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Recent Advances in Stem Cell-Based Therapies for Skin Regeneration

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Abstract

Severe deep tissue injuries, including extensive traumatic injuries, burns, physicochemical damage, or other primary skin loss conditions, continue to present significant clinical challenges. Skin tissue engineering provides promising solutions by developing bioengineered skin substitutes that promote tissue regeneration and enhance patient care. This review paper aims to examine recent advancements and innovations in skin tissue engineering (STE) by exploring traditional treatments and capitalizing on their weaknesses, utilizing stem cell-based therapies in conjunction with biomaterials and scaffolds to enhance skin regeneration. Conventional treatments often lead to the scarring of tissue. The emergence of advanced skin tissue engineering techniques, which integrate stem cells with biomaterial scaffolds to create bio-inks and are printed using inkjet bioprinting, has the potential to provide solutions to current traditional treatments by promoting angiogenesis, paracrine signaling, and extracellular matrix deposition in wound treatment. Stem cells, including mesenchymal (MSCs), epidermal (EpSCs), and induced pluripotent stem cells

(iPSCs), have all demonstrated regenerative potential in independent preclinical studies. These studies have identified limitations, including donor variability, short in vivo survival, and immune response. Hybrid hydrogels combine natural and synthetic hydrogels, such as hyaluronic acid methacrylate (HAMA) and gelatin methacrylate (GelMA), to create a scaffold with both mechanical strength and biocompatibility. Recent progress in 3D bioprinting, particularly ink-jet-based bioprinting, has the potential to overcome the limitations of regenerating vascular networks and skin appendages. Collectively, these clinical applications of stem cells provide a pathway for creating fully functional skin through skin tissue engineering, which restores function, structure, and its appendages.

Keywords: skin tissue engineering, mesenchymal stem cells, epidermal stem cells, hydrogels, 3D bioprinting

Introduction

The skin, the largest organ of the human body, is notorious for being the first primary layer of defence against the outside environment (e.g., pathogens, bacteria, UV rays), as well as helping with body temperature regulation and maintaining homeostasis (Weng et al., 2021). The skin has a complex anatomy that comprises the epidermis, dermis, hypodermis, and appendages (e.g., hair follicles, sweat glands), which enable immune defence and sensory perception (Lotfollahi, 2024). Although skin tissue is known for its remarkable regenerative abilities compared to other tissues, it still falters against severe skin damage such as traumatic injuries, deep burns, and chronic ulcers, leading to fluid loss, life-threatening infections, and

scarring (Takeo et al., 2015). Traditional treatments, such as skin grafts and synthetic substitutes, often fail to fully mimic the functions of human skin, highlighting the need for further advancements in skin tissue engineering, particularly in regenerative cell therapy (Dearman et al., 2021; Dixit et al., 2017). Conventional approaches, such as growth factor treatments, synthetic skin substitutes, autografts, and allografts, to skin repair face significant challenges (Dearman et al., 2021; Dixit et al., 2017). Growth factor treatments, although promising, still suffer from short half-lives and high costs, which limit their clinical efficacy (Ren et al., 2020). Synthetic skin substitutes, such as Matriderm and Integra, often yield poor long-term outcomes, as they fail to integrate with the host's immune system and lack the dynamic remodeling capacity of native tissues (Matei Iordache et al., 2025). Autografts are considered the gold standard for severe burns; however, they are constrained by donor site morbidity and limited availability, while Allografts risk immune rejection at the site during integration (Kenneth et al., 2024). The shortcomings of these conventional approaches highlight the need for innovative solutions that can fully regenerate functional human skin.

Over the past decade, skin tissue engineering (STE) has evolved and progressed through numerous methods of wound healing, continually improving each year. STE leverages stem cells and biomaterials to provide structure and restore function to specific tissues. Unlike traditional and conventional methods, STE aims to recapitulate natural healing processes by promoting cell adhesion, cell proliferation, extracellular matrix (ECM) deposition, and vascularisation (Yu et al., 2019). Stem cells possess promising abilities, including the capacity to differentiate into various cell types (e.g., keratinocytes, fibroblasts, and mesenchymal stem cells), as well as the ability to secrete trophic factors that can

modulate angiogenesis and inflammation. Recent promising successes in STE include the use of mesenchymal stem cells (MSCs) to accelerate wound closure time in diabetic mice by enhancing collagen synthesis and promoting angiogenesis via VEGF secretion (Yu et al., 2023). Moreover, the use of induced pluripotent stem cells (iPSCs) has a similar effect, producing patient-specific solutions. Recent trials have demonstrated the potential of these methods to generate autologous skin grafts for burn victims (Hadzimustafic et al., 2024). Stem cells and biomaterials play complementary roles in skin tissue engineering, providing solutions for the regeneration of functional skin. Types of stem cells include MSCs, induced iPSCs, and epidermal stem cells (EpSCs). MSCs are often derived from bone marrow or fat and are notorious for their ability to reduce inflammation and secrete trophic factors (e.g., VEGF, FGF) (Han et al., 2022), while iPSCs enable patient-specific therapies through the reprogramming of adult somatic cells (Cerneckis et al., 2024).

EpSCs derived from hair follicles also offer an additional autologous option, enabling the maintenance and repair of the skin (Yang et al., 2019). These cells are typically combined with biomaterial scaffolds that are either natural (e.g., fibrin, collagen) or synthetic polymers (PCL, PLGA), each with its own unique properties. Natural polymers are generally more biocompatible, while synthetic polymers exhibit greater mechanical strength (Reddy et al., 2021). Advanced approaches include the use of hybrid materials, such as gelatin methacrylate (GelMA), for 3D printing or decellularized extracellular matrix (ECM), to closely mimic native skin in terms of biocompatibility and mechanical strength. Although progress in skin tissue engineering has been made, one of the main challenges remains the development of vascularization, nerve regeneration, and appendage formation (e.g., sweat glands, hair follicles), driving research into CRISPR-edited stem cells and innovative scaffolds with

controlled growth factor release. This review paper aims to explore the advances of stem cells, as well as their potential roles in skin tissue engineering, focusing on their mechanisms of action, effects with biomaterials, and their translational progress. By analyzing clinical and preclinical studies, I can highlight how stem cell-based strategies can overcome the limitations of current conventional treatments and provide insight into a more effective approach for functional skin regeneration.

Skin Biology and Healing Properties

The skin is a highly complex organ that consists mainly of three critical layers: epidermis, dermis, and hypodermis. These layers are essential as they contain specialized cell types that maintain barrier function, sensory perception, and immune defence. The epidermis comprises keratinocytes and is avascular (Yousef et al., 2024). The epidermis itself can be divided into five different layers: the stratum basale, the stratum spinosum, the stratum granulosum, the stratum lucidum, and the stratum corneum. Four main types of cells reside in these layers: Keratinocytes, melanocytes, Merkel cells, and Langerhans cells (Lotfollahi, 2024). The dermis can be split into two layers, the reticular dermis and the papillary dermis, which appear to be much thicker than the epidermis. The dermis is home to skin appendages, including sweat glands, sebaceous glands, and hair follicles; however, it also provides a pathway for blood vessels and nerves to pass through, allowing for sensation and nutrition (Brown and Krishnamurthy, 2022). The hypodermis (subcutaneous fat) is composed of adipocytes and collagen, allowing it to provide insulation as well as energy storage (Agarwal and Krishnamurthy, 2019). These layers cooperate to create functioning skin, which protects vital organs (Table 1).

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Table 1

Anatomy and physiology of human skin, showing the principal layers and key cell types within them, which are responsible for various functions. This table was created with BioRender.com.

Skin, Anatomy and Physiology

	Layers	Cells, Fibers, Vessels	Function
Epidermis	Stratum Basale Stratum Spinosum Stratum Granulosum Stratum Lucidum Stratum Corneum	Avascular: Keratinocytes; Melanocytes; Merkel cells; Langerhan cells	First layer of defense against the physical environment combating pathogens, UV rays, and chemicals. And also creates a waterproof layer to ensure hydration.
Dermis	Reticulum Dermis Papillary Dermis	Vascular: Mast cells; Macrophages; Fibroblasts; Sweat glands; Sebaceous glands; Hair follicles	Supports the epidermis, provides tensile strength and elasticity improving structure. Also provides sensation from nerve ends.
Hypodermis	Hypodermis	Vascular: Fibroblasts; Adipocytes; Macrophages; Nerves; Blood vessels; Lymphatic nerves;	Deepest layer of the skin providing heat insulation, energy storage and protection of organs.

The skin undergoes a rigorous process to repair damaged areas, ultimately transforming them into healthy, functional skin. It undergoes four main phases: hemostasis, inflammation, proliferation, and remodelling (Almadani et al., 2021). Within minutes to

hours after the occurrence of the injury, platelets aggregate to form a clot and release growth factors, such as PDGF and TGF-β, to recruit immune cells (Opneja et al., 2019). After hemostasis, the wound healing process progresses to the inflammatory stage, which typically takes a couple of days. During this period, macrophages and neutrophils clear pathogens and debris from the wound (Koh & DiPietro, 2011). Moving on with proliferation, which could span weeks, fibroblasts deposit collagen, glycosaminoglycans, fibronectins, and much more to form a new ECM. Keratinocytes would then migrate to the wound, allowing for wound closure, and angiogenesis will be established, creating new blood vessels (Tracy et al., 2016). After this, the skin would progress through the remodelling phase spanning months to years as collagen fibers are reorganised and cross-linked which can often lead to non-functioning scar tissue rather than a complete restoration of functional skin, in many cases, this could lead to the healed skin only having about 80% - 85% of its original tensile strength (Mathew-Steiner et al., 2021). This is the primary issue with natural skin regeneration, as it often fails to produce functional skin.

The frequent failure to achieve the growth of skin appendages, such as sweat glands and hair follicles, or to fully regenerate after intervention highlights the limitations of natural healing. Chronic wounds, such as diabetic foot ulcers and pressure sores, are a prime example of the failure to renew and grow functional skin, characterized by a stalling state known as chronic inflammation that actively prevents wound healing. Three key factors have repeated played a significant role in maintaining this pathological state, first would be frequent infections, where bacterial biofilms form a protective barrier that resists both antibiotics as well as immune clearance which constantly reactivates the inflammation response; ischemia also known as poor blood flow, is common in diseases such as diabetes which deprives the

tissues of nutrients and oxygen that are essential in cell proliferation and tissue building; and third, cellular senescence, also known as non-dividing cells can secrete inflammatory cytokines and matrix degrading enzymes; a phenotype known as senescence associated secretory phenotype of SASP, which damages and degrades the extracellular matrix (Zhao et al., 2016). This challenge of natural regeneration to achieve complete healing without scarring creates a demand for STE.

Skin tissue engineering (STE)

STE helps to overcome these shortcomings by using stem cells to modulate hostile wound environments, simulate angiogenesis, and suppress chronic inflammation. This would be achieved by combining stem cells with biomaterial scaffolds to provide a guiding structure for the growth of functional, vascularized tissue, thereby improving current natural human healing outcomes.

Type of Stem Cells in STE

STE addresses key issues and limitations of natural healing processes and shortcomings of conventional treatments, such as allografts, growth hormone treatments, and synthetic skin substitutes, by leveraging the unique abilities of different types of stem cells. The three main types of stem cells that have revolutionized STE would be mesenchymal stem cells, induced pluripotent stem cells, and epidermal stem cells. These types of stem cells aim to provide a solution for limiting factors that hinder the healing of functional skin, such as ischemia, chronic inflammation, scarring, and failure of skin appendage regeneration (Nourian Dehkordi et al., 2019).

Mesenchymal Stem Cells (MSCs)

MSCs are multipotent cells that are most isolated and extracted from bone marrow, the umbilical cord, or adipose tissue. MSCs are essential and valuable as they possess the mechanism to have paracrine activity (Gerdfaramarzi et al., 2022). MSCs secrete bioactive factors or molecules such as TGF-β (transforming growth factor-beta), VEGF (vascular endothelial growth factor and FGF (fibroblast growth factor) that interact with the tissues and cells around them to reduce inflammation, stimulate collagen production, and promote angiogenesis (Bian et al., 2022; Lee et al, 2016). Although some studies have shown that MSCs can differentiate into fibroblast-like cells under specific microenvironmental cues, their overall role in Skin Tissue Engineering is as paracrine regulators that help with regeneration by contributing to the secretion of their bioactive factors to help with wound closure and more due to their ability to stimulate growth (Maxson et al., 2012). Studies have shown that MSC-loaded decellularized grafts can accelerate wound closure in diabetic mouse models through enhanced collagen synthesis, promotion of neovascularisation, and less oxidative stress, as demonstrated through 13±0.37 days where this was applied, compared to 20±0.71 days with the scaffold-only group and 27±0.44 days in the no-treatment group (Du et al., 2022).

Induced-Pluripotent Stem Cells (iPSCs)

iPSCs are made from the reprogramming of adult somatic cells, such as skin fibroblasts, where they are introduced to specific reprogramming or transcription factors called Yamanaka factors, including Oct4, Sox2, Klf4, and c-Myc, to force the cell to revert

into its embryonic state discovered in mice in the University of Japan in 2006 (Takahashi & Yamanaka, 2006). Since IPSCs can be reverted into an embryonic-like state, they can differentiate into any cell type in the human body, including functional cells, fibroblasts, melanocytes, and vascular endothelial cells, within the context of skin. Since IPSCs are first extracted from patients, the use of these stem cells would be highly personalized, eliminating most factors of immune rejection (Ortuño-Costela et al., 2019). In burn therapy, IPSC-derived keratinocyte sheets have overall demonstrated a positive outcome after transplantation onto second-degree burns, showing integration with host tissue, vascularization, and a reduced risk of immune rejection due to the ability to produce IPSCs autologously (Wu et al., 2023). Nonetheless, concerns persist about using this technology, as it can lead to risks such as genetic instability, tumorigenicity, and the need for stringent quality control in reprogramming protocols (Pasi et al., 2011; Liang et al., 2013).

1.1.1. Epidermal Stem Cells (EpSCs)

EpSCs are formally used for both skin repair and maintenance. EpSCs are located in the basal layer of the epidermis and the hair follicle bulge. EpSCs are primarily known for their roles in wound re-epithelialization, maintaining homeostasis, promoting tissue renewal, and mediating paracrine signaling (Yang et al., 2019; Blanpain & Fuchs, 2006; Balañá, 2015). EpSCs were first found helpful in the 1980s, when Howard Green used these cells to create cultured epithelial autografts for burn patients. Afterwards, EpSCs were recognized for their potential in regenerative medicine, which expanded the use of these cells for therapeutic uses (Pitt, Yoshiyuki Mochida, & Makoto Senoo, 2023). EpSCs are currently used in clinical trials, specifically in burn therapy. Epidermal stem/progenitor cells containing autologous

products, including cultured epithelial autografts (CEAs) and autologous skin cell suspensions (ASCS), have consistently shown positive outcomes, as they possess the ability to rapidly re-epithelialize and integrate into well-vascularized wound beds. Due to these treatments being autologous, they carry less risk of immune rejection compared to other grafts, such as allogenic grafts (Milner, 2023; Kahn et al., 2024). Notably, in a randomized CTP001-5 trial, ASCS had a 97% reduction in donor skin area compared to meshed split-thickness autograft (U.S. Food & Drug Administration, 2018). It is essential to note that ASCS provides a mixed basal keratinocyte and fibroblast-enriched population rather than pure EpSCs (U.S. Food & Drug Administration, 2018).

The combination of all three stem cells cooperates for optimal skin regeneration. MSCs modulate hostile wound environments and stimulate repair via paracrine secretion of trophic factors (Lee et al., 2016), IPSCs provide a personalized cell source for bioengineered grafts and sheets (Ortuño-Costela et al., 2019), and EpSCs help with the regeneration of skin appendages as well as the epidermis (Pitt et al., 2023). When supplemented with biomaterial scaffolds, these stem cells can be mechanically guided to create functional skin rather than merely wound closure, as wound closure itself carries a high risk of scarring and other complications (Kaur et al., 2019). By combining stem cells and biomaterials, the potential applications of this approach could lead to the development of advanced techniques for solving the crisis of regenerating functional skin.

Recent Advancements and Innovations in STE

Scaffolds

Scaffolds derived from biomaterials are the architectural backbone of STE, which is used to mimic the native ECM as closely as possible and to provide critical cellular activities such as proliferation, adhesion, differentiation, and tissue organization. There are different types of scaffolds, including natural (e.g., collagen, fibrin, hyaluronic acid, and chitosan), synthetic (e.g., PCL, PEGDA, and PLGA), and hybrid scaffolds that combine both natural and synthetic components. Scaffolds and biomaterials are often used for a moment to resemble the ECMs, delivering cells and bioactive molecules to wound sites while guiding the growth and regeneration of functional skin layers, as these synthetic ECMs would be replaced by the patient's own cells and ECMs (Riha et al., 2021; Kaur et al., 2019). Scaffolds made by biomaterials facilitate wound healing and closure by maintaining an optimal environment, protecting against external pathogens, promoting angiogenesis, and reducing scarring through controlled degradation and mechanical support. Moreover, these scaffolds are also beneficial as they facilitate guiding cell behaviour and possess the ability to degrade over time (Golebiowska et al., 2024). Without scaffolds, cells would often fail to engraft, migrate, or form organized tissues, leading to poor therapeutic outcomes such as scarring (Chan & Leong, 2008).

Scaffolds Derived from Synthetic Biomaterials

Synthetic hydrogel scaffolds are engineered from man-made polymers, such as polyethylene glycol (PEG) (Zustiak & Leach, 2010), polylactic-co-glycolic acid (PLGA), and polyvinyl alcohol (PVA) (Liang et al., 2024). These materials offer precise control over mechanical properties, degradation rates, and architecture, making them highly reproducible for clinical use. For example, PEG hydrogels are often used for their crosslinking factor,

which allows them to incorporate bioactive peptides such as arginine-glycine-aspartic acid (RGD(Arg-Gly-Asp)) to enhance cell adhesion, a critical component of wound healing (Bellis, 2011). Synthetic scaffolds, such as PLGA scaffolds, offer excellent mechanical strength and controlled release of growth factors, as demonstrated in studies treating full-thickness burns in rodent models (Jiao et al., 2021). However, synthetic hydrogels often lack innate bioactivity, which prevents them from supporting cell interactions (Mancha Sánchez et al., 2020).

Scaffolds Derived from Natural Biomaterials

Natural hydrogel scaffolds, derived from biological sources such as fibrin, hyaluronic acid, chitosan, and collagen, inherently possess biocompatibility properties, low immunogenicity, and bioactive motifs that promote signaling and cell recognition. The promotion of signaling and cell recognition is essential as it allows for spatial organization, differentiation, and functional integration of cells to form a proposed structure, such as the skin's dermal layers. Collagen-based scaffolds (e.g., Integra) closely resemble the native dermal ECM and have been clinically approved for burn and chronic wound treatment (Zhao et al., 2023). Other instances of the use of natural hydrogel scaffolds for clinical purposes would be fibrin hydrogels, derived from blood plasma, which mimic the provisional wound matrix and have been used to deliver MSCs in diabetic murine wounds, which significantly improved cell retention and angiogenesis in regeneration and recovery (Hopfner et al., 2018). Despite the advantages of natural hydrogel scaffolds, they still struggle with creating variability, rapid degradation, and limited mechanical strength (Gounden & Singh, 2024; Ansari & Darvishi, 2024).

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Scaffolds Derived from Hybrid Biomaterials

Hybrid hydrogel scaffolds combine natural and synthetic materials to leverage the properties and strengths of each, creating a superior hydrogel scaffold (Ansari & Darvishi, 2024). For instance, gelatin methacrylate (GelMA) combines the bioactivity of gelatin with the photopolymerization of synthetic methacrylate groups, enabling the 3D printing of structures with enhanced cell viability (Yue et al., 2015). These hybrids address key limitations in both natural and synthetic hydrogels, as they provide mechanical strength while also supporting the biological functions of cells, such as migration and vascularization. Tested in mice, Hybrid hydrogels have demonstrated a higher level of performance in promoting wound healing and closure, resulting in reduced scarring compared to single-component hydrogel scaffolds, such as natural or synthetic ones (Xu et al., 2023).

Application of Hydrogels with Stem Cells

A significant problem with MSC therapy is that it has a substantial loss of transplanted cells due to hostile wound conditions such as hypoxia, nutrient deprivation, inflammation, and oxidative stress. A specific example illustrating this is that at 24 hours of saline delivery, only 10% of cells were retained. In contrast, the use of injectable hydrogels retained 50-60% of cells, representing a significant increase from 10%. This considerable difference demonstrates the capabilities of hydrogels, specifically hybrid hydrogels (Roche et al., 2014).

Hydrogels essentially create a hydrated three-dimensional environment that mimics the native extracellular matrix where cells proliferate, migrate, adhere, and differentiate. This

improves cell adhesion, viability, and paracrine signaling. Specifically in diabetic mouse wounds, delivering MSCs within a thermosensitive hydrogel cut the day 7 residual wound area to 24.6 ± 4.21% versus 66.5 ± 6.67% with hydrogel alone, and 79.54 ± 5.92% in untreated controls, alongside greater keratinocyte proliferations, enhanced differentiation, and reduced scarring by day 35 (Chen et al., 2015). Although natural hydrogels are mostly biocompatible, their mechanical weakness proves a significant limitation. Synthetic hydrogels offer excellent mechanical strength; however, they have weaknesses, including biocompatibility issues. The introduction of hybrid hydrogels addresses these two essential problems, as they possess abilities that provide great mechanical strength and structure while also being biocompatible. An example of greater MSC retention in diabetic wounds would be PEGDA/sodium alginate/collagen-l composite carrying different types of perinatal MSCs in db/db diabetic mice, which demonstrated a two-fold increase in MSC retention in diabetic wounds, with accelerated wound re-epithelialization and neovascularisation via PI3K/AKT pathway activation, which is a key intracellular signaling cascade used to promote cell proliferation, migration, survival, and angiogenesis, making it essential in tissue regeneration and repair. The MSC hydrogel groups showed faster wound closure in the early healing phases (days 3 to 5), and by day 10, most wounds were nearly closed, whilst the control group still had 9.2 ± 4.0% of the wound area remaining. Further histological analysis showed thicker granulation tissue and denser vascular networks in the MSC hydrogel groups (Huang et al., 2025).

Another example related to this is a study that investigated an arginine-based polyester amide/chitosan hybrid hydrogel (AC gel) in a mouse model of third-degree burns.

The use of MSC-loaded AC hydrogels helps maintain cell viability (~95% cell viability in vitro at day 6). With improved survival, this would lead to better healing, allowing in vivo wounds to close at a faster rate by day 8 compared to medium controls. Additionally, it would exhibit more re-epithelialization and a larger tissue granulation area. Following this, Immunostaining was performed further to demonstrate a substantial increase in CD31 blood vessel area, confirming its properties of promoting angiogenesis. The experiments demonstrate the application of stem cells in conjunction with hybrid hydrogels to encourage the development of vascularized tissue during burn repair, as well as to enhance the viability of MSCs (Alapure et al., 2018).

In addition to structural benefits such as wound closure, hydrogels, especially those functionalized with pro-adhesive RGD (Arg-Gly-Asp) peptides, enhance MSC survival and the secretion of proangiogenic factors. A study reported that dissociated MSCs in RGD (Arg-Gly-Asp)- modified alginate had a 4.2-fold higher DNA content compared to unmodified gels, indicating improved MSC survival. Meanwhile, MSC spheroids in unmodified gels had 1.4-fold more VEGF than dissociated cells in RGD (Arg-Gly-Asp) gels. On a per-cell basis, VEGF secretion was 1.8-fold higher in spheroids in RGD (Arg-Gly-Asp) when compared to unmodified alginate; importantly, total angiogenic protein output in spheroids was 2.5-fold and 5-fold higher than dissociated and unmodified controls (Ho et al., 2016). Overall, these findings underscore the transformative potential of hydrogels, specifically hybrid hydrogel formulations for MSC-based skin repair. By mitigating the loss of MSCs from injection, augmenting survival in inflammatory conditions such as wounds, and enhancing paracrine function, this highlights the significant importance of hybrid hydrogels, as they outcompete

single-component systems in preclinical models, including mice (Rustad et al., 2012). These results provide a compelling rationale for further development of hydrogel MSC composites toward effective clinical translation for treating chronic wounds, severe burns, and other conditions (Hopfner et al., 2018).

Recent Approaches

Three-dimensional (3D) bioprinting has emerged as a powerful innovation in skin tissue engineering and regenerative medicine, offering the ability to construct and design layer-by-layer living skin constructs that replicate the architecture, functionality, and structure of native skin more effectively than conventional techniques for scaffold seeding (He et al., 2018). 3D Bioprinting's primary role is to integrate cells, biomaterials, and signaling molecules into precisely organized layers and structures, which overcome conventional methods of skin graft approaches that fail to restore functional skin fully, mostly its appendages (Cui et al., 2016).

3D Bioprinting has been further developed into various versions, each with unique strengths and limitations. The most used technique is extrusion-based bioprinting, as it allows the deposition of highly viscous, cell-laden hydrogels in continuous filaments. This method is excellent as it supports multicellular constructs; however, it subjects cells to stress, which often results in lowering viability compared to other 3D Bioprinting strategies (Malekpour & Chen, 2022). Laser-assisted bioprinting is another type of 3D bioprinting that offers exceptional resolution and high cell viability by propelling cell-laden droplets with laser pulses. However, its weaknesses include being costly and having low clinical scalability

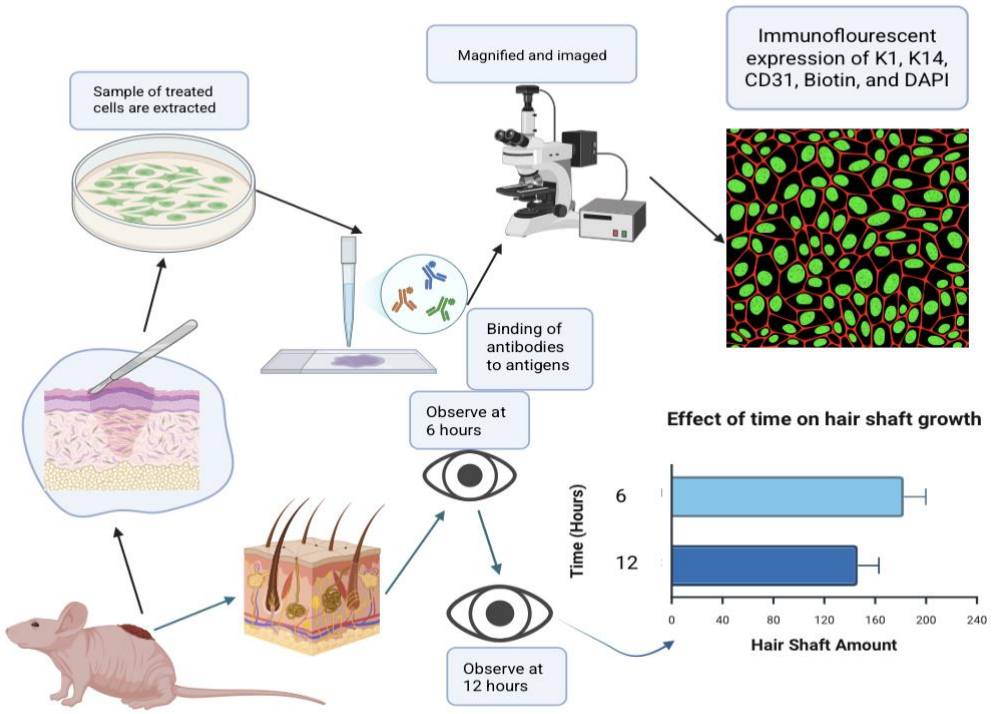
(Guillotin et al., 2010). Another version of 3D bioprinting could also be inkjet bioprinting as it combines, resolution, speed and accessibility, this version relies on non-contact, droplet-based deposition of low viscosity bioinks which ensures reduced shear stress, higher cell viability, and the ability to rapidly pattern multiple bioinks simultaneously eliminating the problem of scalability (Xu et al., 2022; Kavita Kumari Thakur et al., 2023).

The primary use of inkjet bioprinting would be its potential to address major unsolved issues in skin regeneration. This would include the production of fully functional skin with skin appendages such as hair follicles, sweat glands, and sebaceous glands. Conventional grafts and even stem cell therapies still result in tissue scarring, which needs to be addressed (Xu et al., 2022; Kavita Kumari Thakur et al., 2023). In a recent study by Ma et al. (2025), the authors demonstrated that hybrid hydrogel-based inkjet bioprinting can overcome this challenge, achieving functional skin appendages in murine models, specifically mice. This specific study designed prefabricated artificial skin using 5% GelMA and 0.5% hyaluronic acid methacrylate (HAMA) hybrid hydrogels embedded with epidermal stem cells (EpSCs) and skin-derived precursors (SKPs), which are a type of multipotent stem cells found in the dermis of adult skin (Ma et al., 2025). The reason for selecting these cell types was that the study aimed to replicate the epithelial-mesenchymal interactions, which are crucial for the growth of hair follicles and sweat glands. Rheological analysis confirmed that the GelMA/HAMA hybrid exhibited excellent printability, stability, and swelling properties, which sustained cell viability during printing, as tested over a frequency range of 0.1 to 10 rad/s (Ma et al., 2025). Regarding in vivo experiments, the investigation used full-thickness wounds on nude mice treated with bio-printed constructs, which showed rapid wound closure

as well as the integration of host tissue. By day 14 in qualitative results, wounds treated with cell-laden GelMA/HAMA grafts demonstrated near-complete re-epithelialization and an organized dermal structure, reinforcing the healing effects of 3D bioprinting in producing functional skin, as shown through histological staining (Ma et al., 2025) (Figure 1).

Figure 1

This figure highlights that graft-treated wounds developed a multi-layered, stratified epidermis and a structured dermis. The hydrogel control demonstrated thinner, irregular epidermal layers and poorly organised dermal structure. This figure was created with BioRender.com.



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To further validate epidermal renewal, differentiation, and angiogenesis, immunostaining must be imaged through fluorescent microscopy compared with control hydrogels. K14, K1, and CD31 were all used to validate this. K14, used to identify EpSCs, was strongly expressed in the basal layer of the graft-treated wound, indicating progenitor activity. K1 is used to determine the differentiated keratinocytes present in the upper epidermal layer, demonstrating successful epidermal stratification (Guo et al., 2020; Ma et al., 2025). CD31 is used to identify endothelial cells, which line the inner walls of blood vessels. The presence of CD31 staining indicates the density of blood vessels in graft-treated wounds, suggesting the growth of new blood vessels (Pusztaszeri et al., 2006; Ma et al., 2025). Additionally, Biotin was also expressed, indicating the regeneration of sebaceous glands (Ma et al., 2025). Hair growth was also more prominent in the 6-hour culture time compared to the 12-hour culture time, as at 6 hours, there were 800 hair shafts, whereas at 12 hours, there were only 200 hair shafts. The use of 5% GelMA and 0.5% HAMA, infused with EpSCs, restored epidermal stratification, as assessed by K14 and K1 immunostaining. Additionally, it promoted angiogenesis, as indicated by CD31 immunostaining, and increased hair shaft growth. These outcomes were absent in control groups, where hydrogels remained singular, failing to produce and regenerate appendages or develop a functional skin structure (Ma et al., 2025). Figure 1 summarizes these details in a graphical abstract.

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Challenges and Future Direction

Challenges

Despite the promising advances in STE, several significant limitations remain before these methods can be translated into widespread clinical use. The main challenge lies in translating laboratory research and findings into clinical trials, which is constrained by the high costs associated with these methods, primarily including stem cell isolation, expansion, culture, and 3D bioprinting technologies such as Inkjet bioprinting. These extraordinary expenses, combined with the need for proper and specialized biomanufacturing facilities, currently hinder the scalability of therapies for a broader patient population (Yu et al., 2019).

Additionally, another major problem would be the ethical and regulatory bodies. The use of stem cells in regenerative medicine requires extensive oversight, as this allows for the prevention of serious health risks such as infections, tumor formation, and inflammation. Regulatory bodies such as the FDA demand extensive preclinical safety data, and finding these approval pathways is time-consuming and resource-intensive. Moreover, sourcing certain cell types also raises ethical concerns, particularly with the use of fetal and perinatal tissues, which further intensifies the approval process for the FDA (Belsky & Smiell, 2020).

The use of stem cells poses specific risks and side effects, which are significant concerns. However, stem cells such as MSCs are widely studied and researched. These cells still have side effects. MSCs are renowned for their ability to exhibit paracrine activity and immunomodulatory effects; however, studies have shown risks, including ectopic differentiation, reduced potency in long-term culture, and immune activation (Lalu et al.,

2012; Galipeau & Sensébé, 2018). Moreover, MSCs also have donor variability, which means that their regenerative performance relies on the donor's health. These side effects can also lead to fibrosis or ectopic tissue formation, which compromises skin graft quality when MSCs are poorly controlled during the differentiation stage (Lalu et al., 2012; Galipeau & Sensébé, 2018).

EpSCs reside in the basal layer of the epidermis and the hair follicle bulge. Although EpSCs have immense potential based on previous original studies, these stem cells still present risks. Due to EpSCs' high proliferative capacity, they can undergo aberrant or uncontrolled expansion when not rigorously regulated, which can potentially lead to dysplasia or non-functional epidermal tissue (Balañá, 2015). Moreover, another major issue with stem cells is that they have a short lifespan, specifically only up to a couple of days in vivo, which is most likely caused by harsh wound conditions such as inflammation, oxidative stress, or hypoxia. However, it can increase its population through differentiation and self-renewal (Hopfner et al., 2018).

Overall, these limitations highlight the gap between preclinical successes and clinical feasibility, underscoring the need for safety profiling and observation of stem cell therapies, as well as standardized protocols to ensure predictable and reliable outcomes across a diverse patient population. Rather than focusing on cost reduction strategies for scalability, this approach should prioritize the development of effective treatments.

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Future Directions

The clinical translation of skin tissue engineering (STE) faces several pressing challenges that must be addressed before stem cell-based therapies can become standard clinical practice (Heinrich et al., 2019). The most significant pressing issue is the ethical and regulatory bodies, which include the U.S. Food and Drug Administration (FDA) and the Good Manufacturing Practice (GMP) guidelines. Although Mesenchymal stem cells and epidermal stem cells are not subject to the same level of ethical debate regarding sourcing as embryonic stem cells, clinical-grade production requires rigorous quality control, which will be assessed by these large international regulatory bodies (Gerdfaramarzi et al., 2022). Moreover, STE also faces challenges, including scalability. The process of cell isolation, expansion, and long-term monitoring is exceptionally costly, hindering the progress from preclinical to human trials. Thus, the combination of streamlined regulatory frameworks, alongside public and private partnerships, will be essential for the progress of STE clinical translation (Lalu et al., 2012) (Galipeau & Sensébé, 2018).

Another important future direction that needs to be addressed would be the limitations of MSCs and EpSCs-based therapies. To combat this limitation, we could implement genetic modification tools such as CRISPR-Cas9. Studies have shown that CRISPR-Cas9 has the potential to reduce these limitations, as in a specific study, the TLR4 gene was knocked out of MSCs in a lung injury sample, and this created a positive effect as the MSC changed its phenotype to anti-inflammatory instead of pro-inflammatory, which overall improved survival (Wang et al., 2010). By applying this approach to STE, the limitations of MSCs can be mitigated. EpSCs, although valuable for epidermal regeneration and stratification, still

pose risks such as hyperproliferation and dysplasia under prolonged stimulation. To potentially limit the probability of hyperproliferation and dysplasia, careful monitoring of proliferation markers and the cell itself will be required to balance its regenerative capabilities with safety (Balañá, 2015).

Additionally, 4D bioprinting offers a promising pathway to overcome the transient survival of transplanted stem cells. The 4th dimension represents time. In 3D Bioprinting, stem cells often survive for only a few weeks after grafting, which limits their long-term regenerative impact. By contrast, 4D Bioprinting integrates innovative, stimuli-responsive biomaterials that can adapt to environmental stimuli (Morouço et al., 2017). These biomaterials can respond to environmental cues, such as temperature, pH level, or enzymatic activity, enabling the effective release of growth factors and other substances. These materials are engineered to biodegrade, which maintains the regenerative support during the critical stages of wound healing before being eventually replaced by the native extracellular matrix (Wang et al., 2024). 4D Bioprinting aims to mimic stem cell activity after stem cell decline, allowing for a more extended period before being replaced by the native extracellular matrix, thereby promoting tissue organization and reducing inflammation.

Conclusion

Advances in skin tissue engineering underscore the combined potential of stem cells and biomaterials to address the current limitations of traditional wound treatments. Stem cells possess unique regenerative benefits, while hybrid hydrogels offer both biological activity and mechanical strength/ structural support to enhance the survival and functionality of hydrogels. Techniques such as Ink-jet-based 3D bioprinting enable the precise spatial

placement of cells within hydrogel scaffolds, resulting in layered constructs that mimic native skin. In preclinical studies, hybrid hydrogels combining MSCs and EpSCs, along with inkjet bioprinting, enabled researchers to regenerate appendages such as hair follicles, sebaceous glands, and sweat glands. Despite these advances, translation into clinical settings remains limited due to costs, regulatory bodies, and the potential for stem cell-specific side effects. Looking towards the future, the genetic modification of MSCs and the recent development of 4D biomaterials that can adapt to environmental stimuli and respond over time may help provide solutions to these limitations, offering the possibility of long-term functional regeneration of skin and skin appendages.

References

Agarwal, S. and Krishnamurthy, K. (2019). *Histology, Skin*. [online] Nih.gov. Available at: https://www.ncbi.nlm.nih.gov/books/NBK537325/.

Alapure, B.V., Lu, Y., He, M., Chu, C.-C., Peng, H., Muhale, F., Brewerton, Y.-L., Bunnell, B. and Hong, S. (2018). Accelerate Healing of Severe Burn Wounds by Mouse Bone Marrow Mesenchymal Stem Cell-Seeded Biodegradable Hydrogel Scaffold Synthesized from Arginine-Based Poly(ester amide) and Chitosan. *Stem Cells and Development*, 27(23), pp.1605–1620. doi:https://doi.org/10.1089/scd.2018.0106.

Aleksandra Golebiowska, Intravaia, J.T., Sathe, V.M., Kumbar, S.G. and Nukavarapu, S.P. (2024). Decellularized extracellular matrix biomaterials for regenerative therapies: Advances, challenges and clinical prospects. *Bioactive Materials*, 32, pp.98–123. doi:https://doi.org/10.1016/j.bioactmat.2023.09.017.

Almadani, Y.H., Vorstenbosch, J., Davison, P. and Murphy, A. (2021). Wound Healing: A Comprehensive Review. *Seminars in Plastic Surgery*, [online] 35(3). doi:https://doi.org/10.1055/s-0041-1731791.

Ansari, M. and Darvishi, A. (2024). A review of the current state of natural biomaterials in wound healing applications. *Frontiers in bioengineering and biotechnology*, 12. doi:https://doi.org/10.3389/fbioe.2024.1309541.

Balañá, M.E. (2015). Epidermal stem cells and skin tissue engineering in hair follicle regeneration. *World Journal of Stem Cells*, 7(4), p.711. doi:https://doi.org/10.4252/wjsc.v7.i4.711.

Bellis, S.L. (2011). Advantages of RGD peptides for directing cell association with biomaterials. *Biomaterials*, [online] 32(18), pp.4205–4210. doi:https://doi.org/10.1016/j.biomaterials.2011.02.029.

Belsky, K. and Smiell, J. (2020). Navigating the Regulatory Pathways and Requirements for Tissue-Engineered Products in the Treatment of Burns in the United States. *Journal of Burn Care & Research*. doi:https://doi.org/10.1093/jbcr/iraa210.

Bian, D., Wu, Y., Song, G., Azizi, R. and Zamani, A. (2022). The application of mesenchymal stromal cells (MSCs) and their derivative exosome in skin wound healing: a comprehensive review. *Stem Cell Research & Therapy*, 13(1). doi:https://doi.org/10.1186/s13287-021-02697-9.

Blanpain, C. and Fuchs, E. (2006). Epidermal Stem Cells of the Skin. *Annual Review of Cell and Developmental Biology*, [online] 22(1), pp.339–373. doi:https://doi.org/10.1146/annurev.cellbio.22.010305.104357.

Brown, T.M. and Krishnamurthy, K. (2022). *Histology, Dermis*. [online] Nih.gov. Available at: https://www.ncbi.nlm.nih.gov/books/NBK535346/.

Cerneckis, J., Cai, H. and Shi, Y. (2024). Induced Pluripotent Stem Cells (iPSCs): Molecular Mechanisms of Induction and Applications. *Signal Transduction and Targeted Therapy*, 9(1). doi:https://doi.org/10.1038/s41392-024-01809-0.

Chan, B.P. and Leong, K.W. (2008). Scaffolding in tissue engineering: general approaches and tissue-specific considerations. *European Spine Journal*, [online] 17(S4), pp.467–479. doi:https://doi.org/10.1007/s00586-008-0745-3.

Chen, S., Shi, J., Zhang, M., Chen, Y., Wang, X., Zhang, L., Tian, Z., Yan, Y., Li, Q., Zhong, W., Xing, M., Zhang, L. and Zhang, L. (2015). Mesenchymal stem cell-laden anti-inflammatory hydrogel enhances diabetic wound healing. *Scientific Reports*, 5(1). doi:https://doi.org/10.1038/srep18104.

Cui, H., Nowicki, M., Fisher, J.P. and Zhang, L.G. (2016). 3D Bioprinting for Organ Regeneration. *Advanced Healthcare Materials*, [online] 6(1), p.1601118. doi:https://doi.org/10.1002/adhm.201601118.

Dearman, B.L., Boyce, S.T. and Greenwood, J.E. (2021). Advances in Skin Tissue Bioengineering and the Challenges of Clinical Translation. *Frontiers in Surgery*, [online] 8, p.640879. doi:https://doi.org/10.3389/fsurg.2021.640879.

Dixit, S., Baganizi, D.R., Sahu, R., Dosunmu, E., Chaudhari, A., Vig, K., Pillai, S.R., Singh, S.R. and Dennis, V.A. (2017). Immunological challenges associated with artificial skin grafts: available solutions and stem cells in future design of synthetic skin. *Journal of Biological Engineering*, [online] 11. doi:https://doi.org/10.1186/s13036-017-0089-9.

Du, S., Zeugolis, D.I. and O'Brien, T. (2022). Scaffold-based delivery of mesenchymal stromal cells to diabetic wounds. *Stem Cell Research & Therapy*, 13(1). doi:https://doi.org/10.1186/s13287-022-03115-4.

Galipeau, J. and Sensébé, L. (2018). Mesenchymal Stromal Cells: Clinical Challenges and Therapeutic Opportunities. *Cell Stem Cell*, 22(6), pp.824–833. doi:https://doi.org/10.1016/j.stem.2018.05.004.

Gerdfaramarzi, M.S., Bazmi, S., Kiani, M., Afshar, L., Fadavi, M. and Enjoo, S.A. (2022). Ethical challenges of cord blood banks: a scoping review. *Journal of Medicine and Life*, [online] 15(6). doi:https://doi.org/10.25122/jml-2021-0162.

Gounden, V. and Singh, M. (2024). Hydrogels and Wound Healing: Current and Future Prospects. *Gels*, [online] 10(1), pp.43–43. doi:https://doi.org/10.3390/gels10010043.

Guillotin, B., Souquet, A., Catros, S., Duocastella, M., Pippenger, B., Bellance, S., Bareille, R., Rémy, M., Bordenave, L., Amédée, J. and Guillemot, F. (2010). Laser assisted bioprinting of engineered tissue with high cell density and microscale organization. *Biomaterials*, 31(28), pp.7250–7256. doi:https://doi.org/10.1016/j.biomaterials.2010.05.055.

Guo, Y., Redmond, C.J., Leacock, K.A., Brovkina, M.V., Ji, S., Vinod Jaskula-Ranga and Coulombe, P.A. (2020). Keratin 14-dependent disulfides regulate epidermal homeostasis and barrier function via 14-3-3σ and YAP1. *eLife*, [online] 9. doi:https://doi.org/10.7554/elife.53165.

Hadzimustafic, N., D'Elia, A., Shamoun, V. and Siba Haykal (2024). Human-Induced Pluripotent Stem Cells in Plastic and Reconstructive Surgery. *International Journal of Molecular Sciences*, 25(3), pp.1863–1863. doi:https://doi.org/10.3390/ijms25031863.

Han, Y., Yang, J., Fang, J., Zhou, Y., Candi, E., Wang, J., Hua, D., Shao, C. and Shi, Y. (2022). The secretion profile of mesenchymal stem cells and potential applications in treating human diseases. *Signal Transduction and Targeted Therapy*, 7(1), pp.1–19. doi:https://doi.org/10.1038/s41392-022-00932-0.

He, P., Zhao, J., Zhang, J., Li, B., Gou, Z., Gou, M. and Li, X. (2018). Bioprinting of skin constructs for wound healing. *Burns & Trauma*, [online] 6(1). doi:https://doi.org/10.1186/s41038-017-0104-x.

Heinrich, M.A., Liu, W., Jimenez, A., Yang, J., Akpek, A., Liu, X., Pi, Q., Mu, X., Hu, N., Schiffelers, R.M., Prakash, J., Xie, J. and Zhang, Y.S. (2019). 3D Bioprinting: from Benches to Translational Applications. *Small (Weinheim an Der Bergstrasse, Germany)*, [online] 15(23), p.e1805510. doi:https://doi.org/10.1002/smll.201805510.

Ho, S.S., Murphy, K.C., Binder, B.Y.K., Vissers, C.B. and Leach, J.K. (2016). Increased Survival and Function of Mesenchymal Stem Cell Spheroids Entrapped in Instructive Alginate Hydrogels. *STEM CELLS Translational Medicine*, 5(6), pp.773–781. doi:https://doi.org/10.5966/sctm.2015-0211.

Hopfner, U., Aitzetmueller, M.M., Neßbach, P., Hu, M.S., Machens, H.-G., Maan, Z.N. and Duscher, D. (2018). Fibrin Glue Enhances Adipose-Derived Stromal Cell Cytokine Secretion and Survival Conferring Accelerated Diabetic Wound Healing. *Stem Cells International*, [online] 2018, pp.1–8. doi:https://doi.org/10.1155/2018/1353085.

Huang, J., Deng, Q., Tsang, L.L., Chang, G., Guo, J., Ruan, Y.C., Wang, C.C., Li, G., Chan, H.F., Zhang, X. and Jiang, X. (2025). Mesenchymal stem cells from perinatal tissues

promote diabetic wound healing via PI3K/AKT activation. *Stem Cell Research & Therapy*, 16(1). doi:https://doi.org/10.1186/s13287-025-04141-8.

Jiao, J., Peng, C., Li, C., Qi, Z., Zhan, J. and Pan, S. (2021). Dual bio-active factors with adhesion function modified electrospun fibrous scaffold for skin wound and infections therapeutics. *Scientific Reports*, 11(1). doi:https://doi.org/10.1038/s41598-020-80269-2.

Kahn, S.A., Carter, J.E., Wilde, S., Chamberlain, A., Walsh, T.P. and Sparks, J.A. (2024). Autologous Skin Cell Suspension for Full-Thickness Skin Defect Reconstruction: Current Evidence and Health Economic Expectations. *Advances in Therapy*. doi:https://doi.org/10.1007/s12325-023-02777-7.

Kaur, A., Midha, S., Giri, S. and Mohanty, S. (2019). Functional Skin Grafts: Where Biomaterials Meet Stem Cells. *Stem Cells International*, [online] 2019, pp.1–20. doi:https://doi.org/10.1155/2019/1286054.

Kavita Kumari Thakur, Ramesh Lekurwale, Sangita Bansode and Rajesh Pansare (2023). 3D Bioprinting: A Systematic Review for Future Research Direction. *Indian Journal of Orthopaedics*, 57(12), pp.1949–1967. doi:https://doi.org/10.1007/s43465-023-01000-7.

Kenneth, A.P., C, S.R.J., R, F.V.J., Castillo, J.L., Mauricio, M.Q., J, M.D.F., A, de la C.D.H., L, N.M.C. and J, N.V.E. (2024). A Comparative Analysis of the Outcomes of Various Graft Types in Burn Reconstruction Over the Past 24 Years: A Systematic Review. *ProQuest*, [online] 16(2). doi:https://doi.org/10.7759/cureus.54277.

Koh, T.J. and DiPietro, L.A. (2011). Inflammation and wound healing: the role of the macrophage. *Expert Reviews in Molecular Medicine*, 13(23). doi:https://doi.org/10.1017/s1462399411001943.

Lalu, M.M., McIntyre, L., Pugliese, C., Fergusson, D., Winston, B.W., Marshall, J.C., Granton, J. and Stewart, D.J. (2012). Safety of Cell Therapy with Mesenchymal Stromal Cells (SafeCell): A Systematic Review and Meta-Analysis of Clinical Trials. *PLoS ONE*, [online] 7(10), p.e47559. doi:https://doi.org/10.1371/journal.pone.0047559.

Lee, D.E., Ayoub, N. and Agrawal, D.K. (2016). Mesenchymal stem cells and cutaneous wound healing: novel methods to increase cell delivery and therapeutic efficacy. *Stem Cell Research & Therapy*, 7(1). doi:https://doi.org/10.1186/s13287-016-0303-6.

Liang, X., Zhong, H.-J., Ding, H., Yu, B., Ma, X., Liu, X., Chong, C.-M. and He, J. (2024). Polyvinyl Alcohol (PVA)-Based Hydrogels: Recent Progress in Fabrication, Properties, and Multifunctional Applications. *Polymers*, [online] 16(19), p.2755. doi:https://doi.org/10.3390/polym16192755.

Liang, Y., Zhang, H., Feng, Q.-S., Cai, M.-B., Deng, W., Qin, D., Yun, J.-P., Tsao, G.S.W., Kang, T., Esteban, M.A., Pei, D. and Zeng, Y.-X. (2013). The propensity for tumorigenesis in human induced pluripotent stem cells is related with genomic instability. *Chinese Journal of Cancer*, [online] 32(4), pp.205–212. doi:https://doi.org/10.5732/cjc.012.10065.

Lotfollahi, Z. (2024). The anatomy, physiology and function of all skin layers and the impact of ageing on the skin. *Wound practice & research*, 32(1), pp.6–10. doi:https://doi.org/10.33235/wpr.32.1.6-10.

Ma, X., Zhu, X., Sheng Lv, Yang, C., Wang, Z., Liao, M., Zhou, B., Zhang, Y., Sun, S., Chen, P., Liu, Z. and Chen, H. (2025). 3D bioprinting of prefabricated artificial skin with multicomponent hydrogel for skin and hair follicle regeneration. *Theranostics*, 15(7), pp.2933–2950. doi:https://doi.org/10.7150/thno.104854.

Malekpour, A. and Chen, X. (2022). Printability and Cell Viability in Extrusion-Based Bioprinting from Experimental, Computational, and Machine Learning Views. *Journal of Functional Biomaterials*, 13(2), p.40. doi:https://doi.org/10.3390/jfb13020040.

Mancha Sánchez, E., Gómez-Blanco, J.C., López Nieto, E., Casado, J.G., Macías-García, A., Díaz Díez, M.A., Carrasco-Amador, J.P., Torrejón Martín, D., Sánchez-Margallo, F.M. and Pagador, J.B. (2020). Hydrogels for Bioprinting: A Systematic Review of Hydrogels Synthesis, Bioprinting Parameters, and Bioprinted Structures Behavior. *Frontiers in Bioengineering and Biotechnology*, [online] 8, p.776. doi:https://doi.org/10.3389/fbioe.2020.00776.

Matei Iordache, Avram, L., Ioan Lascar and Frunza, A. (2025). The Role of Skin Substitutes in the Therapeutical Management of Burns Affecting Functional Areas. *Medicina*, [online] 61(6), pp.947–947. doi:https://doi.org/10.3390/medicina61060947.

Mathew-Steiner, S.S., Roy, S. and Sen, C.K. (2021). Collagen in Wound Healing. *Bioengineering*, 8(5), p.63. doi:https://doi.org/10.3390/bioengineering8050063.

Maxson, S., Lopez, E.A., Yoo, D., Danilkovitch-Miagkova, A. and LeRoux, M.A. (2012). Concise Review: Role of Mesenchymal Stem Cells in Wound Repair. *STEM CELLS Translational Medicine*, 1(2), pp.142–149. doi:https://doi.org/10.5966/sctm.2011-0018.

Milner, S.M. (2023). Cultured Epithelial Autograft. *Eplasty*, [online] 23, p.QA14. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC10794035/.

Morouço, P., Lattanzi, W. and Alves, N. (2017). Four-Dimensional Bioprinting As a New Era for Tissue Engineering and Regenerative Medicine. *Frontiers in Bioengineering and Biotechnology*, 5. doi:https://doi.org/10.3389/fbioe.2017.00061.

Nourian Dehkordi, A., Mirahmadi Babaheydari, F., Chehelgerdi, M. and Raeisi Dehkordi, S. (2019). Skin tissue engineering: wound healing based on stem-cell-based therapeutic strategies. *Stem Cell Research & Therapy*, 10(1). doi:https://doi.org/10.1186/s13287-019-1212-2.

Opneja, A., Kapoor, S. and Stavrou, E.X. (2019). Contribution of platelets, the coagulation and fibrinolytic systems to cutaneous wound healing. *Thrombosis Research*, [online] 179, pp.56–63. doi:https://doi.org/10.1016/j.thromres.2019.05.001.

Ortuño-Costela, M. del C., Cerrada, V., García-López, M. and Gallardo, M.E. (2019). The Challenge of Bringing iPSCs to the Patient. *International Journal of Molecular Sciences*, [online] 20(24), p.6305. doi:https://doi.org/10.3390/ijms20246305.

Pasi, C.E., Dereli-Öz, A., Negrini, S., Friedli, M., Fragola, G., Lombardo, A., Van Houwe, G., Naldini, L., Casola, S., Testa, G., Trono, D., Pelicci, P.G. and Halazonetis, T.D. (2011). Genomic instability in induced stem cells. *Cell Death & Differentiation*, 18(5), pp.745–753. doi:https://doi.org/10.1038/cdd.2011.9.

Pitt, K., Yoshiyuki Mochida and Makoto Senoo (2023). Greener Grass: The Modern History of Epithelial Stem Cell Innovation. *Life*, [online] 13(3), pp.688–688. doi:https://doi.org/10.3390/life13030688.

Pusztaszeri, M.P., Seelentag, W. and Bosman, F.T. (2006). Immunohistochemical Expression of Endothelial Markers CD31, CD34, von Willebrand Factor, and Fli-1 in Normal Human Tissues. *Journal of Histochemistry & Cytochemistry*, 54(4), pp.385–395. doi:https://doi.org/10.1369/jhc.4a6514.2005.

Reddy, M.S.B., Ponnamma, D., Choudhary, R. and Sadasivuni, K.K. (2021). A Comparative Review of Natural and Synthetic Biopolymer Composite Scaffolds. *Polymers*, 13(7), p.1105. doi:https://doi.org/10.3390/polym13071105.

Ren, X., Zhao, M., Lash, B., Martino, M.M. and Julier, Z. (2020). Growth Factor Engineering Strategies for Regenerative Medicine Applications. *Frontiers in Bioengineering and Biotechnology*, [online] 7. doi:https://doi.org/10.3389/fbioe.2019.00469.

Riha, S.M., Maarof, M. and Fauzi, M.B. (2021). Synergistic Effect of Biomaterial and Stem Cell for Skin Tissue Engineering in Cutaneous Wound Healing: A Concise Review. *Polymers*, [online] 13(10), p.1546. doi:https://doi.org/10.3390/polym13101546.

Roche, E.T., Hastings, C.L., Lewin, S.A., Shvartsman, D.E., Brudno, Y., Vasilyev, N.V., O'Brien, F.J., Walsh, C.J., Duffy, G.P. and Mooney, D.J. (2014). Comparison of biomaterial delivery vehicles for improving acute retention of stem cells in the infarcted heart. *Biomaterials*, [online] 35(25), pp.6850–6858. doi:https://doi.org/10.1016/j.biomaterials.2014.04.114.

Rustad, K.C., Wong, V.W., Sorkin, M., Glotzbach, J.P., Major, M.R., Rajadas, J., Longaker, M.T. and Gurtner, G.C. (2012). Enhancement of mesenchymal stem cell angiogenic capacity and stemness by a biomimetic hydrogel scaffold. *Biomaterials*, [online] 33(1), pp.80–90. doi:https://doi.org/10.1016/j.biomaterials.2011.09.041.

Takahashi, K. and Yamanaka, S. (2006). Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. *Cell*, [online] 126(4), pp.663–676. Available at: https://pubmed.ncbi.nlm.nih.gov/16904174/.

Takeo, M., Lee, W. and Ito, M. (2015). Wound Healing and Skin Regeneration. *Cold Spring Harbor Perspectives in Medicine*, [online] 5(1). doi:https://doi.org/10.1101/cshperspect.a023267.

Tracy, L.E., Minasian, R.A. and Caterson, E.J. (2016). Extracellular Matrix and Dermal Fibroblast Function in the Healing Wound. *Advances in Wound Care*, [online] 5(3), pp.119–136. doi:https://doi.org/10.1089/wound.2014.0561.

U.S. Food & Drug Administration (2018). *SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)*. [online] Available at: https://www.fda.gov/media/117049/download.

Wang, Y., Abarbanell, A.M., Herrmann, J.L., Weil, B.R., Manukyan, M.C., Poynter, J.A. and Meldrum, D.R. (2010). TLR4 Inhibits Mesenchymal Stem Cell (MSC) STAT3 Activation and Thereby Exerts Deleterious Effects on MSC–Mediated Cardioprotection. *PLoS ONE*, [online] 5(12), p.e14206. doi:https://doi.org/10.1371/journal.pone.0014206.

Wang, Z., Jiang, C., Fan, Y., Hao, X., Dong, Y., He, X., Gao, J., Zhang, Y., Li, M., Wang, M., Liu, Y. and Xu, W. (2024). The application of a 4D-printed chitosan-based stem cell carrier for the repair of corneal alkali burns. *Stem cell research & therapy*, 15(1). doi:https://doi.org/10.1186/s13287-024-03653-z.

Weng, T., Zhang, W., Xia, Y., Wu, P., Yang, M., Jin, R., Xia, S., Wang, J., You, C., Han, C. and Wang, X. (2021). 3D bioprinting for skin tissue engineering: Current status and perspectives. *Journal of Tissue Engineering*, [online] 12, p.204173142110285. doi:https://doi.org/10.1177/20417314211028574.

Wu, L.-J., Lin, W., Liu, J.-J., Chen, W.-X., He, W.-J., Shi, Y., Liu, X. and Li, K. (2023). Transplantation of human induced pluripotent stem cell derived keratinocytes accelerates deep second-degree burn wound healing. *World Journal of Stem Cells*, [online] 15(7), pp.713–733. doi:https://doi.org/10.4252/wjsc.v15.i7.713.

Xu, H.-Q., Liu, J.-C., Zhang, Z.-Y. and Xu, C.-X. (2022). A review on cell damage, viability, and functionality during 3D bioprinting. *Military Medical Research*, 9(1). doi:https://doi.org/10.1186/s40779-022-00429-5.

Xu, L., Zhang, Z., Jorgensen, A., Yang, Y., Jin, Q., Zhang, G., Cao, G., Fu, Y., Zhao, W., Ju, J. and Hou, R. (2023). Bioprinting a skin patch with dual-crosslinked gelatin (GelMA) and silk fibroin (SilMA): An approach to accelerating cutaneous wound healing. *Materials today bio*, 18, pp.100550–100550. doi:https://doi.org/10.1016/j.mtbio.2023.100550.

Yang, R., Liu, F., Wang, J., Chen, X., Xie, J. and Xiong, K. (2019). Epidermal stem cells in wound healing and their clinical applications. *Stem Cell Research & Therapy*, [online] 10(1). doi:https://doi.org/10.1186/s13287-019-1312-z.

Yousef, H., Alhajj, M. and Sharma, S. (2024). *Anatomy, Skin (Integument), Epidermis*. [online] PubMed. Available at: https://www.ncbi.nlm.nih.gov/books/NBK470464/.

Yu, J.R., Navarro, J., Coburn, J.C., Mahadik, B., Molnar, J., Holmes, J.H., Nam, A.J. and Fisher, J.P. (2019). Current and Future Perspectives on Skin Tissue Engineering: Key Features of Biomedical Research, Translational Assessment, and Clinical Application. *Advanced Healthcare Materials*, 8(5), p.1801471. doi:https://doi.org/10.1002/adhm.201801471.

Yu, X., Liu, P., Li, Z. and Zhang, Z. (2023). Function and mechanism of mesenchymal stem cells in the healing of diabetic foot wounds. *Frontiers in Endocrinology*, 14. doi:https://doi.org/10.3389/fendo.2023.1099310.

Yue, K., Trujillo-de Santiago, G., Alvarez, M.M., Tamayol, A., Annabi, N. and Khademhosseini, A. (2015). Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels. *Biomaterials*, 73, pp.254–271. doi:https://doi.org/10.1016/j.biomaterials.2015.08.045.

Zhao, L., Zhou, Y., Zhang, J., Liang, H., Chen, X. and Tan, H. (2023). Natural Polymer-Based Hydrogels: From Polymer to Biomedical Applications. *Pharmaceutics*, 15(10), pp.2514–2514. doi:https://doi.org/10.3390/pharmaceutics15102514.

Zhao, R., Liang, H., Clarke, E., Jackson, C. and Xue, M. (2016). Inflammation in Chronic Wounds. *International Journal of Molecular Sciences*, 17(12), p.2085. doi:https://doi.org/10.3390/ijms17122085.

Zustiak, S.P. and Leach, J.B. (2010). Hydrolytically Degradable Poly(Ethylene Glycol) Hydrogel Scaffolds with Tunable Degradation and Mechanical Properties. *Biomacromolecules*, 11(5), pp.1348–1357. doi:https://doi.org/10.1021/bm100137q.