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REVIEW ARTICLE

Recent advances and challenges in 3D bioprinting for skin tissue regeneration

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Abstract

Three-dimensional (3D) bioprinting has transformed skin tissue regeneration by enabling the fabrication of skin-like structures with precisely controlled properties. This review critically examines recent advances and challenges in 3D bioprinting for skin tissue engineering (2020–2026), organized around a unifying materials-design framework linking bioink properties to wound healing phase requirements and printing technology selection. Wound healing mechanisms, cell types, bioink formulations, and major bioprinting technologies (inkjet, extrusion, laser-assisted, light-curing) are comparatively evaluated for resolution, cell viability, material compatibility, and scalability. 3D bioprinting enables vascular network formation, nerve regeneration, and regrowth of skin appendages, including sweat glands, hair follicles, and pigmentation, while patient-specific constructs reduce rejection risk and improve outcomes. Four clinical niches where bioprinting offers a genuine advantage are identified: chronic wounds, cosmetically critical areas, full-thickness burns exceeding 40% total body surface area, and *in vitro* pharmaceutical testing. Existing approaches remain limited in mimicking physiological complexity, multi-material compatibility, and long-term stability. Critical gaps persist in elastin regeneration, matrix mechanotransduction, immune-material interactions, and transition to Good Manufacturing Practice-compliant manufacturing. This review also evaluates under-addressed translational barriers, including regulatory pathways, scalability, and cost-effectiveness. Further progress requires convergence of stem cell technology, advanced bioink design, and artificial intelligence-driven optimization. Interdisciplinary collaboration remains essential to advance bioprinting toward clinical application in severe skin injuries and regenerative medicine.

Keywords: 3D bioprinting; Biomaterials; Wound healing; Skin tissue engineering

1. Introduction

The skin serves as the first line of defense, and severe skin destruction can cause shock or death due to fluid loss and infection.[1] While conventional skin grafting remains the preferred technique for extensive skin damage, limited donor-site availability and immune rejection associated with xenograft and allogeneic grafts remain major challenges.[2] Current synthetic skin systems typically act as temporary wound coverings and do not induce new tissue formation, highlighting the need for more advanced solutions.[3] The development of three-dimensional (3D) bioprinting technology has emerged as a promising approach, offering compatibility with biological tissue reconstruction (Figure 1). 3D bioprinting is a precise process combining cells, biomaterials, and physiologically active substances using automated manufacturing techniques. It is a layer-by-layer additive manufacturing process that combines cells, biomaterials, and physiologically active substances through automated deposition.[4] Since its first application to skin regeneration by Vijayavenkataraman *et al.*[5] in 2009, the field has gained significant interest, though the faithful reproduction of tissue architecture and physiological properties of skin remains a challenging issue.[6]

Despite over 15 years of development, current bioprinted constructs fail to replicate the hierarchical complexity of native skin, particularly the dermal-epidermal junction and skin appendages.[7] Most approaches produce simplified bilayer structures lacking vascularization, innervation, and functional appendages (hair follicles, sweat glands). Existing bioink formulations struggle to balance printability, biocompatibility, and mechanical properties matching native tissue simultaneously.[8] Furthermore, few studies demonstrate long-term functional outcomes beyond basic wound closure, with critical parameters such as barrier function restoration and aesthetic outcomes rarely achieving native tissue performance.[9] The scalability

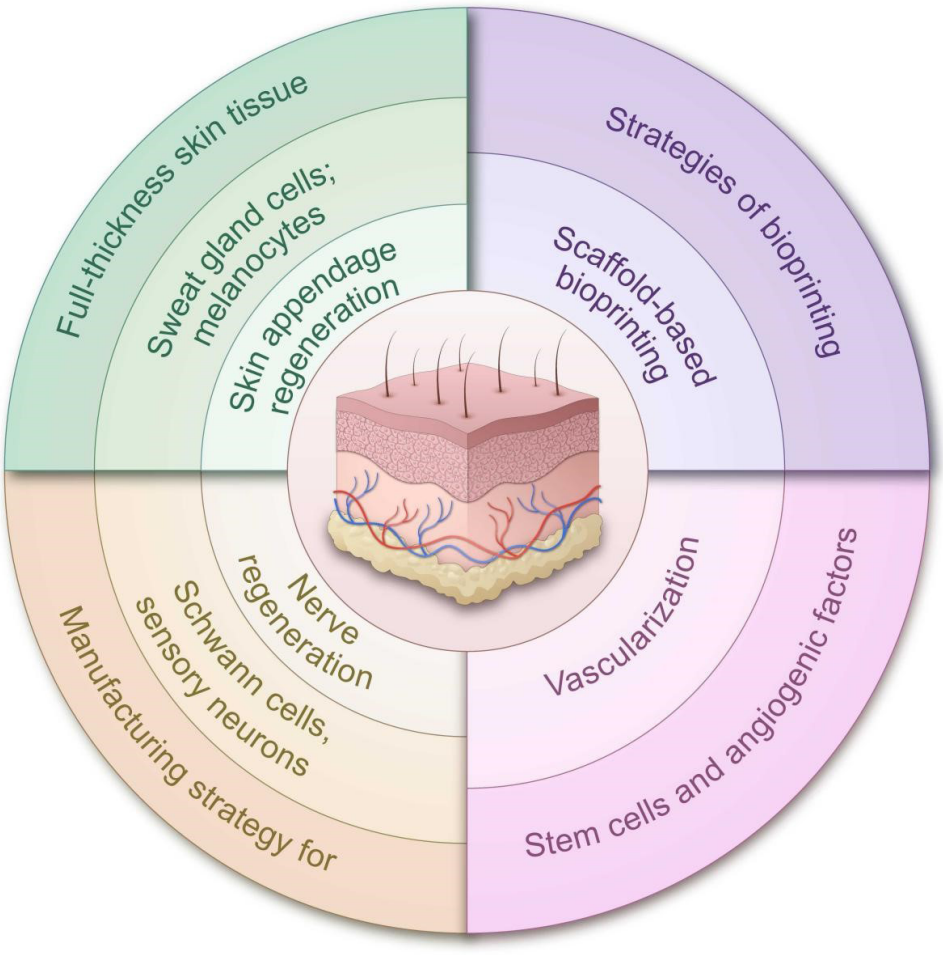

Figure 1. 3D bioprinting-based fabrication strategies for skin scaffolds and skin tissue regeneration. Created by the authors using Adobe Illustrator 2024.

from small-scale demonstrations to clinically relevant wound sizes, while maintaining print resolution and cell viability, remains a significant manufacturing challenge.[10]

While several recently published reviews (2024–2025) have addressed overlapping aspects of 3D bioprinting for skin tissue engineering, including bioprinting techniques and future perspectives,[11,12] cells, biomaterials, and methods, biomacromolecule-based fabrication strategies,[13] and biomaterials and fabrication challenges,[14] the present work offers distinct contributions not collectively present in prior literature. Existing reviews provide valuable overviews of technologies, materials, and applications; however, none collectively deliver a unifying materials-design framework tied to wound healing phase biology, quantitative mechanobiological design criteria, or an explicit translational-readiness evaluation encompassing regulatory barriers and Good Manufacturing Practice (GMP) manufacturing feasibility. Furthermore, existing reviews do not critically identify the specific clinical niches where bioprinting demonstrably offers an advantage over conventional grafting, nor do they systematically distinguish proof-of-concept findings from clinical readiness.

This review critically examines recent innovations (2020–2026) in bioink formulations, printing strategies for complex tissue architecture, vascularization and innervation approaches, and skin appendage regeneration. It goes beyond descriptive enumeration to develop a unifying materials-design framework, address mechanobiological design rationale, and critically evaluate translational readiness, including regulatory barriers and GMP manufacturing feasibility. Where reported advances remain at the proof-of-concept stage, this is explicitly distinguished from clinical readiness. The goal is to provide a field-defining perspective on the path from experimental demonstration to clinically viable bioprinted skin.

2. Wound healing process and bioprinting design criteria

The wound healing process involves three major phases: inflammation, tissue regeneration, and matrix remodeling.[15] Understanding these mechanisms is not merely contextual background but establishes the quantitative biological design criteria that bioprinted constructs must satisfy at each phase. The initial stages involve hemostasis and acute inflammation with recruitment of platelets and leukocytes. The proliferative phase is characterized by wound contraction, granulation tissue formation, new blood vessel development, and provisional extracellular matrix (ECM) formation. The final stage involves tissue remodeling, where the ECM is modified to become either fully functional skin or compromised scar tissue.[16] The phase-specific design criteria are as follows:

(i) Inflammatory phase (days 0–5): Constructs must modulate, rather than merely tolerate, the inflammatory environment. This requires bioinks with controlled macrophage-polarizing capacity, favoring M2 over M1 phenotypes to suppress fibrotic signaling. Materials must resist proteolytic degradation long enough to provide structural support during peak matrix metalloproteinase activity, while releasing anti-inflammatory mediators (e.g., interleukin-10, transforming growth factor beta 1 [TGF-β1]) in a temporally controlled manner.

(ii) Proliferative phase (days 5–21): Constructs must support angiogenesis, fibroblast migration, collagen deposition, and re-epithelialization. To meet oxygen-diffusion requirements, vascular network spacing should generally not exceed 200 μm.[17] Bioink degradation kinetics must be synchronized with ECM replacement, as premature degradation causes structural collapse, whereas delayed degradation impedes cellular remodeling. Pore sizes of 100–300 μm are generally required to support vascularization and cell infiltration.

(iii) Remodeling phase (weeks 3 onward): Constructs must guide the transition from type III collagen predominance to type I collagen predominance and promote basket-weave-like collagen organization, thereby reducing the risk of disorganized scar-like matrix deposition.[18] This requires mechanically dynamic scaffolds whose stiffness decreases as native ECM matures, preventing aberrant mechanotransduction through YAP/TAZ pathways, which may drive myofibroblast persistence and fibrosis.

In addition to these phase-specific requirements, mechanotransduction-related criteria must also be considered. Native dermis exhibits stiffness in the range of 5–50 kPa depending on anatomical location. Bioinks must be designed to match this range post-crosslinking, as substrate stiffness directly governs cell fate through the integrin–FAK–YAP/TAZ signaling axis. Excessive matrix stiffness promotes myofibroblast differentiation and scar formation; insufficient stiffness impairs keratinocyte stratification and barrier function.

3. Complex wounds and 3D bioprinting value proposition

Skin loss following burns or traumatic injury presents major clinical challenges. Traditional skin transplantation is limited by donor site availability, graft rejection, and poor

cosmetic outcomes,[19] while current wound dressings lack biomodulatory qualities for large wounds.[20] Autografts, allografts, and xenografts remain constrained by donor suitability, safety, and availability,[21] and skin tissue-engineered substitutes categorized into epidermal, dermal, and composite types face persistent obstacles, including difficulty replicating skin's multilayered architecture and inadequate control over cell proliferation, vasculature, sensory nerves, and adnexa (Figure 2).

While 3D bioprinting theoretically offers patient-specific customization, multi-material complexity, and appendage integration, the current reality falls short. No clinical studies have demonstrated superiority over conventional grafting;[22] autologous cell expansion requires weeks, rendering it impractical for acute wounds, and current implementations achieve only basic bilayer structures rather than truly complex tissues.[23] Perfusable vascular networks that survive transplantation and anastomose with host vasculature remain challenging, with neural integration even less developed.[24]

The value of bioprinting lies in four specific clinical niches: chronic wounds where controlled cell and growth factor delivery overcomes biological deficiencies that conventional dressings cannot address;[25] cosmetically critical areas where superior aesthetic outcomes justify increased complexity; full-thickness burns exceeding 40% total body surface area where conventional donor sites are insufficient; and *in vitro* pharmaceutical testing platforms where native-architecture skin models provide superior predictive value.[26] This niche-based classification, adopted from established literature,[25,27] is used as an organizing framework throughout this review, as each niche requires fundamentally different design approaches, bioink compositions, and regulatory pathways.

4. Bioprinting technologies for skin tissue engineering

Three-dimensional bioprinting has emerged as a sophisticated method for generating skin tissue through computer-assisted manipulation of scaffold materials, bioactive compounds, and tissue-specific cellular design.[28] The process involves scanning and modeling skin wounds, preparing biomaterials and cells, executing the 3D print, and nurturing the printed tissues (Figure 3). Four primary bioprinting methodologies dominate skin tissue engineering: inkjet bioprinting, extrusion-based bioprinting, laser-assisted bioprinting (LaBP), and digital light processing (DLP)-based bioprinting.[29,30] However, each technology presents distinct trade-offs between resolution, throughput, cell viability, material compatibility, and scalability. This section critically compares these technologies based on their performance in skin tissue fabrication, identifying optimal applications and persistent limitations.

4.1. Cell viability and density: Critical performance differences

Cell viability during and after printing directly impacts

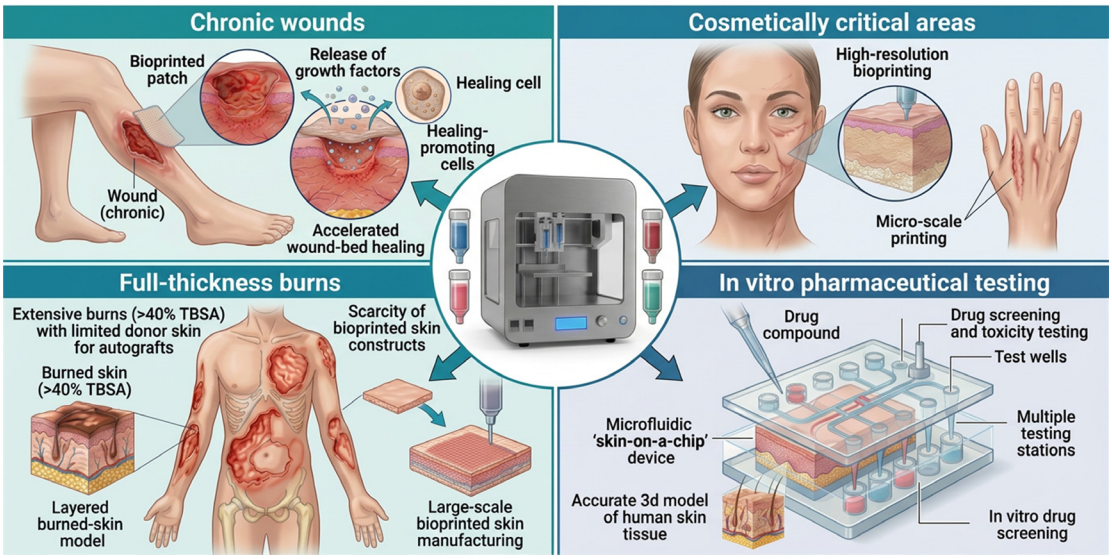

Figure 2. Schematic depiction of existing conventional treatment modalities for extensive skin defects, alongside a schematic illustration of bioprinted skin substitutes. Created by the authors using Adobe Illustrator 2024.
Abbreviation: TBSA: Total body surface area.

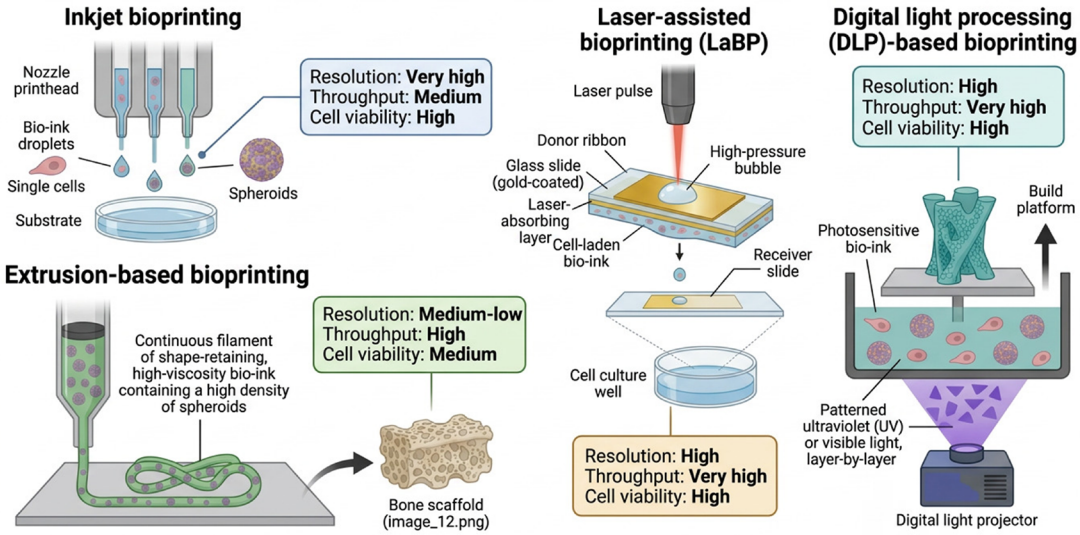

Figure 3. Workflow schematic for 3D bioprinting of full-thickness skin, encompassing bioink component preparation (seed cells, extracellular matrix, bioactive substances), technology selection (inkjet, extrusion, laser-assisted, DLP), and post-printing cultivation to consolidate construct structure and enhance biological activity. Created by the authors using Adobe Illustrator 2024.

construct functionality, yet different technologies impose distinct stresses on cells. Inkjet bioprinting offers rapid printing rates and good cell survival rates due to minimal mechanical stress.[31] However, thermal or piezoelectric actuation can damage cells through temperature exposure and mechanical strain, and nozzle obstruction issues limit achievable cell densities below native skin. Sharma *et al.* successfully demonstrated multi-component bioink deposition with living cells, but acknowledged density limitations.[32]

Extrusion bioprinting achieves superior cell densities compared to inkjet approaches, enabling constructs that more closely approximate native tissue cellularity (Figure 4A–F).[30] However, shear forces during extrusion significantly reduce cell survival compared to inkjet and light-cured printing.[33] Recent integration with microfluidics has mitigated this limitation by decreasing shear stress and enabling concurrent extrusion of multiple inks through single nozzles, facilitating the creation of hollow, vascularized structures that improve cell survival. LaBP avoids nozzle clogging through its nozzle-less approach, but the energy-absorbing metal layer causes cellular contamination, and localized evaporation generates elevated air pressure that adversely affects cell function.[34] DLP-based bioprinting eliminates nozzle clogging issues and enables high-cell-density printing, but ultraviolet (UV) light irradiation and photoinitiator toxicity inevitably cause cellular damage.[35] The requirement for photoinitiators to accelerate curing introduces additional cytotoxicity concerns that must be balanced against printing performance.

4.2. Comparative analysis of resolution and printing speed

Resolution and printing speed represent critical performance parameters that often exist in tension. Inkjet bioprinting achieves high-throughput printing with precise drop-by-drop ink ejection, capable of encapsulating cells ranging from 30 μm single cells to 80 μm multiple cell clusters.[30] This enables rapid generation of large-scale, accurately configured 3D structured hydrogels. Park *et al.* demonstrated this capability by creating patterns of fibroblasts within hydrogels that replicated human skin papillary structures at the dermal-epidermal junction.[36] However, inkjet printing typically achieves moderate resolution compared to laser-based approaches.[37]

Extrusion bioprinting operates at modest speeds and resolutions, frequently below 50 μm, representing a significant limitation for replicating fine skin microarchitecture.[38] The layer-by-layer deposition of cylindrical filaments through nozzles moving along the X, Y, and Z axes enables printing of high-viscosity materials (up to 600 kPa) but sacrifices speed and resolution.[39] In contrast, LaBP achieves exceptional precision control and is considered the most advanced bioprinting technique in terms of resolution, making it particularly suitable for printing microvascular networks.

Boland *et al.*[40] demonstrated this precision by printing 40 layers of bioink containing fibroblasts and keratinocytes with defined intercellular adhesion, creating a bilayer

architecture that emulates native skin (Figure 4G–N). DLP-based bioprinting achieves the optimal balance, enabling quick, high-resolution prints with structures as fine as 100 μm while maintaining rapid production regardless of complexity.[40] This capability has been leveraged to construct vascularized skin substitutes with precise spatial organization of endothelial cells (ECs) and fibroblasts.

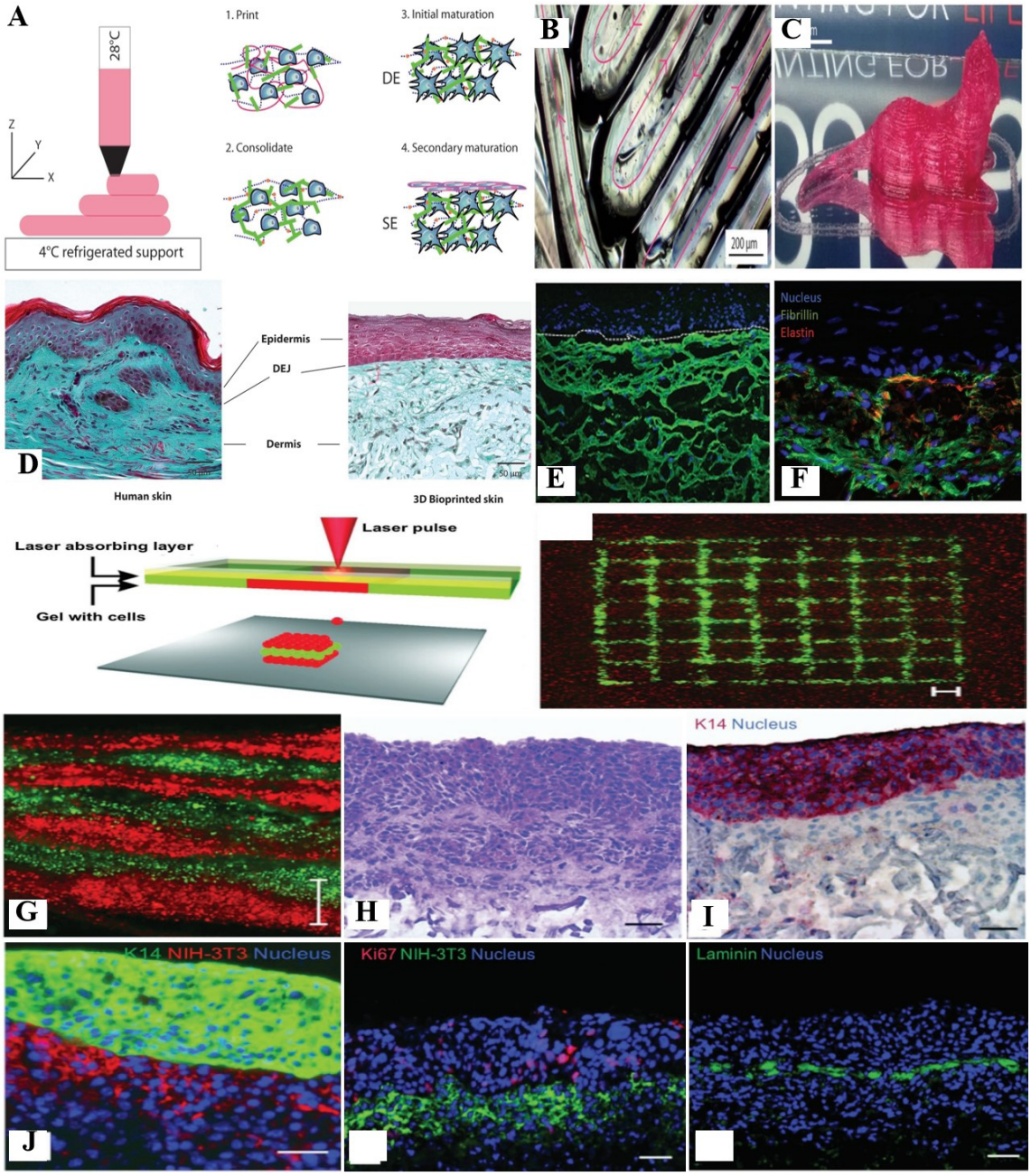

Figure 4. Comparison of extrusion-based and laser-assisted bioprinting (LaBP) technologies for skin tissue engineering. **(A)** Extrusion bioprinting setup at 4 °C refrigerated support. **(B)** Extruded filament trajectory. **(C)** 3D-bioprinted construct. **(D–F)** Hematoxylin and eosin (H&E) staining and immunostaining showing skin-layered architecture with ECM components (collagen I, fibrillin, elastin). **(G)** Schematic of LaBP setup. **(H)** Cell patterning via LaBP with fibroblasts (green) and keratinocytes (red) in a grid configuration. **(I)** Layered HaCaT keratinocyte printing. **(J)** H&E staining showing bilayer skin architecture emulating native skin. **(K)** Keratin 14 (K14) expression. **(L)** Co-localization of K14, NIH-3T3, and nucleus. **(M)** Ki67 and NIH-3T3 co-localization. **(N)** Laminin expression. Scale bar: 500 μm (A–B); 50 μm (C–N). Reproduced with permission from Ref.[41] Copyright © 2022, Wiley-VCH.

4.3. Material compatibility and bioink requirements

Material compatibility varies dramatically across technologies, fundamentally constraining bioink selection. Inkjet bioprinting requires low-viscosity, liquid-form bioinks due to the direct relationship between viscosity and droplet expulsion force.[42] This severely restricts the range of printable materials and prevents the use of high-viscosity natural polymers that better match native ECM properties. Extrusion bioprinting accommodates the broadest range of viscosities (up to 600 kPa), enabling use of sodium alginate, fibronectin, methacrylated gelatin, gelatin, and collagen, the most commonly utilized biomaterials for skin repair (Table 1).[43] Temperature-controlled nozzles and molding platforms can optimize results for temperature-sensitive materials, providing advantages for gelatin-based bioinks. However, certain temperature-sensitive materials exhibit viscosity fluctuations that complicate process control.

Laser-assisted bioprinting is compatible with a limited range of printable materials, limiting its versatility despite superior resolution.[29,30] The requirement for materials compatible with laser energy absorption and the donor slide system constrains bioink formulation options. DLP-based bioprinting faces the narrowest material compatibility, requiring photosensitive materials that undergo crosslinking upon UV exposure.[44] Chemical modifications to incorporate photosensitizable functional groups are usually needed to obtain printable bioink composites, adding complexity and potential cytotoxicity. Fang *et al.* addressed this by developing cell-compatible prepolymer solutions with precisely controlled UV curing, enabling vascularized skin tissue printing.[45] However, the fundamental constraint of requiring photopolymerizable materials remains a significant limitation for material selection.

4.4. Scalability and clinical translation

Translational viability depends on scalability, cost, and operational complexity factors, where technologies differ markedly. Inkjet bioprinting offers economical manufacturing with simple, reliable equipment, making it attractive for clinical translation.[46,47] However, its inability to print large cell densities or thick structures limits applications to thin constructs. Extrusion bioprinting employs the most affordable equipment with intuitive operation and meticulous control, making it the most promising technique for bioprinting synthetic skin at scale.[48] The integration of microfluidic systems enhances this advantage by enabling the creation of complex vascularized structures with a single nozzle, reducing manufacturing complexity while improving functionality.[49]

Laser-assisted bioprinting suffers from prohibitive equipment costs, long printing periods, and the inability to print large, clinically relevant constructs, severely limiting extensive clinical application despite superior resolution.[50] The nozzle-less approach prevents scaling to clinically relevant wound sizes within practical timeframes. DLP-based bioprinting achieves rapid production with high resolution, but requires investigation of non-UV light sources and non-toxic photoinitiator systems to address cytotoxicity concerns before widespread clinical adoption.[51,52] The need for lower-intensity UV light that still enables rapid curing represents an ongoing challenge in balancing throughput with cell viability.

4.5. Technology selection: Matching capabilities to application requirements

No single technology optimally addresses all performance requirements for skin bioprinting, necessitating strategic selection based on application priorities (Figure 5). For applications requiring high throughput with moderate complexity (e.g., *in vitro* skin models for pharmaceutical testing), inkjet bioprinting offers the optimal balance of speed, cost, and cell viability.[45,53] For clinically sized constructs requiring native-like cellularity and ECM composition, extrusion bioprinting remains the most practical choice, particularly with microfluidic integration for vascularization.[54] For applications demanding exceptional spatial precision (e.g., replicating dermal-epidermal junction microarchitecture or printing capillary networks), LaBP provides unmatched resolution despite scalability limitations. For complex geometries requiring rapid production with high cell density (e.g., patient-specific constructs with intricate vascular networks), DLP-based bioprinting offers superior performance, provided photoinitiator cytotoxicity can be adequately managed.[55]

Future advances require not merely incremental improvements to individual technologies, but strategic integration combining complementary capabilities. Hybrid approaches utilizing extrusion bioprinting for bulk tissue with DLP-based or laser-assisted printing for fine features may overcome current limitations. The field must move beyond technology development for its own sake toward systematic optimization, matching bioprinting capabilities to specific clinical needs. Only through honest assessment of each technology's performance trade-offs can researchers make informed decisions about technology selection and development priorities for clinical translation.

Figure 5 presents a hierarchical multi-parameter comparison of the four bioprinting platforms across six clinically relevant criteria: resolution, printing speed, cell viability, material versatility, scalability, and cost-effectiveness. Parameters were selected based on their

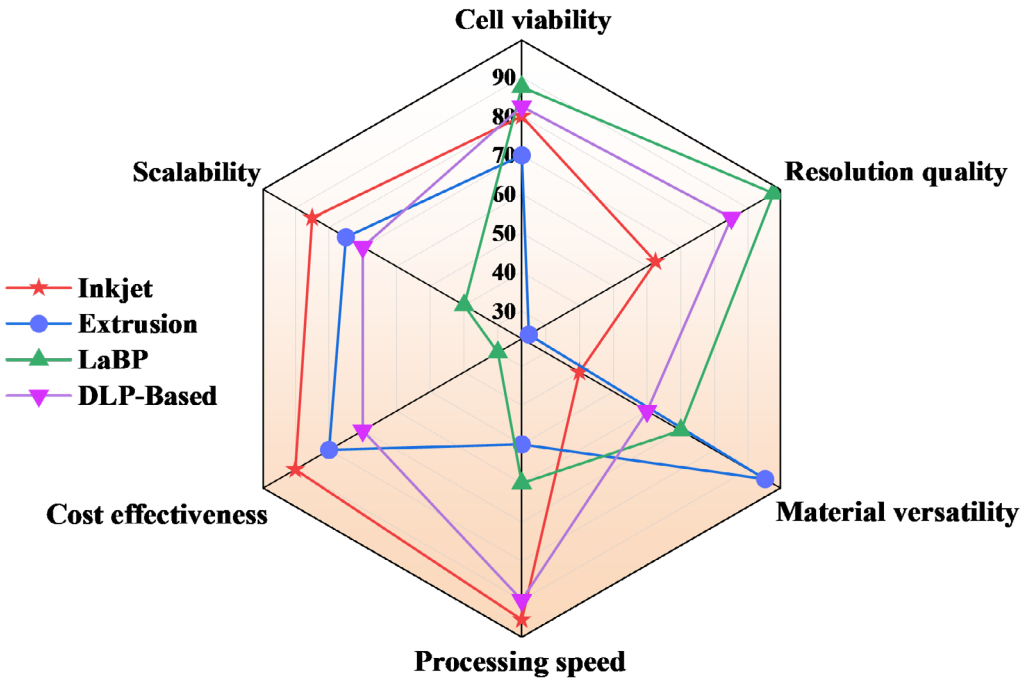

Figure 5. Comparative analysis of four 3D bioprinting technologies (inkjet, extrusion, LaBP, and DLP-based) across six performance parameters: cell viability, resolution quality, material versatility, processing speed, cost effectiveness, and scalability. LaBP demonstrates superior resolution and cell viability, while inkjet excels in cost-effectiveness. Created by the authors using OriginPro software 2025.

direct relevance to clinical translation and scored on a 1–5 scale derived from quantitative and qualitative data presented in Sections 4.1–4.4, with scoring definitions and data sources detailed in the accompanying Methods Note. Extrusion bioprinting scores highest overall for scalability and material versatility, making it the most clinically practical platform; inkjet bioprinting leads in cost-effectiveness and speed; LaBP achieves the highest resolution but scores lowest in scalability; and DLP offers the best balance of resolution and throughput but is constrained by photoinitiator cytotoxicity. No single platform dominates all criteria, reinforcing the rationale for hybrid approaches.

4.6. Strategic material selection

Table 1 provides a unified strategic material selection framework, mapping bioink material classes to wound healing phases, target skin layers, compatible printing technologies, functional requirements, and current limitations.

5. Bioink materials for skin bioprinting

Bioprinting technologies are directly related to bioink formulations, which represent the core materials determining the precision of cell distribution, printed structure fidelity, cell viability, and capacity to support reproducible tissue regeneration. The performance of bioinks directly affects bioprinting outcomes, yet current formulations remain far from ideal for printing complex skin structures.[56] Desirable bioinks must balance multiple competing requirements: biocompatibility, printability, mechanical stability, and ability to support cell proliferation and differentiation. Groll *et al.*[56] provided a systematic approach for bioink characterization with standardized parameters for rheological properties, printability, and biocompatibility to enable reproducibility among studies,[57] greatly facilitating advancement toward clinically applicable bioinks. However, formulation standardization remains a critical issue, and bespoke bioink formulations are required for different bioprinting approaches and tissue types. This section critically evaluates bioink materials based on their performance in skin bioprinting applications, compares their advantages and limitations, and provides strategic guidance for material selection (Figure 6, Table S1). Figure 6 compares bioink material classes across key performance parameters including biocompatibility, mechanical strength, degradation stability, printability, and cell proliferation capacity. Values represent ranges reported across cited studies rather than absolute scores, with confidence qualifiers indicating

Table 1. Unified materials-design framework for skin bioprinting

Material class	Target skin layer	Healing phase activity	Compatible technology	Key functional requirement	Primary limitation
Collagen type I	Dermis	Proliferative, remodeling	Inkjet, LaBP, extrusion	Fiber alignment, mechanotransduction	Rapid degradation, poor printability alone
GelMA	Dermis, dermal–epidermal junction	All three phases	Extrusion, DLP, LaBP	Tunable stiffness, inflammatory modulation	Photoinitiator toxicity
Fibrinogen/fibrin	Dermis	Inflammatory, proliferative	Inkjet, extrusion	Provisional scaffold, hemostasis	Weak mechanics, rapid degradation
Decellularized extracellular matrix	Dermis	All three phases	Extrusion	Full signaling complexity	Batch variability, immune risk
Alginate	Structural support	Structural only	Extrusion	Gelation control	No cell adhesion without modification
Chitosan	Epidermis, wound surface	Inflammatory	Inkjet, extrusion	Antimicrobial, hemostatic	Immunostimulatory risk
Polyethylene glycol	Structural/ mechanical	Remodeling	DLP, extrusion	Tunable mechanics, low immunogenicity	No bioactivity without functionalization
Polycaprolactone	Structural scaffold	Remodeling	Extrusion	Mechanical strength, slow degradation	Poor cell adhesion
Tropoelastin	Dermis	Remodeling	Extrusion	Elastic recoil, cyclic load resistance	Largely unexplored in skin bioprinting
Platelet biologics/ GelMA	Dermis	Inflammatory → proliferative	Extrusion, inkjet	Phase-matched growth factor release	Release kinetics control; cost

Abbreviations: DLP: Digital light processing; GelMA: Gelatin methacryloyl; LaBP: Laser-assisted bioprinting.

whether data derive from multiple independent studies or limited reports. Natural polymers consistently demonstrate superior biocompatibility and cell interaction but inferior mechanical properties compared to synthetic alternatives, reinforcing the strategic rationale for hybrid formulations combining the bioactivity of natural polymers with the mechanical tunability of synthetic components.

5.1. Natural versus synthetic polymers

Materials can be categorized into natural polymers (collagen, gelatin, fibrinogen, decellularized extracellular matrix [dECM], pectins, alginate, chitosan) and synthetic polymers (polyethylene glycol [PEG], polycaprolactone [PCL]). This categorization reflects a fundamental trade-off in bioink design.[58] Natural polymers offer excellent biocompatibility, bioactivity, and similarity to native skin ECM, promoting cell adhesion, migration, and differentiation through intrinsic biological recognition motifs.[59] However, they typically suffer from poor mechanical properties, batch-to-batch variability, rapid degradation, potential immunogenicity, and high costs. Synthetic polymers provide tunable mechanical properties, reproducible manufacturing, controlled degradation kinetics, and lower immunogenicity, but lack inherent bioactivity and cell recognition sites, requiring chemical modification to incorporate biological functionality.[60] Neither category alone adequately addresses all requirements for skin bioprinting, driving the development of hybrid formulations combining natural and synthetic components. The critical question is not which category is superior, but rather how to strategically combine materials to achieve optimal performance for specific applications.

5.2. Extracellular matrix-mimetic materials

Type I collagen, the main component of dermal ECM, represents the gold standard for biomimicry in skin bioprinting due to high biocompatibility, biodegradability, and promotion of cell adhesion and ECM interaction.[61,62] However, clinical application remains limited by expensive preparation, rapid *in vivo* degradation, and possible immunogenicity. To overcome these limitations, collagen-based bioinks are typically combined with synthetic polymers or chemically modified to improve mechanical properties. Singh *et al.* demonstrated that combining PCL

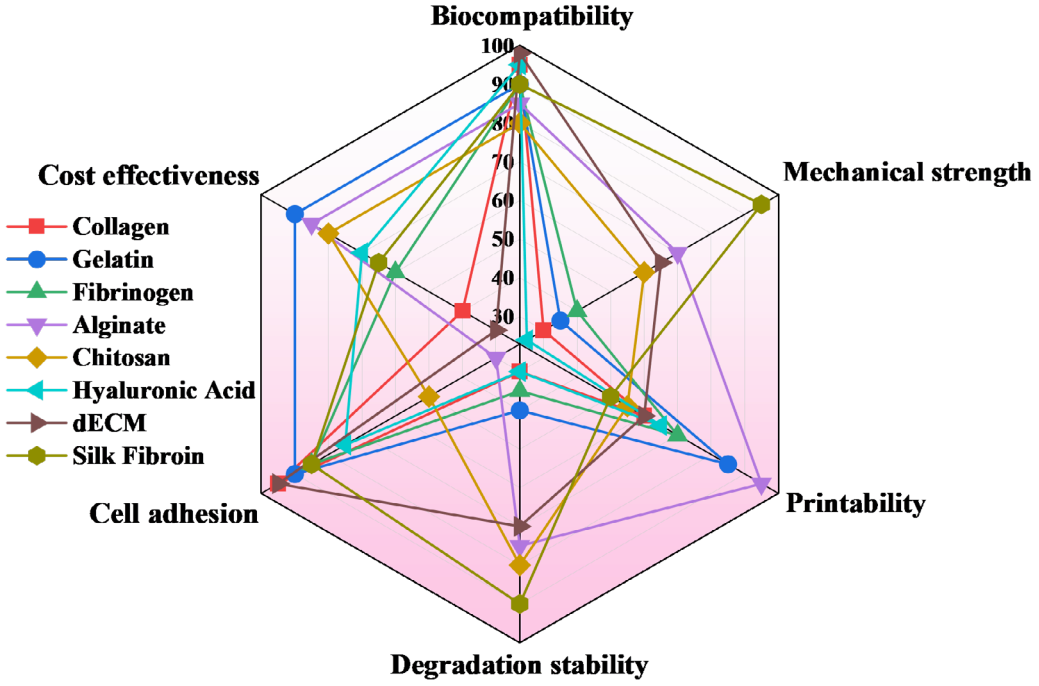

Figure 6. Multi-dimensional comparison of eight natural polymer biomaterials (collagen, gelatin, fibrinogen, alginate, chitosan, hyaluronic acid, decellularized extracellular matrix [dECM], and silk fibroin) used in skin bioprinting. The radar chart evaluates biocompatibility, mechanical strength, printability, degradation stability, cell adhesion, and cost effectiveness. All materials show high biocompatibility (>90%), with silk fibroin demonstrating superior mechanical strength. Created by the authors using OriginPro software 2025.

mesh with collagen scaffolds minimized shrinkage during remodeling without compromising fibroblast viability, exemplifying successful hybrid approaches. Low-viscosity collagen formulations suit inkjet and LaBP,[63] but poor mechanical properties necessitate structural reinforcement strategies for extrusion-based approaches requiring higher viscosities.

Gelatin, a denatured collagen derivative, offers similar biocompatibility and cell recognition motifs but provides greater cost-effectiveness, reduced immunogenicity, and thermally reversible gelation.[64] These properties make gelatin particularly attractive for sacrificial microchannel fabrication in vascularized constructs and as a rheological modifier in multi-material bioinks. For instance, the addition of gelatin to dermal fibroblast-containing bioinks enabled printing of bilayered skin constructs with increased printability.[65] Chemical modification through methacrylation produces gelatin methacryloyl (GelMA), a photocrosslinkable hydrogel combining tunable mechanical properties with cell-protective effects. The shear-thinning nature of GelMA minimizes nozzle clogging during extrusion while preserving cell viability,[66] making it among the most versatile bioink components currently available. Fibrinogen complements these materials through its intrinsic role in wound healing. Upon conversion to fibrin by thrombin, it forms networks serving as temporary scaffolding for fibroblast migration. Li *et al.*[67] employed fibrinogen/gelatin bioinks crosslinked with thrombin and calcium chloride to fabricate dermal-like structures, subsequently seeding keratinocytes to form epidermis. However, fibrin networks demonstrate relatively weak mechanical properties and rapid degradation, limiting their use as standalone bioinks for load-bearing applications. The optimal strategy combines these ECM-mimetic materials: collagen provides biological fidelity, gelatin offers processing advantages, and fibrinogen contributes wound-healing functionality, while synthetic reinforcement addresses mechanical limitations.

5.3. Decellularized extracellular matrix

Decellularized extracellular matrix represents an advanced biomaterial approach, preserving native 3D architecture and fibrous components while eliminating cellular elements.[68] Derived from human, porcine, or bovine dermis, dECM bioinks retain numerous cellular growth factors (fibroblast growth factor, TGF-β1, hepatocyte growth factor) that facilitate seed cell attachment, migration, proliferation, differentiation, and angiogenesis. This real-time interaction capability enables tissue structure modification during

regeneration, theoretically providing superior biomimicry compared to purified component-based bioinks.[69] However, significant practical limitations constrain widespread adoption. The possibility of disease transmission requires comprehensive pathogen screening before clinical use, substantially increasing production costs. Batch-to-batch variability in composition and mechanical properties complicates standardization and reproducibility. Source tissue availability limits scalability, particularly for human-derived dECM.[70] Furthermore, printability challenges arise from heterogeneous composition and variable viscosity after solubilization. While dECM bioinks show promise for specialized applications where superior biological activity justifies increased cost and complexity, they are unlikely to become standard materials for routine skin bioprinting until these limitations are addressed. Current evidence suggests dECM may be most valuable as a minor component within hybrid formulations, providing biological signals while other materials ensure printability and mechanical integrity.[71]

5.4. Polysaccharide-based materials

Polysaccharides, including pectins, alginate, and chitosan, serve primarily as structural components in skin bioinks, providing mechanical support and controlled gelation but lacking intrinsic cell adhesion capacity. Pectins, obtained from plant cell walls, exhibit biocompatibility and biodegradability with physical gelation upon Ca^{2+} addition.[72] However, the absence of cell adhesion motifs prevents the attachment of adherent mammalian cells without modification. Bojorges *et al.* addressed this by creating RGD-conjugated pectin bioinks that successfully promoted fibroblast adhesion, proliferation, and ECM deposition in 3D skin-like constructs. Alginate, an anionic polymer from brown seaweed, similarly gels with divalent cations but requires chemical modification to link cell adhesion capacity.[73] Its primary role in skin bioprinting is providing structural support when combined with other biomaterials. Chitosan, derived from chitin deacetylation, offers unique antimicrobial, hemostatic, and wound-healing properties, particularly suitable for skin applications.[74] Its ability to control bleeding makes it prominent in wound dressings. However, like other polysaccharides, chitosan lacks inherent cell adhesion capacity, requiring appropriate modification.

The common limitation across polysaccharide materials, the absence of cell recognition sites, necessitates chemical modification or combination with bioactive components.[75] This requirement adds complexity and cost while potentially reducing biocompatibility through modification chemistry. The strategic value of polysaccharides lies in their ability to provide structural integrity and controlled gelation kinetics at a lower cost than protein-based materials. They function most effectively as supporting components within multi-material bioinks rather than as standalone formulations.[76] Future development should focus on standardized modification protocols that reliably incorporate cell adhesion capacity while maintaining favorable processing characteristics.

5.5. Synthetic polymers

Polyethylene glycol exemplifies synthetic polymer advantages: Food and Drug Administration (FDA) approval for biomedical use, excellent biocompatibility and biodegradability, non-toxicity, and highly tunable physicochemical properties.[77] Functional groups can be incorporated to provide cell adhesion capacity and enzyme sensitivity, enabling control over biological functions including migration and adhesion. Low immunogenicity and adjustable mechanical strength and elasticity make PEG a favored candidate for 3D bioprinting bioinks.[78] However, PEG-based bioinks face inherent limitations. Lack of native biological recognition requires extensive functionalization, increasing complexity and potentially reducing cytocompatibility.[79] Synthetic polymers generally provide poor cell adhesion and limited biological signaling compared to natural materials, requiring careful design to support cell function. Degradation products, while generally biocompatible, lack the beneficial biological activity of natural polymer degradation products. The optimal strategy combines PEG's engineering advantages with natural polymer bioactivity.[80] For instance, PEG can provide a mechanical framework and controlled degradation while conjugated peptides or incorporated growth factors supply biological signals. This hybrid approach requires sophisticated formulation chemistry but potentially delivers superior performance by combining synthetic precision with biological functionality.

5.6. Bioactive additives

Incorporating bioactive factors represents an advanced strategy for enhancing bioink functionality beyond passive structural support. Platelet biologics, including platelet-rich plasma and platelet lysates, contain high concentrations of growth factors (platelet-derived growth factor, basic fibroblast growth factor, vascular endothelial growth factor [VEGF], TGF-β) that promote wound healing.[81] Studies demonstrate that platelet biologics enhance skin wound healing and soft tissue repair.[82] However, poor retention within wound beds and substantial enzymatic degradation limit their effectiveness. Combining platelet biologics with bioprinting fabrication techniques offers potential solutions by providing controlled spatial distribution and protection from degradation. For example, 3D-printed skin

models incorporating platelet lysate within GelMA bioinks successfully supported fibroblast function.[83] Despite these improvements, optimal methodologies for incorporating platelet biologics within bioink formulations remain under development.

Topically applied recombinant growth factors, while clinically approved, demonstrate unclear effectiveness due to poor stability, rapid loss from wound beds, high degradation rates, and inadequate healing promotion.[26] Integrating growth factors with 3D bioprinting enables tight control over release kinetics and spatial distribution, potentially enhancing treatment individualization. Biomaterials supporting controlled release may represent next-generation approaches. However, significant challenges remain: growth factor stability during printing processes, maintaining bioactivity after encapsulation, achieving appropriate release kinetics matching healing phases, and managing costs for clinical translation.[84] The field must move beyond simple growth factor incorporation toward sophisticated systems providing temporally and spatially controlled release responsive to tissue healing state. Current approaches remain largely empirical; systematic optimization relating growth factor type, concentration, release kinetics, and spatial distribution to healing outcomes is needed.

5.7. Cell selection strategies

Cell proliferation is the predominant factor sustaining the functionality of regenerated dermal tissue. Traditional cell-based therapies use fibroblasts and keratinocytes from non-damaged areas seeded onto injury sites.[85] While autologous therapies restore skin barrier function, they do not fully encompass the spectrum of skin functions, leaving a need for additional cell types and appendages. Endothelial cells support neovascularization while melanocytes enable melanin synthesis.[86] Recovering normal skin and appendages requires careful selection of appropriate cell types and functioning biomaterials.[87] Incorporation of stem cells in 3D printing attempts to improve regeneration through enhanced proliferation capacity and paracrine signaling. Stem cells' self-renewal and multi-lineage differentiation capacity, combined with growth factor and cytokine secretion, increase skin flexibility and induce basal cell proliferation, promoting keratinocyte proliferation and epidermal regeneration.[88] Studies demonstrate that stem cell-loaded skin substitutes significantly support new skin structure formation, accelerate re-epithelialization, and enhance wound healing in burn models, positioning stem cells as promising precursors for skin tissue engineering (Figure 7; Table S2).[89]

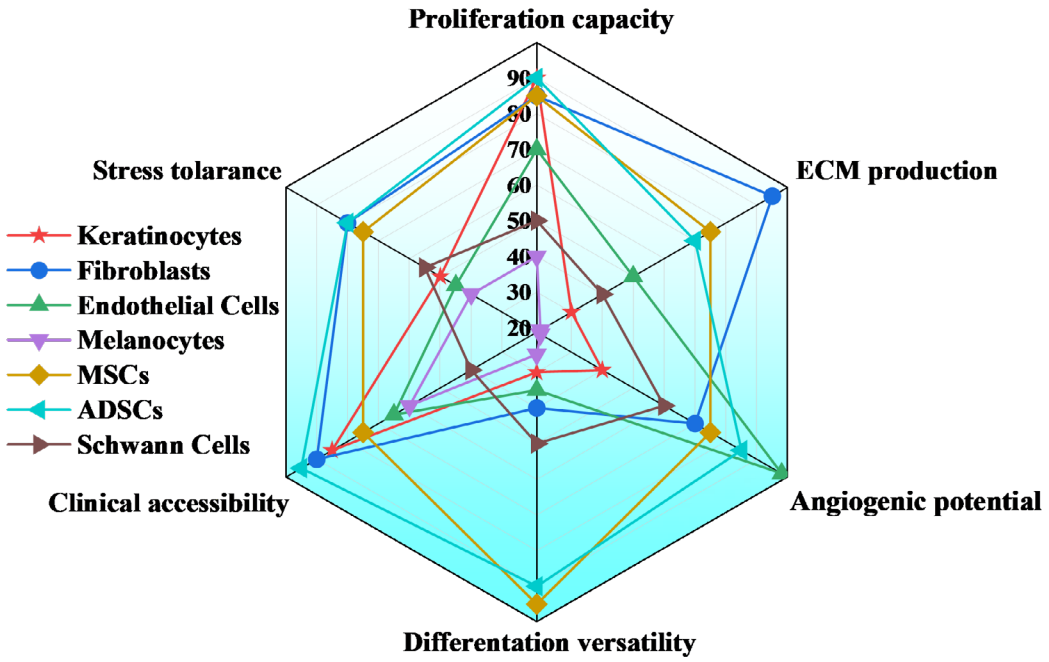

Figure 7. Functional characterization of seven cell types (keratinocytes, fibroblasts, endothelial cells, melanocytes, mesenchymal stem cells (MSCs), adipose-derived stem cells (ADSCs), and Schwann cells) in 3D-bioprinted skin constructs. The chart compares proliferation capacity, extracellular matrix (ECM) production, angiogenic potential, differentiation versatility, clinical accessibility, and stress tolerance. Fibroblasts and ADSCs exhibit high ECM production, while MSCs and ADSCs show superior differentiation potential. Data derived from Table S3. Created by the authors using OriginPro software 2025.

However, stem cell use in 3D bioprinting faces a significant challenge: extensive *ex vivo* expansion is required to meet bioprinting cell density requirements. Different strategies have been developed for large-scale culture, including 2D culture, which is simple but influences cell physiology through planar constraints;[90] 3D culture in hydrogels, which better recapitulates the *in vivo* environment, promoting pluripotency; porous scaffold culture, which enables size-appropriate replication; bioreactor culture, which provides a controlled environment with nutrient and oxygen supply;[91] and microcarrier culture, which is suitable for adherent cells allowing extensive amplification. Each method presents benefits and limitations depending on cell type, required numbers, intended use, and cost.[92] Integration of different technologies typically provides the most promising approach for well-functioning, high-quality stem cell expansion for 3D bioprinting applications. The field must address not only expansion efficiency but also maintenance of stem cell phenotype, differentiation capacity, and paracrine function throughout expansion and printing processes.[22] Current evidence suggests that expansion conditions profoundly affect stem cell performance after bioprinting, yet systematic optimization relating expansion protocols to post-printing outcomes remains insufficient.

6. Bioprinting of complex skin substitutes

6.1. Full-thickness bioprinting of skin with integrated structural functionality

The skin is a composite organ comprising dermis, epidermis, and subcutaneous fat, whose complex multilayered architecture 3D bioprinting can replicate with greater fidelity than traditional engineered skin, though high resolution and long-term functional equivalence remain challenging.[93] Bilayer membrane scaffolds comprising a lower alginate dermal layer and an upper poly(lactic-co-glycolic) acid nanofiber epidermal layer accelerate wound healing by promoting collagen I/III deposition, cellular proliferation, and angiogenesis. The interplay between the cells and ECM is critical in the biofabrication of 3D skin layers because they help maintain appropriate cell populations.[94] Recombinant human type III collagen combined with varying GelMA concentrations improves cellular activity in printed constructs.[95] Critically, however, no full-thickness bioprinted construct has demonstrated simultaneous functional equivalence across all skin layers in a large animal model beyond 12 weeks; most studies evaluate wound closure and basic histology without assessing barrier function, mechanical properties, appendage functionality, sensory recovery, or scar formation—parameters that define true skin regeneration versus mere wound coverage.

6.2. Bioprinting of vascularized skin tissue

Demand for comprehensive skin substitutes rises with the increasing structural complexity of their appendages.[96] The increased metabolic activity of skin substitutes is not matched by adequate diffusion of nutrients and oxygen, and their thickness frequently makes delivery less effective. To enhance the delivery of nutrients and oxygen, researchers are striving to optimize the circulatory system in these substitutes or ensure that wounded regions, especially those on the hands, face, and joints, possess a well-vascularized foundation.[96] Research has indicated that the range of 100–200 μm is the maximum distance at which nutrients can diffuse, allowing cells to survive independently of vascular distribution.[97] Therefore, the maintenance of tissue structures thicker than 100–200 μm requires a highly developed blood vessel system. The creation of vascularized skin structures has gained importance due to the significant impact that vascularization has on the functionality of implants. Figure 8 demonstrates three advanced fabrication strategies for 3D bioprinting to achieve skin vascularization, including the use of vascular bioinks, co-printing approaches, and DLP 3D printing technology. Yanez *et al.*[98] created synthetic skin using inkjet printing technology to increase blood flow to the printed skin tissue. They achieved this by grafting human umbilical vein endothelial cells (HUVECs), epidermal cells, and newborn dermal cells onto collagen and fibrinogen scaffolding materials. The outcomes of the wound healing trials performed on mice indicated that the 3D-printed skin grafts exhibited enhanced cell viability and accelerated wound healing relative to the commercially available skin grafts. Furthermore, the histological composition of the regenerated skin was found to be analogous to that of natural skin and was accompanied by the formation of new blood vessels. Abaci *et al.*[99] developed a novel technique for creating bioengineered 3D bionic skin. The researchers employed native and induced pluripotent stem cell (iPSC)-derived ECs to construct a completely functional vascular network capable of enabling fluid circulation. 3D printing facilitates the modification of the configuration of the micropatterned vascular network.

Other techniques for vascularization create microchannels with sacrificial inks that are then gently removed. The sacrificial ink frequently encloses ECs. Following the formation of the microchannels, the cells arrange themselves along their inner surfaces to form structures that resemble blood vessels. In sacrificial inks, gelatin and Pluronic F127 are the two principal components. Kim *et al.*[60] developed a 3D-printed skin model capable of vascularization and perfusion. The researchers constructed a homemade PCL Transwell chamber with fibrinogen as the

subcutaneous layer and a decellularized fat matrix as the matrix. Using thrombin as a sacrificial material and gelatin loaded with HUVECs, vascular channels were formed. The dermis layer consisted of fibroblasts and decellularized dermis, while inkjet technology was employed to deposit epidermal cells onto the scaffold. After gelatin was liquefied at 37 °C, ECs expressing CD31 were seen to be present in the walls of the vascular channels that were created. The skin model showed promising biological properties. After seven days of culture, the dermis and subcutaneous layers were discovered to be interconnected, closely resembling human skin. This approach fabricated channels with tube widths under 45 μm with Pluronic F127 as a sacrificial ink. This segment of the outer ring structure was fabricated using GelMA loaded with fibroblasts. The Pluronic F127 was subsequently cooled to 4 °C to achieve a liquid state. An empty syringe was employed to withdraw the liquid Pluronic F127 from the channel. Next, an endothelial layer was formed on the vessel by introducing HUVECs into the channel.

Three-dimensional bioprinting enables precise spatial control over vascular network formation by integrating ECs and bioactive cues within bioinks. VEGF can be encapsulated in bioinks to stimulate EC migration and lumen formation. For instance, bioinks functionalized with VEGF-loaded nanoparticles (e.g., gelatin microspheres) achieve sustained release, activating VEGF receptor-2 signaling pathways in ECs, thereby promoting capillary-like structure formation *in vitro*.[100] Additionally, bioprinted microchannels lined with ECs mimic native vasculature, enhancing nutrient perfusion and oxygen delivery to thick skin constructs. The findings indicate that vascularized bionic skin can facilitate and direct the development of new blood vessels during wound healing. Together, in Figure 8, these strategies demonstrate how skin vascularization can be achieved through different bioprinting techniques, providing a new approach to skin tissue engineering.

6.3. Bioprinting of skin tissue innervated by nerves

The skin is a richly innervated organ. The receptors and nerve fibers in the skin transmit sensory messages to the central nervous system. Moreover, they play an essential role in several skin processes and the wound healing

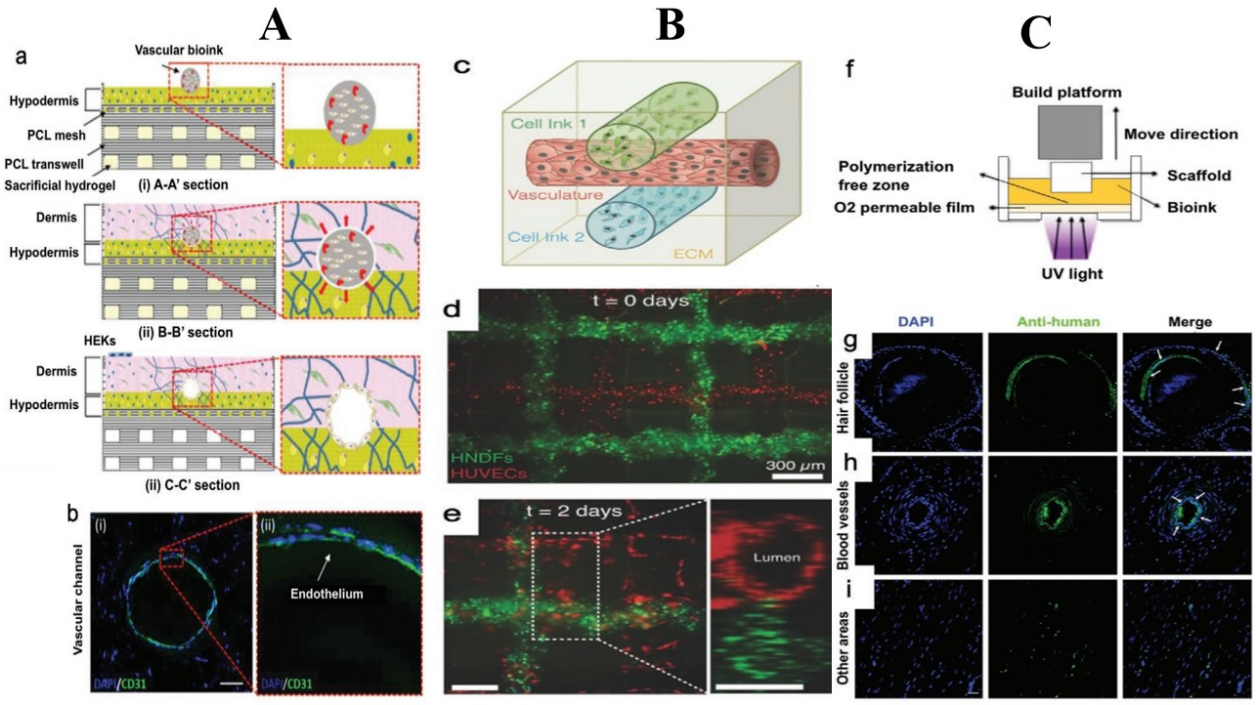

Figure 8. Three 3D bioprinting strategies for skin vascularization. (A) Vascular bioinks (human umbilical vein endothelial cells [HUVECs], gelatin, glycerol, thrombin) with decellularized extracellular matrix bioinks to create vascular channels, confirmed by CD31-positive endothelial staining. (B) Co-printing of vascular system, cells, and extracellular matrix to form microchannels, with fluorescence images showing HUVECs (red) within a 3D microvascular network in GFP-fibroblast-laden GelMA (green). (C) Digital light processing printing using adhesive and cellular polymer bioinks cured by dynamic UV patterning to construct interconnected channels, with fluorescence images showing hair follicles, blood vessels, and repaired tissue regions. Reproduced with permission from Ref.[41] Copyright © 2022, Wiley-VCH.

process. After a dermal lesion has occurred, the cutaneous nerve may be damaged. If the level of nerve regeneration is not sufficient, this could lead to sensory disturbances, chronic pain, or even permanent loss of sensation. Thus, the recovery of cutaneous sensation could produce a major effect on the quality of life in these patients.[101] The prolonged healing of denervated wounds demonstrates the critical role of cutaneous nerves in wound closure. Late wound healing in diabetic patients could be due to peripheral neuropathy.

Neural regeneration bioprinting approaches are geared towards the re-creation of the microenvironment of peripheral nerves by means of controlled nerve growth factor (NGF) release and scaffold topography. NGF-containing bioinks (e.g., collagen/silk fibroin composite) could promote the proliferation of Schwann cells and axonal growth.[102] Zhang *et al.*[103] reported a novel type of structure of uniaxially aligned nanofiber yarns combined with electrosprayed microparticles encapsulating nerve growth factors, which significantly promote the directional outgrowth of axons, alignment of Schwann cells, and migration of neural stem cells. In addition, co-printing sensory neurons with supporting cells (e.g., adipose-derived stem cells) in bioinks will induce the secretion of neurotrophic factors through stimulation, exerting a synergetic effect on the promotion of nerve regeneration *in vivo*.[104]

Muller *et al.*[105] established a skin model using tissue engineering techniques. A model including epidermal, dermal, and innervated skin was developed by adding keratinocytes, dermal fibroblasts, iPSC-derived sensory neurons, and Schwann cells to a collagen sponge. The co-culture of sensory neurons with Schwann cells was important for the promotion of nerve regeneration in tissue-engineered skin.[105] Hu *et al.*[106] employed inkjet bioprinting to produce adipose stem cells and a GelMA-based patterned nerve conduit with the desired scaffold structure for peripheral nerve regeneration. In addition, *in vivo* models have also shown that nerve guidance conduits with adipose stem cells can successfully promote nerve regeneration. These results indicated an optimistic application of 3D-printed conduits in peripheral nerve repair. These strategies demonstrate the capability of bioprinting to pattern biochemical and mechanical cues for successful nerve regeneration.

6.4. Regeneration of skin appendages during the bioprinting of skin tissue

Hair follicles, pigmentation, and sweat glands are essential for restoring functional and cosmetically acceptable skin, respectively; it is therefore of paramount interest to develop strategies for regenerating and renewing these skin appendages. In mammals, sweat glands play an important role in thermoregulation, and their absence frequently results in impaired regulation of body temperature in humans. As a result, promoting skin regeneration requires continuous repair and development of damaged sweat gland tissues.[107,108] Huang *et al.*[107] manufactured *in vitro* 3D-printed substrates with bioink composites consisting of gelatin and sodium alginate. Meanwhile, mouse epidermal stem cells, plantar dermal homogenates, and human epidermal growth factors were embedded in this 3D matrix to mimic the process of sweat gland regeneration. One *in vivo* study showed that on day 14 after implantation, sweat gland cells differentiated from epidermal stem cells, suggesting the possibility of 3D-printed constructs to restore burned mice's sweat glands.[107] Figure 9A–D shows the promoted regeneration of sweat glands in a thermally injured mouse model after transplantation with induced sweat gland cells (iSGCs), including engineering approaches, assay results on sweat function, histology, and engagement of green fluorescent protein-labeled iSGCs in target-directed regeneration.

Yao *et al.*[105] stimulated mesenchymal stem cells (MSCs) to form sweat glands by using alginate and gelatin hydrogel as a bioink in 3D bioprinting that mimicked regenerative circumstances. The interdisciplinary potential of this technique was emphasized with developments in organoid bioprinting. Researchers from the Hubrecht Institute in the Netherlands have further developed the technique by combining 3D bioprinting with stem cell-derived organoids, which allows for more spatially organized skin models complete with functional appendages such as hair follicles and sweat glands.[109] These results suggested that the directed differentiation of MSCs to sweat glands was possible *in vitro* and *in vivo* within a 3D-printed matrix.[108] Generating hyperpigmented skin tissue that meets patients' expectations for a natural appearance remains a major challenge in the field of 3D bioprinting skin.

Min *et al.*[110] established a 3D bioprinting approach that could create complete hyperpigmented whole skin tissues. A dermal layer composed of printed and crosslinked multilayered collagen hydrogel precursors with fibroblasts was fabricated and neutralized using sodium bicarbonate. Melanocytes and epidermal cells were printed onto the dermal layer in a sequential manner, followed by air-liquid interface culturing in order to promote skin pigmentation. The results indicated that the epidermis, the layer where melanocyte cells (involved in melanin production) reside, showed pigmentation directly underneath the dermal–epidermal junction, resembling freckles.[110] The above findings demonstrate the potential utility of melanocytes

for pigmentation engineering. There are other unanswered questions in these studies, however, such as whether the printed melanocytes will overgrow and how much of the melanin has transferred to neighboring epidermal cells. Moreover, it is not known whether a sustained or long-term improvement in pigmentation is established with the use of 3D-printed skin grafts.

Formation of hair follicles is a prerequisite for the development of tissue-engineered skin with hair. The key issue in hair follicle regeneration is the discovery of such growth factors or further improvement in the capability of seed cells to induce hair proliferation. Wu *et al.*[111] combined dermal papilla cells, hair follicle epithelial cells, dermal sheath cells, and collagen to generate a dermis-mimetic construct. The analogs were subsequently implanted in the subcutaneous region of hairless mice, through which the hair fibers grew out. A recent study demonstrates that the $CD34^+$ population of epidermal stem cells, which is a subset of keratinocytes located in the lower permanent cell nests of the follicular bulge, can induce the generation of new hair follicles and enhance wound healing after transplantation.[112] Recent improvements in stem cell research and 3D bioprinting technologies have facilitated progress in hair follicle regeneration. Abaci *et al.*[110] utilized biomimetic techniques to stimulate the regrowth of hair follicles in skin tissues. This was achieved by replicating the structure of hair follicles using 3D bioprinting technology to create 3D microenvironments. With 3D bioprinting, researchers successfully produced human hair follicle structures with high aspect ratios, a feat that was unattainable with previous processing approaches. **Figure 9E–G** demonstrates how collagen gels patterned with dermal fibroblasts via 3D-printed molds can attain a physiological organization of cells within hair follicles and facilitate hair regrowth, showing the design of hair follicle molds, improved differentiation efficiency, and successful hair growth induction after transplantation.

7. The challenges and future prospects of skin bioprinting

Three-dimensional bioprinting offers remarkable precision, versatility, and effectiveness in tissue engineering, yet high equipment costs and technical complexity continue to limit widespread adoption. Efforts to reduce barriers focus on cost-effective bioink development through careful biomaterial selection and material minimization.[113] Current bioinks remain far from ideal. An optimal formulation must balance mechanical strength, printability, stability, and biocompatibility to sustain cell proliferation and function.[114] Skin's inherent complexity, comprising ECM, multiple cell types, vasculature, nerve endings, and appendages, demands specialized bioinks capable of directing cells toward their specific biological roles. Personalized formulations can reconstitute microvasculature, innervation, pigmentation, and appendages, though each bioprinting method requires its own tailored recipe to preserve structural and physiological integrity. Incorporating human stem cells into bioinks reduces the variety and quantity of cell types required, leveraging their natural capacity for maturation and differentiation.[115] Hydrogels play a central role, mimicking native skin's molecular architecture while providing moisture, nutrient transport, and a porous ECM-analog scaffold that supports cell migration, adhesion, growth, and differentiation.[116] *In vivo* bioprinting holds particular promise for emergency medicine. By combining 3D scanning, computer-aided design, and direct deposition of living skin onto wounds, treatment lag time is dramatically reduced, a critical factor in preventing infection and optimizing recovery. The successful incorporation of functional structures such as sweat glands marks a significant milestone toward full skin functionality. Digital tissue modeling of the damaged site precedes fabrication, with bioink compositions incorporating biomaterials, bioactive compounds, tissue-specific cells, and bioscaffolds carefully optimized for structural integrity, physiological function, and cell viability.[117,118]

Despite this progress, challenges persist across material selection, bioink composition, technical execution, and appendage regeneration.[119] Bioactive molecules, growth factors, stem cells, and multifunctional bioscaffolds all contribute to improving biocompatibility, histocompatibility, and wound healing outcomes. Emerging approaches, including in situ bioprinting, microfluidics, and four-dimensional bioprinting, continue to expand the field's capabilities. Beyond technical challenges, clinical translation faces substantial regulatory and manufacturing hurdles. Bioprinted constructs may be classified as HCT/P products, medical devices, or combination products under FDA regulations, with CE marking under EU MDR imposing similarly rigorous requirements. GMP-compliant manufacturing, autologous cell expansion timelines, allogeneic immune safety concerns, scalability limitations, and insufficient long-term safety and cost-effectiveness data collectively represent critical barriers to widespread clinical deployment.[120] The long-term trajectory points toward artificial intelligence-driven robotic systems capable of autonomously assessing trauma, planning treatment, and executing patient-matched grafts on demand.[121] This convergence promises faster care delivery with optimized functional and aesthetic outcomes at an entirely new level of clinical precision.

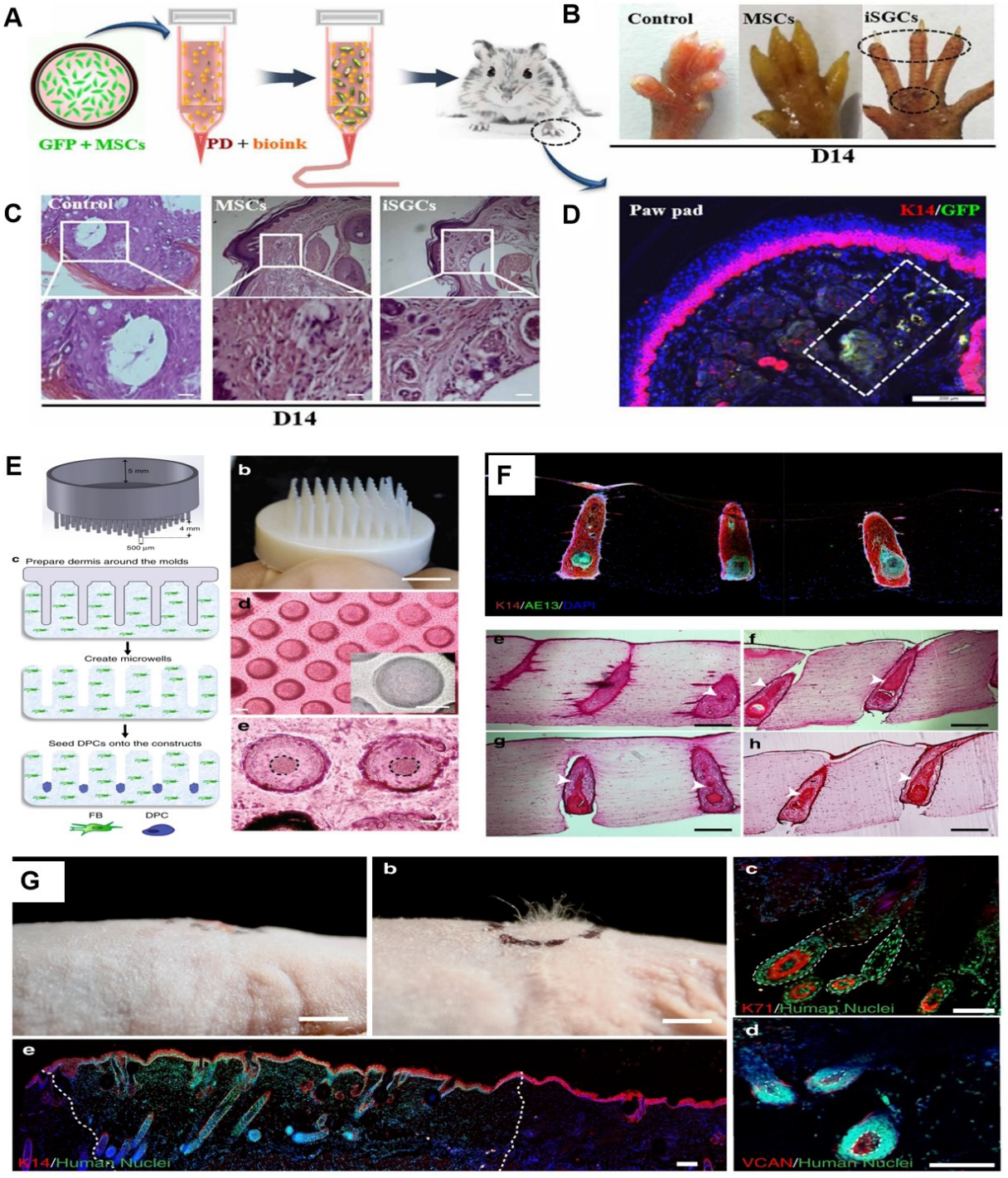

Figure 9. Regeneration of skin appendages using 3D bioprinting strategies. **(A)** Schematic of induced sweat gland cells (iSGCs) engineering and transplantation methodology. **(B)** Sweat assay of mice administered various cell types on day 14. **(C)** Histology of the plantar region comparing control, mesenchymal stem cells (MSCs), and iSGCs groups at Day 14 (scale bar, 200 μm). **(D)** GFP-labeled iSGC participation in targeted sweat gland regeneration (K14, red; GFP, green; DAPI, blue; scale bar, 200 μm). **(E)** Hair follicle mold design with microporous arrays enabling dermal papilla cell (DPC) aggregation, dermis preparation, and microwell formation for DPC seeding. **(F)** Immunostaining showing K14/AE13/DAPI expression and hair follicle morphology after transplantation (e–h). **(G)** Macroscopic view of hair growth before (a) and after (b) transplantation, with immunostaining confirming human-specific K71/Human Nuclei (c), VCAN/Human Nuclei (d), and K14/Human Nuclei (e) expression in regenerated follicles. Reproduced with permission from Ref.[105] Copyright © 2020, American Association for the Advancement of Science, and from Ref.[110] Copyright 2018, Springer Nature Limited.

8. Conclusion

Three-dimensional bioprinting is reshaping regenerative medicine by enabling on-demand fabrication of patient-specific skin grafts, directly addressing donor tissue scarcity and rejection risk. However, no clinical studies have yet demonstrated superiority over conventional grafting, and current implementations remain largely at the proof-of-concept stage. Tailored constructs may improve anatomical fit and cosmetic outcomes. Bioprinted skin models also serve as valuable tools for *in vitro* pharmaceutical testing, surgical training, and pre-operative simulation.

Engineering full skin equivalents remains technically demanding; constructs must replicate epidermis, dermis, subcutaneous tissue, vasculature, nerves, and appendages. Patient-derived stem cells simplify this challenge through their innate regenerative and differentiation capacity, though extensive *ex vivo* expansion limits acute clinical applicability. Composite natural-synthetic polymer systems offer affordable structural support, while growth factor-loaded matrices activate endogenous healing pathways. Critical translational barriers, including GMP manufacturing, regulatory classification, scalability, long-term safety, and cost-effectiveness, must be addressed before clinical deployment. The convergence of bioprinting with AI and robotics holds transformative potential; automated adaptive systems could enhance precision and compress fabrication timelines significantly. Realizing this potential requires sustained interdisciplinary collaboration and rigorous translational validation.

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Conflict of interest

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Ethics approval and consent to participate

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Consent for publication

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Availability of data

The resources that support this review work are available upon request from the corresponding author.

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