cells, exosomes
Antimicrobial	Addresses infection	Resistance, toxicity	4	510(k)/PMA	Biofilm-specific strategies
Smart	Precision delivery	Complex design	2-3	Combination	Multi-stimuli, wearables
Exosome/EV	Cell-free, stable	Scalability challenges	2-3	Biologic	Engineered exosomes

*Scalability: 1 (very low) to 5 (high)

Softer matrices (0.1-1 kPa) promote M2 polarization; stiffer matrices favor M1 [11,40]. Degradation half-lives range from days (acute) to weeks (chronic) [24,25]. Injectable hydrogels enable minimally invasive delivery. Self-healing hydrogels autonomously repair mechanical damage [15,39]. Conductive hydrogels enable electrical stimulation [17,36].

CHALLENGES AND FUTURE DIRECTIONS

Achieving precise modulation without over/under-suppression is challenging. Patient-specific variability (age, comorbidities) affects responses [9,32,28,20]. Synthetic/modified hydrogels may induce immune responses. Degradation products must be non-toxic [11,30]. GMP production of complex formulations is challenging. Quality-by-design approaches may accelerate scale-up [10,11,13,40]. Combination product classification increases complexity. Smart hydrogel systems present additional regulatory challenges [10,14,30,31].

FUTURE PERSPECTIVES

Hydrogels with diagnostic sensors monitoring wound

state (pH, temperature, ROS, bacterial presence) enable real-time adjustment. Patient stratification based on biomarkers will guide formulation selection [12,14,20,28]. AI/ML accelerate hydrogel design by predicting optimal formulations from high-throughput screening data [10,11,31,40]. MSC-embedded hydrogels show 50-80% improved healing [38,39]. EV-loaded hydrogels offer cell-free alternatives [14,38]. Bioprinting enables complex wound dressings with spatially patterned cells and growth factors [38,40]. Integration with flexible electronics enables closed-loop therapeutic systems with automated treatment adjustment [12,14,17,36-50].

CONCLUSION

Immunomodulatory hydrogels represent a transformative paradigm in wound management, offering multifunctional capabilities beyond passive dressings. By actively engaging wound microenvironments through immune regulation, tissue repair promotion, and microbial burden control, they address multifactorial pathophysiology. Preclinical evidence demonstrates improved closure (40-70% acceleration), collagen deposition (1.5-2×), angiogenesis (2-3×), re-

epithelialization (50-80%), reduced inflammation (50-80% cytokine reduction), and bacterial burden (3-6 log reduction). Emerging clinical data support translational potential. Challenges remain in precision modulation, manufacturing scalability, and regulatory navigation. Future personalized, multifunctional, and intelligent platforms—integrated with stem cells, EVs, AI, or smart wearables—promise further advances. Immunomodulatory hydrogels offer an innovative, adaptive approach to improving healing outcomes and quality of life.

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