Review

PROGRESS IN THE APPLICATION OF MICRONEEDLE-MEDIATED CELL IMPLANTATION COMBINED WITH ARTIFICIAL DERMAL SCAFFOLDS

Z.F. Wu[1], W. Cheng[2] and J.D. Su[1,*]

[1]Department of Burn and Plastic Surgery, Suzhou Hospital Affiliated to Nanjing Medical University, 215000 Suzhou, Jiangsu, China
[2]School of Physical Science and Technology, Soochow University, and Jiangsu Key Laboratory of Thin Films, 215006 Suzhou, Jiangsu, China

Abstract

Tissue-engineered skin represents a transformative approach for treating chronic wounds and extensive burns; however, challenges such as low cell survival rates and insufficient microenvironmental support remain. This review highlights the synergistic potential of microneedle (MN)-mediated cell implantation and decellularized extracellular matrix (dECM) scaffolds in addressing these limitations. MNs enable minimally invasive, targeted delivery of therapeutic cells (e.g., mesenchymal stem cells, keratinocytes) into the skin layers, while dECM scaffolds provide a biomimetic microenvironment rich in collagen and growth factors that enhance cell adhesion, proliferation, and differentiation. We critically analyze (1) MN designs (e.g., hollow, soluble) optimized for skin-compatible cell delivery; (2) advanced dECM fabrication techniques that preserve extracellular matrix (ECM) bioactivity; and (3) emerging combinatorial strategies in which MN-delivered cells integrate with dECM to accelerate wound closure and functional skin regeneration. By bridging precise delivery with microenvironmental engineering, this integrated platform offers a scalable solution for clinical translation, with applications extending to chronic wound repair, appendage-bearing skin models, and immunotherapy.

Keywords: Microneedles, cell implantation, decellularization, tissue-engineered skin, regeneration medicine.

***Address for correspondence**: J.D. Su, Department of Burn and Plastic Surgery, Suzhou Hospital Affiliated to Nanjing Medical University, 215000 Suzhou, Jiangsu, China. Email: jiandongsu@njmu.edu.cn.

Introduction

Chronic wounds—such as diabetic foot ulcers, venous leg ulcers, and pressure injuries—pose a significant and growing healthcare challenge worldwide. Epidemiological data indicate a global prevalence of 1.67 cases per 1000 population [1], with substantial associated economic costs. In USA alone, chronic wounds affect approximately 5.7 million people (2 % of the population), with annual treatment costs reaching $20 billion. Similarly, in the UK, chronic wound management accounts for 3 %–5.5 % of total healthcare expenditure [2]. Moreover, thermal burns account for approximately 265,000 deaths globally each year, with millions more experiencing long-term disability and scarring [3]. Traditional skin grafting faces critical limitations, including donor skin shortages and the risk of immune rejection [4]. Even commercially available tissue-engineered skin substitutes (e.g., Integra®, Apligraf®) exhibit low cell survival rates and fail to fully regenerate skin appendages such as sweat glands and hair follicles, resulting in non-functional skin [5].

To overcome these challenges, microneedle (MN)-mediated cell implantation and decellularized extracellular matrix (dECM) scaffolds have emerged as promising strategies. MNs enable minimally invasive, high-precision delivery of therapeutic cells (e.g., mesenchymal stem cells (MSCs), keratinocytes) into the deeper layers of the skin, achieving >80 % cell viability in preclinical models [6]. Concurrently, dECM scaffolds provide a biomimetic microenvironment rich in collagen, elastin, and growth factors, significantly enhancing angiogenesis and re-epithelialization in chronic wounds [7]. By bridging precise cell delivery with microenvironmental engineering, this platform offers a scalable and clinically translatable solution, with potential applications in chronic wound repair, appendage regeneration, and immunotherapy.

This article highlights the synergistic potential of MN-mediated cell implantation combined with dECM scaffolds for skin regeneration. It critically analyzes MN designs optimized for skin-compatible cell delivery, advanced dECM fabrication techniques that preserve extracellular matrix (ECM) bioactivity, and emerging combinatorial strategies

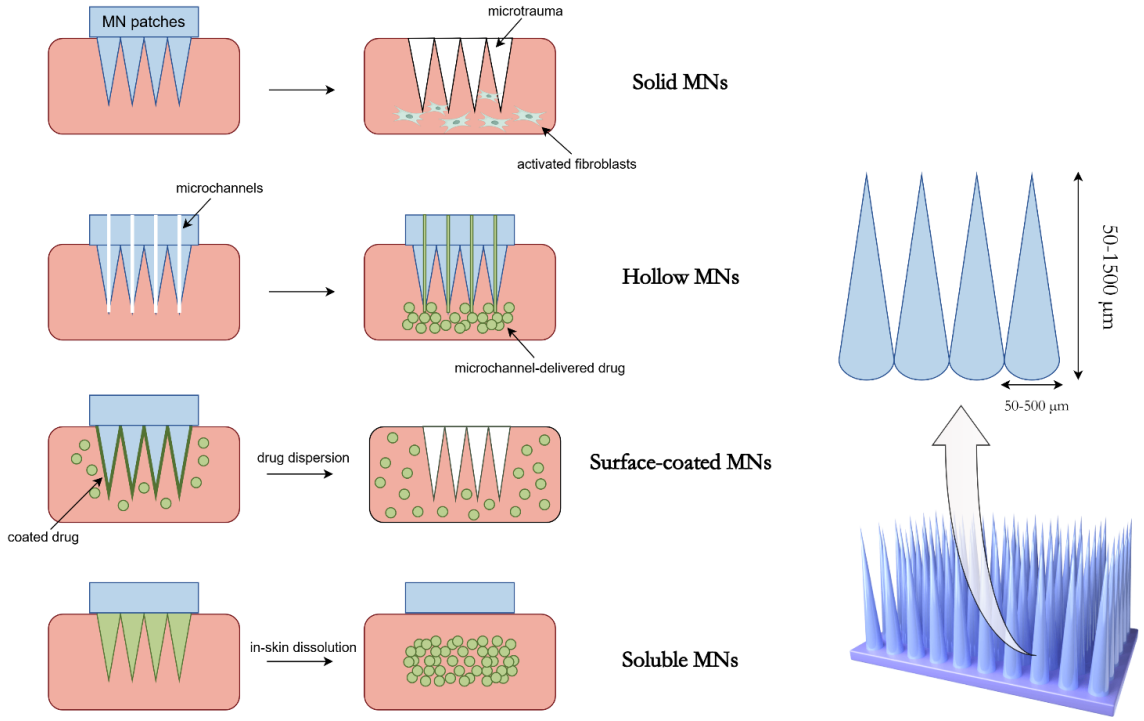

Fig. 1. Scale and categories of microneedles (By Figdraw ID: PPWIO565c1). Solid MNs induce microtrauma to activate fibroblasts; Hollow MNs deliver drugs via microchannels; Surface-coated MNs release coated drugs upon insertion; Soluble MNs dissolve completely in skin. MN, microneedle.

that accelerate wound closure and promote functional skin regeneration.

Microneedles

MNs are minimally invasive, needle-like devices designed to create microscopic channels in the skin without causing significant damage. Typically, MNs range in length from 50 to 1500 μm and in width from 50 to 500 μm. These devices enable the precise delivery of drugs or cells to specific skin sites [8]. Their minimally invasive nature and associated painlessness make them highly patient-compliant, which is particularly beneficial for applications such as treating diabetic ulcers and delivering therapeutics to solid tumors on the body surface. Furthermore, the controlled trauma induced by MNs stimulates the body's natural repair mechanisms, promoting collagen production [6] and contributing to their popularity in the field of cosmetology.

Classification of Microneedles

According to their mechanism of cargo release, MNs are generally classified into four types: solid, hollow, surface-coated, and soluble MNs (Fig. 1).

Solid MNs have a simple structure and are typically fabricated from materials such as silicon, metal, or polymers, offering high mechanical strength to effectively pierce the stratum corneum of the skin. They are widely applied in transdermal drug delivery, particularly in regenerative medicine. For instance, in the treatment of keloids, solid MNs are used to deliver 5-fluorouracil (5-FU)-loaded nanoparticles into the scar tissue [9]. This approach not only increases local drug concentration and reduces systemic side effects but also shows significant potential in keloid therapy by inhibiting the proliferation of keloid fibroblasts. Furthermore, solid MNs are widely used in cosmetic dermatology, as MN puncture can stimulate the skin's self-repair mechanisms, promoting collagen production and ultimately improving skin texture and reducing wrinkles [10].

Hollow MNs feature a unique "poke-and-flow" delivery mechanism, enabling direct drug administration into skin tissue with greater dosing precision compared to other MN types [11]. By penetrating the stratum corneum and targeting the dermis at a depth of 0.5–3 mm, hollow MNs enhance localized drug delivery. This is exemplified by the use of finasteride for treating androgenetic alopecia, where hollow MNs are combined with ultrasound-induced cavitation (109 kHz, 2.99 W/cm^2) to improve tissue diffusion and therapeutic efficacy [12]. The ability of hollow MNs to achieve precise, high-dose intradermal delivery positions

them as a transformative tool in skin regenerative medicine, particularly for conditions requiring deep tissue drug deposition and improved bioavailability.

Surface-coated MNs are fabricated by depositing drugs or bioactive compounds onto MN surfaces using techniques such as dip-coating, spray-coating, and spin-coating [13–16]. After skin penetration, these MNs enable rapid drug release at the target site, achieving high local drug concentrations. The coating encapsulation protects the therapeutic payload from environmental degradation, significantly reducing the risk of drug inactivation. Surface-coated MNs functionalized with young fibroblast-derived exosomes (Y-EXOs) have demonstrated remarkable potential in skin rejuvenation. Prepared via spraying and freeze-drying cycles—a low-cost, scalable method that preserves bioactivity by avoiding high temperatures—these MNs achieve uniform Y-EXO coating while maintaining exosomal integrity. Upon application, Y-EXOs are rapidly released into the dermal layer, where they precisely stimulate senescent fibroblasts and immune cells to enhance proliferation, migration, and collagen deposition, thereby restoring the regenerative capacity of aged skin [17]. This clinically viable system enables precise exosome delivery for effective skin regeneration.

Soluble MNs are typically fabricated from biodegradable polymers such as hyaluronic acid (HA) or poly(lactic-co-glycolic acid) (PLGA) [18,19]. Upon skin penetration, these MNs gradually dissolve in the interstitial fluid, releasing encapsulated drugs or bioactive compounds. Unlike traditional non-dissolving MNs, the dissolved polymer materials are naturally metabolized and cleared by the body, eliminating the risk of residual foreign-body reactions in the skin. In the treatment of skin diseases and cosmetic applications, the delivery of adipose-derived stem cell-derived extracellular vesicles (ADSC-EVs) via soluble MNs has demonstrated superior efficacy compared to intradermal injection or topical application. Specifically, ADSC-EVs loaded into MNs significantly enhance dermal thickness, upregulate collagen I and elastin expression, and promote fibroblast proliferation while modulating fibroblast phenotype. This optimized delivery system enables deeper and more sustained EV penetration into the dermis, thereby maximizing their reparative and regenerative effects on skin tissue [20].

Materials for Microneedle Production

Taking into account factors such as mechanical strength and production cost, researchers use materials such as silicon, metal, ceramics, and polymers to manufacture MNs.

Silicon's compatibility with precision microfabrication techniques enables the production of MNs with customized geometries, including solid, hollow, and surface-coated variants [21–23]. This versatility has made silicon a widely adopted material in MN manufacturing since the late 1990s. While silicon offers exceptional versatility, ongoing innovations have further refined its functionality. For instance, Pradeep Narayanan and Raghavan [24] enhanced the mechanical robustness of silicon MNs by applying a gold coating via metal sputtering, effectively addressing earlier concerns regarding structural integrity. Such advancements underscore the iterative progress in MN materials science, ensuring mechanical reliability while preserving silicon's inherent biocompatibility for biomedical applications.

Metals, including stainless steel, titanium and nickel, are widely used for MN fabrication due to their exceptional mechanical strength and ability to penetrate the skin without fracture [9,25,26]. However, their clinical application in skin regeneration faces several challenges, including poor biocompatibility, non-degradability, and the risk of allergic reactions. For example, nickel-containing MNs have been reported to trigger localized adverse effects, such as erythematous papular lesions and pustules in sensitive patients [27]. To address these limitations, recent innovations have focused on integrating biocompatible materials to enhance both safety and functionality. In particular, biodegradable hybrids that combine metals with porous metal-organic frameworks (MOFs) have been developed to improve drug-loading efficiency and enable controlled release kinetics [28].

Ceramic materials, such as alumina, exhibit excellent mechanical strength and high-temperature stability due to the strong covalent bonds formed during the sintering process. Bystrova and Luttge [29] demonstrated the scalability of alumina ceramic MN arrays for skin applications using micromolding and sintering techniques. While ceramic MNs are valued for their durability, their limited tensile strength restricts their application in longer needle designs. Advances in composite materials and hybrid fabrication methods could further improve their suitability for transdermal delivery in skin regeneration. Beyond mechanical performance, ceramic materials also exhibit excellent biocompatibility with skin tissue. Their chemical stability and low immunogenicity minimize adverse reactions, while their tunable surface properties support cell adhesion and proliferation [30,31].

Polymer materials are widely used for MN array fabrication owing to their excellent moldability, rapid processing cycles, and cost-effectiveness, making them ideal for large-scale production. Commonly employed polymers include polyethylene glycol (PEG), poly(vinyl alcohol) (PVA), polyacrylic acid (PAA), and poly(lactic-co-glycolic acid) (PLGA) [19,32–34]. A key advantage of polymer-based MNs is the tunability of their material properties to meet specific application requirements. For example, Zhang *et al.* [35] developed an innovative MN system for diabetic ulcer treatment by leveraging the ion-responsive behavior of PVA. In their design, PVA serves as the MN matrix, where sulfate ions enhance its mechan-

ical strength to enable effective skin penetration, while subsequent exposure to nitrate ions softens the material, promoting tissue compatibility and enabling controlled release of mesenchymal stem cell-derived exosomes (MSC-EVs). This dynamic adaptability highlights the versatility of polymer-based MN systems for therapeutic applications.

Microneedle-Mediated Cell Implantation

MN technology has demonstrated transformative potential in regenerative medicine and wound therapy due to its minimally invasive nature, high delivery efficiency, and precise targeting capabilities. In recent years, MN systems have enabled applications ranging from antibacterial immunomodulation to stem cell delivery and stimuli-responsive controlled release. These platforms offer precision, personalization, and intelligent therapeutic potential.

The minimally invasive nature of MNs enables nearly painless penetration of the stratum corneum, bypassing nerve endings in deeper skin layers while creating transient microchannels for the targeted delivery of drugs or cell-based products. This localized approach allows for the precise modulation of therapeutic agent concentrations at the wound site, minimizing systemic exposure and off-target effects. For example, in a study by Jiang *et al*. [36], MN patches composed of photocrosslinked gelatin methacryloyl (GelMA) hydrogel loaded with multifunctional nanoparticles synergistically combined the antibacterial properties of fucoidan and zinc ions with the immunomodulatory effects of HA, achieving potent methicillin-resistant Staphylococcus aureus (MRSA) eradication and accelerated wound healing. The sustained release of bioactive components from degradable MNs further ensures prolonged antimicrobial and anti-inflammatory activity, addressing key challenges in infected wound management.

MNs have demonstrated significant potential in enhancing cell viability and therapeutic efficacy. A Recent study has shown that hydrogel-based MNs composed of decellularized adipose matrix (DAM) and hyaluronic acid methacrylic acid (HAMA) can effectively encapsulate and protect adipose-derived stem cells (ADSCs) and their secreted mitochondria-enriched extracellular vesicles (MetEVs). This system not only preserves the biological activity of therapeutic components but also enables their sustained release into wound tissues. In a radiation-induced chronic wound model, this treatment significantly accelerated wound closure (achieving near-complete healing by postoperative day 12), enhanced re-epithelialization (epithelial thickness restored to 92.14 μm), and promoted collagen deposition (48.15 % volume fraction), outperforming control groups [37].

A recent study has shown that MNs integrated with stimuli-responsive materials can enable controlled cell or drug release triggered by external stimuli such as light or temperature. For example, Zhang *et al*. [38] developed a core-shell-structured MN system incorporating light-responsive components for programmable drug release and enhanced wound healing. The MN shell was fabricated using PVA and a reactive oxygen species (ROS)-sensitive crosslinker to encapsulate the photodynamic therapy drug verteporfin (VP). Upon laser irradiation, VP-generated ROS triggered the degradation of the ROS-responsive shell, allowing for sequential release of VP to address bacterial infection, modulate inflammation, and suppress scar formation. This dynamic, material-responsive design leverages the photoresponsive properties of the MN matrix to achieve spatiotemporal control over therapeutic delivery, demonstrating the potential of stimuli-responsive MNs in adaptive wound therapy.

In summary, MN technology addresses the limitations of conventional therapies through its unique structural design and integration with functional materials, offering a versatile platform for multimodal wound healing. While MNs enable precise cell delivery, their regenerative potential can be further amplified when combined with dECM scaffolds. These biomimetic scaffolds provide essential microenvironmental cues that enhance cell survival, proliferation, and differentiation—complementing MN-mediated delivery to form a synergistic system for tissue regeneration.

Dermal Decellularized Extracellular Matrix Scaffolds

Dermal dECM scaffolds are bioactive materials derived from decellularized skin tissue, retaining key ECM components such as collagen, elastin, fibronectin, and glycosaminoglycans. Their three-dimensional porous structure mimics the architecture of native ECM, providing both mechanical support and essential biological cues to promote cell adhesion, proliferation, and differentiation [39].

Fabrication of Dermal Decellularized Extracellular Matrix Scaffolds

Decellularization is the process of removing cellular components from tissues using physical, chemical, or biological methods while preserving the extracellular matrix (ECM), thereby producing dECM scaffolds (Fig. 2**a**). Cellular structures—including nuclei, membranes, organelles, and extracellular vesicles (EVs)—contain immunogenic substances such as major histocompatibility complexes (MHCs), minor histocompatibility antigens (mHAs), cytokines, and damage-associated molecular patterns (DAMPs) [40–45]. Additionally, certain ECM-associated antigens, such as α-galactose and N-glycolylneuraminic acid (Neu5Gc), contribute to immunogenicity [46,47]. These antigens are key drivers of immune rejection in xenotransplantation. By employing targeted decellularization techniques, these immunogenic components can be removed, thereby reducing the immunogenicity of the resulting biomaterials [42,48].

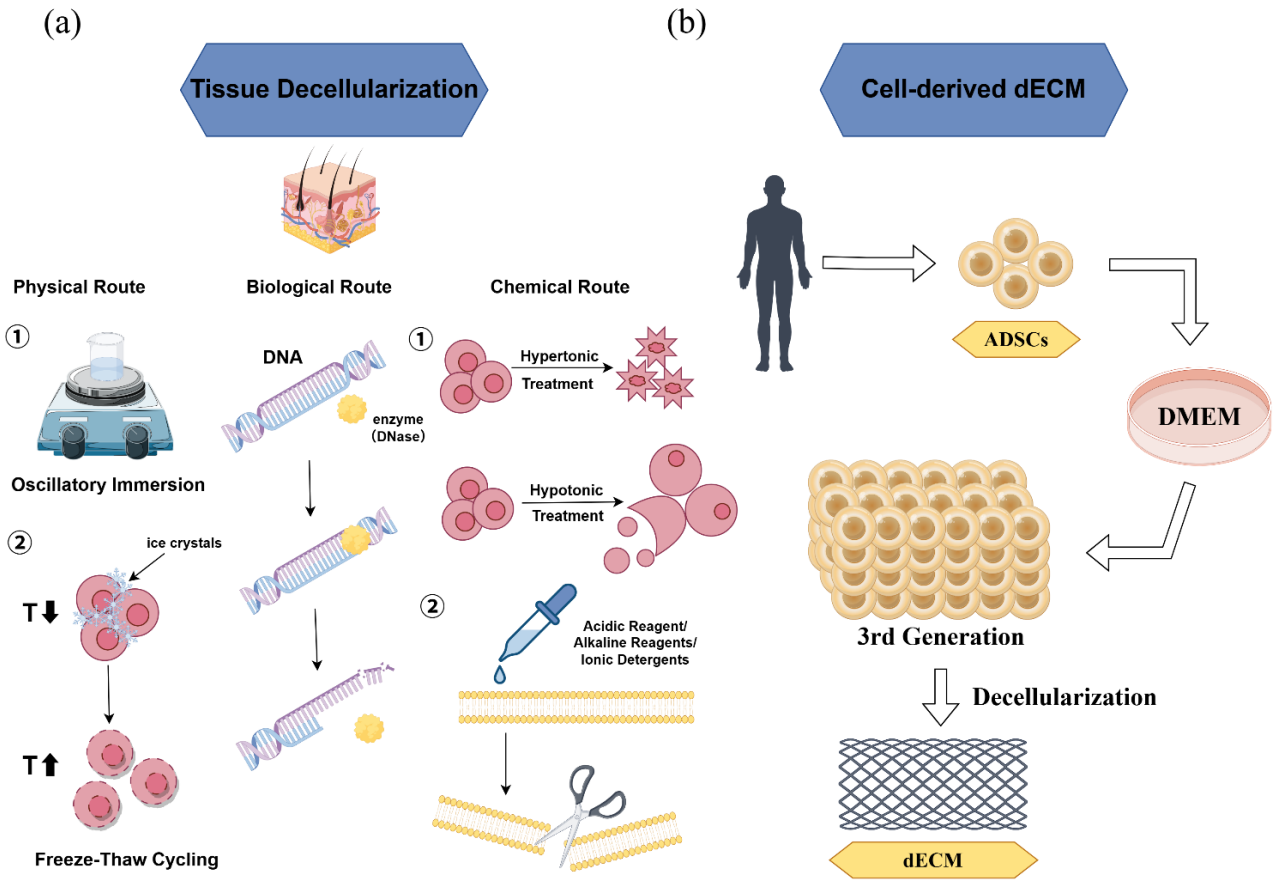

Fig. 2. Two methods of obtaining dECM scaffolds (By Figdraw ID: ASRWU84c4e). (**a**) Tissue decellularization methods: physical, biological, and chemical approaches. (**b**) ADSCs were extracted from fat tissue, cultured to the third generation, and then decellularized to obtain dECM scaffolds. dECM, decellularized extracellular matrix; ADSC, adipose-derived stem cell; DMEM, Dulbecco's modified Eagle's medium.

Physical Methods

Perfusion-based decellularization relies on a tissue's intrinsic vascular network to uniformly distribute decellularizing agents through circulatory perfusion. This method is effective for highly vascularized organs such as the heart (via the coronary arteries) and liver (via the portal vein) [49–52]. However, it is not suitable for avascular tissues such as the skin and cornea.

For skin decellularization, oscillatory immersion is commonly employed. In this method, skin tissues are submerged in decellularizing solutions and subjected to continuous mechanical agitation, which promotes cell lysis and detachment while preserving ECM integrity [53,54]. Alternatively, the freeze-thaw cycling method involves rapid freezing (e.g., with liquid nitrogen) to induce intracellular ice crystal formation, followed by thawing in a buffer solution. The repeated expansion and contraction of ice disrupts cell membranes, thereby facilitating decellularization [7]. However, this method may compromise ECM ultrastructure and often requires supplemental chemical treatments to eliminate residual cellular debris [55]. Both oscillatory immersion and freeze-thaw cycling are gentler than harsh chemical or enzymatic treatments, making them preferable for skin tissue decellularization while maintaining ECM functionality.

Chemical Methods

Acidic reagents such as hydrochloric acid, acetic acid, and peroxyacetic acid donate protons (H^+) to form covalent bonds with biomolecules, enabling them to disrupt cell membranes, lyse organelles, and induce cell lysis [56–58]. In comparison, alkaline substances such as ammonia, sodium hydroxide, and sodium sulfide release hydroxide ions (OH^-), which denature chromosomal DNA and facilitate cell lysis and decellularization [59,60]. Cell lysis and decellularization can also be achieved using hypertonic-hypotonic washing procedures [61–63]. Hypertonic solutions cause intracellular water loss and the outward diffusion of cellular contents, leading to cellular shrinkage and death. Conversely, hypotonic solutions increase intracellular pressure, ultimately causing membrane rupture and cell death. Ionic detergents, such as sodium dodecyl sulfate

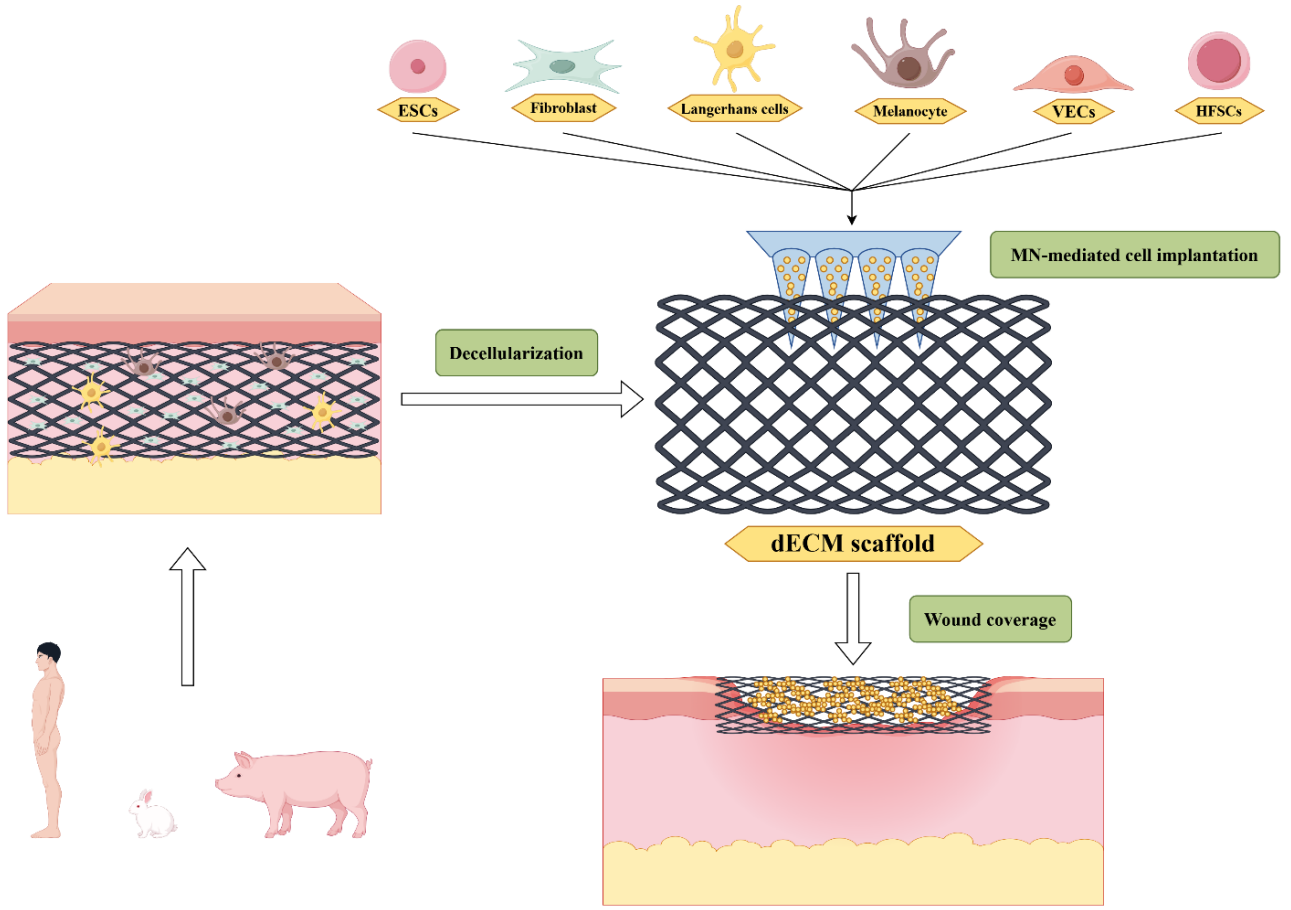

Fig. 3. Application of dECM scaffolds combined with MN technology (By Figdraw ID: UURAU1e1e1). Microneedle cell implantation after decellularization of whole layers of skin obtained from humans and animals can result in deimmunogenic skin substitutes, which can then be used in wound coverage. ESC, embryonic stem cell; HFSC, hair follicle stem cell; VEC, vascular endothelial cell.

(SDS), sodium deoxycholate (SDC), and sodium lauryl sulfate (SLS), efficiently remove cellular components by disrupting lipid-lipid, lipid-protein, DNA-protein, and protein-protein interactions [64–66]. However, residual cytotoxicity remains a concern. Recent protocols that combine SDS with nuclease treatment or replace it with nonionic detergents (e.g., Triton X-100) have demonstrated improved biocompatibility [65,67].

Biological Methods

Nuclease treatment plays a critical role in decellularization by selectively hydrolyzing nucleic acids while preserving structural ECM proteins. When combined with detergent pretreatment—which increases tissue porosity—nuclease treatment can achieve over 95 % DNA-removal efficiency, significantly reducing immunogenicity and improving recellularization outcomes [67,68]. However, enzymatic methods, such as trypsin—which cleaves peptide bonds at arginine and lysine residues—carry the risk of damaging ECM proteins that are essential for cell adhesion and growth factor retention.

A breakthrough by Zhang *et al.* [69] (Fig. 2**b**) demonstrated the potential of cell-derived dECM for skin regeneration, in which decellularization of cultured ADSCs yields scaffolds that remove xenogenic immunogens while preserving critical ECM components such as collagen, elastin, laminin, and endogenous growth factors. This ADSC-dECM platform synergizes with microneedle-based cell delivery by providing a bioactive microenvironment that: enhances cell viability through improved adhesion of MN-delivered keratinocytes and MSCs, promotes paracrine signaling via retained growth factors (e.g., hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF)) to support angiogenesis and epithelialization, and ensures immunocompatibility by removing MHC antigens that could trigger rejection post-implantation. A preclinical evaluation demonstrated that the ADSC-derived dECM scaffolds significantly enhanced wound healing outcomes, as evidenced by accelerated epithelial closure and improved tissue regeneration, supporting their potential for integration with MN-mediated cell delivery approaches in regenerative medicine applications [70].

The dECM scaffolds produced by these methods retain a natural three-dimensional structure and abundant bioactive components, creating an optimal microenvironment that supports cell growth, adhesion, and differentiation. When recellularized with appropriate cell types, these scaffolds can be engineered into functional skin substitutes capable of promoting wound healing and tissue regeneration.

The cell types currently used for dECM scaffold recellularization—embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs) [71,72]—present unique advantages and challenges. While ESCs offer high differentiation potential, their use remains ethically controversial due to the destruction of embryos. In contrast, iPSCs, derived from reprogrammed adult cells, avoid such ethical concerns but raise questions regarding genetic stability and long-term safety [73,74]. MSCs, sourced from bone marrow, adipose tissue, or umbilical cord blood, are less ethically contentious and possess immunomodulatory properties that enhance transplant compatibility [75–77]. However, the clinical translation of these cell-based therapies faces regulatory hurdles, including stringent safety and efficacy evaluations by agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), as well as ethical considerations around donor consent and standardized manufacturing. Addressing these challenges will be critical for advancing dECM-based regenerative medicine.

The recellularization of dECM scaffolds employs several methods, including direct seeding, cell layering, and bioprinting, each with distinct advantages and limitations. Direct seeding, the simplest approach, involves inoculating cell suspensions into the scaffold's surface pores using tools such as pipettes or sprays; however, this method may result in uneven cell distribution [7,78]. In contrast, the cell layering method is more complex, requiring the alternating stacking of pre-formed dECM layers and cell layers, followed by fixation to create a composite scaffold [79]. Under suitable culture conditions, the cells grow, differentiate, and mature within the dECM framework. Alternatively, bioprinting combines dECM with stem cells to create a bioink [80], enabling the precise three-dimensional printing of tissue constructs with specific architectures, which is ideal for engineering complex structures. However, despite its precision, the high cost and technical challenges of bioprinting currently hinder its widespread clinical adoption.

Moreover, dECM scaffolds can be functionalized by combining them with other materials to enhance their mechanical, biological, or therapeutic properties. For instance, Chandika *et al*. [81] developed a composite nanofibrous scaffold by integrating dECM with polycaprolactone and uronic acid, which demonstrated inherent antimicrobial activity against multiple pathogens, biofilm inhibition, and enhanced full-thickness wound healing *in vivo*. This scaffold not only inhibited the growth of various bacteria and fungi but also accelerated chronic wound healing. Similarly, Bhar *et al*. [82] demonstrated that silk fibroin, known for its excellent biocompatibility, enhances cell adhesion, proliferation, and differentiation. By combining dECM with silk fibroin, they improved the mechanical strength of the scaffold while preserving its bioactivity, further supporting wound regeneration.

Microneedle-Mediated Cell Implantation Combined with Artificial Dermal Scaffolds

In the field of tissue-engineered skin, researchers have explored strategies to develop *in vitro* skin models incorporating specific cell types or skin appendages (Fig. 3). For example, one study successfully differentiated iPSCs into skin models containing hair follicles by precisely regulating transforming growth factor-beta (TGF-β) and fibroblast growth factor (FGF) signaling pathways [83]. However, this approach faces several challenges, including technical complexity, poor reproducibility, and lengthy protocols that limit its clinical applicability. The integration of MNs with artificial dermal scaffolds offers a promising solution by simplifying and accelerating the construction of skin models. For instance, Sumathy and Velayudhan [84] developed a double-layer nanofiber scaffold mimicking the epidermis and dermis, combined with PVA-based MNs to precisely implant hair follicle stem cells (isolated from rabbit whiskers), keratinocytes, and dermal fibroblasts into the respective scaffold layers. This approach resulted in a full-thickness skin model in which cells maintained viability and stem cell properties [84]. Compared to traditional hair follicle culturing, this method significantly reduces preparation time and demonstrates strong clinical potential. Beyond hair follicle stem cells, previous studies have also incorporated melanocytes and Langerhans cells into skin simulants [85,86], although without using MNs as delivery vehicles. Leveraging the precision of MN technology for targeted cell implantation may facilitate the future development of engineered skin tissues with more complex structures and enhanced functional completeness.

Chronic wounds—characterized by complex etiology, prolonged healing time, and high recurrence rates—pose significant clinical challenges, prompting researchers to explore innovative tissue engineering strategies. For instance, Yao *et al*. [37] demonstrated promising therapeutic outcomes by delivering ADSCs and their EVs via MNs in a mouse model of radiation-induced ulcers, highlighting the potential of this approach for wound repair. Chen *et al*. [87] developed a human decellularized adipose matrix (hDAM)-hydrogel composite as a bioactive scaffold for subcutaneous ADSC delivery, which effectively accelerated angiogenesis and wound healing in diabetic mice with chronic wounds. Their study demonstrated that the hDAM-hydrogel composite supported ADSC adhe-

sion, survival, and proliferation while enhancing paracrine activity (e.g., HGF secretion), thereby promoting neovascularization. Although the original study utilized direct injection, the hydrogel's thermoresponsive sol-gel transition properties suggest compatibility with MN-mediated delivery. Future adaptation of this system with MN arrays could enable minimally invasive, spatially controlled ADSC administration—particularly advantageous for large or anatomically complex wounds. These findings collectively highlight the dual potential of ADSC-laden hDAM hydrogels: as an injectable therapy and as a versatile platform for advanced delivery technologies like MNs.

The combination of MN-mediated cell implantation and dECM scaffolds holds significant promise in the field of immunotherapy. Dendritic cell vaccines (DCVs)—prepared by loading tumor antigens onto dendritic cells to activate T-cell–mediated antitumor immune responses—have demonstrated promise in the treatment of melanoma. For example, Chang *et al*. [88] showed that frozen MNs loaded with DCVs effectively penetrated a melanoma skin model and delivered the vaccine into the tissue, resulting in targeted tumor cell killing. However, the clinical efficacy and stability of MN-delivered cell vaccines remain limited due to an incomplete understanding of the interactions between biological components in human skin and the vaccine's mechanism of action. To address these limitations, future studies could explore the implantation of different cell combinations into dECM scaffolds via MNs, allowing comparative analyses of vaccine efficacy across distinct microenvironments. Additionally, recent advances in artificial intelligence (AI) are being integrated into biomedical research. For instance, Suriyaamporn *et al*. [89] developed an AI-optimized hydrogel MN system incorporating 5-FU-loaded flexible liposomes. While traditional DCVs continue to face challenges related to clinical stability and incomplete mechanistic understanding, AI-driven platforms represent a new paradigm in cell-based therapy by enabling precise computational modeling of drug delivery parameters. The success of such intelligent systems suggests promising applications in future research that combines dECM scaffolds with MN-delivered cell combinations. In particular, AI-based optimization could support microenvironment-specific vaccine development while enabling real-time performance monitoring, thereby improving therapeutic outcomes and enhancing clinical translation potential.

Summary and Prospects

The integration of MN-mediated cell implantation with dECM scaffolds represents a significant advancement in skin tissue engineering, offering innovative solutions for wound healing and skin regeneration. This combined strategy synergizes the precise delivery capabilities of MN technology with the biomimetic properties of dECM scaffolds to generate functional tissue-engineered skin with enhanced therapeutic potential. Recent advances have demonstrated this system's capacity to construct complex skin models that closely replicate native tissue architecture and physiology, while also showing considerable promise in treating chronic wounds and supporting emerging applications in immunotherapy [37,84,88,89].

Clinical Translation Challenges and Standardization Needs

Despite promising advancements, several critical challenges must be addressed to fully realize the clinical potential of MN-mediated cell implantation combined with dECM scaffolds. A key priority is the establishment of standardized clinical trials to rigorously evaluate long-term efficacy and safety. These trials should incorporate comprehensive evaluation metrics, including (1) quantitative wound healing parameters (e.g., re-epithelialization rate, scar formation index); (2) immune response monitoring (e.g., macrophage polarization profiles, cytokine dynamics); and (3) scaffold biocompatibility assessments over extended periods (6–12 months) to track degradation kinetics and foreign body responses.

Scalability and Cost-Effectiveness Considerations

While MN-dECM systems show promising preclinical results, their clinical translation depends on overcoming key challenges related to scalability and cost. For microneedles, material selection critically impacts manufacturability. Although silicon MNs enable high-precision fabrication [22], their production typically requires cleanroom-based photolithography or etching processes, which significantly increase manufacturing costs compared to alternative methods [90]. In contrast, polymer-based soluble MNs—such as those made from PVA or PLGA—can be mass-produced via micromolding at <$5 per array [91], though they offer reduced mechanical precision. Hybrid approaches, such as ceramic-polymer composites [92], may balance cost and performance. For dECM scaffolds, batch-to-batch variability remains a key challenge due to donor tissue heterogeneity [42]. Automated decellularization systems [49] and xenogeneic sources (e.g., porcine skin) could reduce processing costs by 40 %–60 % versus human-derived ECM. Emerging bioprinting technologies [93,94] further enable standardized dECM bioink production at $0.2/mL, though post-printing crosslinking adds complexity.

Conclusions

This review highlights the transformative potential of MN-dECM scaffold composites in skin regeneration, demonstrating how their combined use bridges critical gaps in minimally invasive cell delivery and bioactive microenvironment engineering. The technology's ability to precisely deliver therapeutic agents while preserving optimal cellular viability and function addresses longstanding limi-

tations in traditional wound care approaches. Notably, the path to widespread clinical implementation requires overcoming substantial technical and regulatory hurdles, particularly in manufacturing standardization and safety validation. Future progress will depend on coordinated efforts to optimize material properties, establish reliable quality control measures, and demonstrate clinical efficacy through rigorous trials. As the field advances, these integrated systems are poised to revolutionize not only dermatological treatments but also broader applications in regenerative medicine, provided that current challenges in scalability and regulatory compliance are successfully addressed. The coming years will be crucial in determining whether this promising technology can transition from laboratory success to mainstream clinical practice, potentially establishing a new gold standard in skin regeneration therapies.

List of Abbreviations

ADSC, adipose-derived stem cell; DAMP, damage-associated molecular pattern; DCV, dendritic cell vaccine; dECM, decellularized extracellular matrix; ECM, extracellular matrix; ESC, embryonic stem cell; EV, extracellular vesicle; FGF, fibroblast growth factor; GelMA, gelatin methacryloyl; HGF, hepatocyte growth factor; hDAM, human decellularized adipose matrix; iPSCs, induced pluripotent stem cells; MHC, major histocompatibility complex; mHA, minor histocompatibility antigen; MN, microneedle; MRSA, methicillin-resistant Staphylococcus aureus; MSC, Mesenchymal stem cell; PAA, polyacrylic acid; PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic acid); PVA, poly(vinyl alcohol); ROS, reactive oxygen species; SDS, sodium dodecyl sulfate; SDC, sodium deoxycholate; SLS, sodium lauryl sulfate; TGF, transforming growth factor; VEGF, vascular endothelial growth factor; Y-EXO, young fibroblast-derived exosome; HFSC, hair follicle stem cell; VEC, vascular endothelial cell; HA, hyaluronic acid; DAM, decellularized adipose matrix; VP, verteporfin; 5-FU, 5-fluorouracil.

Availability of Data and Materials

No new data were generated or analyzed in this review. All cited literature and datasets are publicly available in the references listed.

Author Contributions

ZFW made substantial contributions to the conception and design of the work, drafted the manuscript, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work. WC contributed substantially to data visualization and interpretation, critically revised the manuscript for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work. JDS contributed to the study design and data interpretation, supervised the project implementation, secured funding acquisition, critically revised the manuscript for important intellectual content, approved the final version, and agreed to be accountable for all aspects of the work. All authors have read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgments

Not applicable.

Funding

This work was funded by the Suzhou Burn Clinical Medical Center Project, grant number Szlcyxzx202105 and the Suzhou Key Clinical Diseases Project, grant number LCZX202315.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Martinengo L, Olsson M, Bajpai R, Soljak M, Upton Z, Schmidtchen A, *et al*. Prevalence of chronic wounds in the general population: systematic review and meta-analysis of observational studies. Annals of Epidemiology. 2019; 29: 8–15. https://doi.org/10.1016/j.annepidem.2018.10.005.

[2] Järbrink K, Ni G, Sönnergren H, Schmidtchen A, Pang C, Bajpai R, *et al.* The humanistic and economic burden of chronic wounds: a protocol for a systematic review. Systematic Reviews. 2017; 6: 15. https://doi.org/10.1186/s13643-016-0400-8.

[3] Smolle C, Cambiaso-Daniel J, Forbes AA, Wurzer P, Hundeshagen G, Branski LK, *et al*. Recent trends in burn epidemiology worldwide: A systematic review. Burns: Journal of the International Society for Burn Injuries. 2017; 43: 249–257. https://doi.org/10.1016/j.burns.2016.08.013.

[4] Ozhathil DK, Tay MW, Wolf SE, Branski LK. A Narrative Review of the History of Skin Grafting in Burn Care. Medicina. 2021; 57: 380. https://doi.org/10.3390/medicina57040380.

[5] Riha SM, Maarof M, Fauzi MB. Synergistic Effect of Biomaterial and Stem Cell for Skin Tissue Engineering in Cutaneous Wound Healing: A Concise Review. Polymers. 2021; 13: 1546. https://doi.org/10.3390/polym13101546.

[6] Gao Z, Sheng T, Zhang W, Feng H, Yu J, Gu Z, *et al*. Microneedle-Mediated Cell Therapy. Advanced Science. 2024; 11: e2304124. https://doi.org/10.1002/advs.202304124.

[7] Sharma NS, Karan A, Tran HQ, John JV, Andrabi SM, Shatil Shahriar SM, *et al*. Decellularized extracellular matrix-decorated 3D nanofiber scaffolds enhance cellular responses and tissue regeneration. Acta Biomaterialia. 2024; 184: 81–97. https://doi.org/10.1016/j.actbio.2024.06.020.

[8] Chu S, Foulad DP, Atanaskova Mesinkovska N. Safety Profile for Microneedling: A Systematic Review. Dermatologic Surgery: Official Publication for American Society for Dermatologic Surgery [*et al*.]. 2021; 47: 1249–1254. https://doi.org/10.1097/01.DSS.0000790428.70373.f6.

[9] Park J, Kim YC. Topical delivery of 5-fluorouracil-loaded carboxymethyl chitosan nanoparticles using microneedles for keloid treatment. Drug Delivery and Translational Research. 2021; 11: 205–213. https://doi.org/10.1007/s13346-020-00781-w.

[10] Carver C, Rashid Z, Shuker S. Microneedling versus microcoring: A review of percutaneous collagen induction for the face and neck. Journal of Cosmetic Dermatology. 2024; 23: 1541–1550. https://doi.org/10.1111/jocd.16175.

[11] Ye R, Yang J, Li Y, Zheng Y, Yang J, Li Y, *et al.* Fabrication of Tip-Hollow and Tip-Dissolvable Microneedle Arrays for Transdermal Drug Delivery. ACS Biomaterials Science & Engineering. 2020; 6: 2487–2494. https://doi.org/10.1021/acsbiomaterials.0c00120.

[12] Wu H, Chen Z, Jiang Z, Chen M, Shan H, Lin Q, *et al*. Ultrasonic Hollow Microneedle Array (USHM) for Androgenetic Alopecia Treatment through Modulating the Expression of Hair-Growth-Associated Genes. ACS Applied Materials & Interfaces. 2025; 17: 21419–21430. https://doi.org/10.1021/acsami.5c00379.

[13] Fu X, Zhang T, Xia C, Du S, Wang B, Pan Z, *et al*. Spiderweb-Shaped Iron-Coordinated Polymeric Network as the Novel Coating on Microneedles for Transdermal Drug Delivery Against Infectious Wounds. Advanced Healthcare Materials. 2024; 13: e2401788. https://doi.org/10.1002/adhm.202401788.

[14] McGrath MG, Vrdoljak A, O'Mahony C, Oliveira JC, Moore AC, Crean AM. Determination of parameters for successful spray coating of silicon microneedle arrays. International Journal of Pharmaceutics. 2011; 415: 140–149. https://doi.org/10.1016/j.ijpharm.2011.05.064.

[15] Caudill CL, Perry JL, Tian S, Luft JC, DeSimone JM. Spatially controlled coating of continuous liquid interface production microneedles for transdermal protein delivery. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2018; 284: 122–132. https://doi.org/10.1016/j.jconrel.2018.05.042.

[16] Matadh AV, Jakka D, Pragathi SG, Rangappa S, Shivakumar HN, Maibach H, *et al*. Polymer-Coated Polymeric (PCP) Microneedles for Controlled Dermal Delivery of 5-Fluorouracil. AAPS PharmSciTech. 2022; 24: 9. https://doi.org/10.1208/s12249-022-02471-x.

[17] Xu J, Lin S, Chen H, Yang G, Zhou M, Liu Y, *et al*. Highly Active Frozen Nanovesicles Microneedles for Senile Wound Healing via Antibacteria, Immunotherapy, and Skin Regeneration. Advanced Healthcare Materials. 2024; 13: e2304315. https://doi.org/10.1002/adhm.202304315.

[18] Li X, Xiao X, Zhang Y, Long R, Kankala RK, Wang S, *et al*. Microneedles based on hyaluronic acid-polyvinyl alcohol with antibacterial, anti-inflammatory, and antioxidant effects promote diabetic wound healing. International Journal of Biological Macromolecules. 2024; 282: 137185. https://doi.org/10.1016/j.ijbiomac.2024.137185.

[19] Shrestha N, Karve T, Kipping T, Banga AK. Fabrication of Poly Lactic-*co*-Glycolic Acid Microneedles for Sustained Delivery of Lipophilic Peptide-Carfilzomib. Molecular Pharmaceutics. 2024; 21: 5192–5204. https://doi.org/10.1021/acs.molpharmaceut.4c00593.

[20] Bui VD, Son S, Xavier W, Nguyen VQ, Jung JM, Lee J, *et al*. Dissolving microneedles for long-term storage and transdermal delivery of extracellular vesicles. Biomaterials. 2022; 287: 121644. https://doi.org/10.1016/j.biomaterials.2022.121644.

[21] Howells O, Blayney GJ, Gualeni B, Birchall JC, Eng PF, Ashraf H, *et al*. Design, fabrication, and characterisation of a silicon microneedle array for transdermal therapeutic delivery using a single step wet etch process. European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V. 2022; 171: 19–28. https://doi.org/10.1016/j.ejpb.2021.06.005.

[22] O'Mahony C, Sebastian R, Tjulkins F, Whelan D, Bocchino A, Hu Y, *et al*. Hollow silicon microneedles, fabricated using combined wet and dry etching techniques, for transdermal delivery and diagnostics. International Journal of Pharmaceutics. 2023; 637: 122888. https://doi.org/10.1016/j.ijpharm.2023.122888.

[23] Dervisevic M, Alba M, Adams TE, Prieto-Simon B, Voelcker NH. Electrochemical immunosensor for breast cancer biomarker detection using high-density silicon microneedle array. Biosensors & Bioelectronics. 2021; 192: 113496. https://doi.org/10.1016/j.bios.2021.113496.

[24] Pradeep Narayanan S, Raghavan S. Fabrication and characterization of gold-coated solid silicon microneedles with improved biocompatibility. The International Journal of Advanced Manufacturing Technology. 2019; 104: 3327–3333. https://doi.org/10.1007/s00170-018-2596-3.

[25] Cahill EM, Keaveney S, Stuettgen V, Eberts P, Ramos-Luna P, Zhang N, *et al*. Metallic microneedles with interconnected porosity: a scalable platform for biosensing and drug delivery. Acta Biomaterialia. 2018; 80: 401–411. https://doi.org/10.1016/j.actbio.2018.09.007.

[26] Skoog SA, Miller PR, Boehm RD, Sumant AV, Polsky R, Narayan RJ. Nitrogen-incorporated ultrananocrystalline diamond microneedle arrays for electrochemical biosensing. Diamond and Related Materials. 2015; 54: 39–46. https://doi.org/10.1016/j.diamond.2014.11.016.

[27] Yadav S, Dogra S. A Cutaneous Reaction to Microneedling for Postacne Scarring Caused by Nickel Hypersensitivity. Aesthetic Surgery Journal/The American Society for Aesthetic Plastic Surgery. 2016; 36: NP168–NP170. https://doi.org/10.1093/asj/sjv229.

[28] Zong Q, Peng X, Wu H, Ding Y, Ye X, Gao X, *et al*. Copper-gallate metal-organic framework encapsulated multifunctional konjac glucomannan microneedles patches for promoting wound healing. International Journal of Biological Macromolecules. 2024; 257: 128581. https://doi.org/10.1016/j.ijbiomac.2023.128581.

[29] Bystrova S, Luttge R. Micromolding for ceramic microneedle arrays. Microelectronic Engineering. 2011; 88: 1681–1684. https://doi.org/10.1016/j.mee.2010.12.067.

[30] Kargozar S, Singh RK, Kim HW, Baino F. "Hard" ceramics for "Soft" tissue engineering: Paradox or opportunity? Acta Biomaterialia. 2020; 115: 1–28. https://doi.org/10.1016/j.actbio.2020.08.014.

[31] Gholami S, Mohebi MM, Hajizadeh-Saffar E, Ghanian MH, Zarkesh I, Baharvand H. Fabrication of microporous inorganic microneedles by centrifugal casting method for transdermal extraction and delivery. International Journal of Pharmaceutics. 2019; 558: 299–310. https://doi.org/10.1016/j.ijpharm.2018.12.089.

[32] Liu P, Du H, Wu Z, Wang H, Tao J, Zhang L, *et al*. Hydrophilic and anti-adhesive modification of porous polymer microneedles for rapid dermal interstitial fluid extraction. Journal of Materials Chemistry. B. 2021; 9: 5476–5483. https://doi.org/10.1039/d1tb00873k.

[33] Sabbagh F, Kim BS. Ex Vivo Transdermal Delivery of Nicotinamide Mononucleotide Using Polyvinyl Alcohol Microneedles. Polymers. 2023; 15: 2031. https://doi.org/10.3390/polym15092031.

[34] Li Y, Vora LK, Wang J, Sabri AHB, Graham A, McCarthy HO, *et al*. Poly(acrylic acid)/Poly(vinyl alcohol) Microarray Patches for Continuous Transdermal Delivery of Levodopa and Carbidopa: *In Vitro* and *In Vivo* Studies. Pharmaceutics. 2024; 16: 676. https://doi.org/10.3390/pharmaceutics16050676.

[35] Zhang X, Gan J, Fan L, Luo Z, Zhao Y. Bioinspired Adaptable Indwelling Microneedles for Treatment of Diabetic Ulcers. Advanced Materials. 2023; 35: e2210903. https://doi.org/10.1002/adma.202210903.

[36] Jiang Z, Li J, Wang J, Pan Y, Liang S, Hu Y, *et al*. Multifunctional fucoidan-loaded Zn-MOF-encapsulated microneedles for MRSA-infected wound healing. Journal of Nanobiotechnology. 2024; 22: 152. https://doi.org/10.1186/s12951-024-02398-4.

[37] Yao WD, Zhou JN, Tang C, Zhang JL, Chen ZY, Li Y, *et al*. Hydrogel Microneedle Patches Loaded with Stem Cell Mitochondria-Enriched Microvesicles Boost the Chronic Wound Healing. ACS Nano. 2024; 18: 26733–26750. https://doi.org/10.1021/acsnano.4c06921.

[38] Zhang Y, Wang S, Yang Y, Zhao S, You J, Wang J, *et al*. Scarless wound healing programmed by core-shell microneedles. Nature Communications. 2023; 14: 3431. https://doi.org/10.1038/s41467-023-39129-6.

[39] Zhang X, Chen X, Hong H, Hu R, Liu J, Liu C. Decellularized extracellular matrix scaffolds: Recent trends and emerging strategies in tissue engineering. Bioactive Materials. 2021; 10: 15–31. https://doi.org/10.1016/j.bioactmat.2021.09.014.

[40] Shimoda H, Yagi H, Higashi H, Tajima K, Kuroda K, Abe Y, *et al*. Decellularized liver scaffolds promote liver regeneration after partial hepatectomy. Scientific Reports. 2019; 9: 12543. https://doi.org/10.1038/s41598-019-48948-x.

[41] Wang Z, Sun F, Lu Y, Pan S, Yang W, Zhang G, *et al*. Rapid preparation of decellularized trachea as a 3D scaffold for organ engineering. The International Journal of Artificial Organs. 2021; 44: 55–64. https://doi.org/10.1177/0391398820924041.

[42] Barajaa MA, Otsuka T, Ghosh D, Kan HM, Laurencin CT. Development of porcine skeletal muscle extracellular matrix-derived hydrogels with improved properties and low immunogenicity. Proceedings of the National Academy of Sciences of the United States of America. 2024; 121: e2322822121. https://doi.org/10.1073/pnas.2322822121.

[43] Ma H, Xu J, Fang H, Su Y, Lu Y, Shu Y, *et al*. A capsule-based scaffold incorporating decellularized extracellular matrix and curcumin for islet beta cell therapy in type 1 diabetes mellitus. Biofabrication. 2024; 16: 45038. https://doi.org/10.1088/1758-5090/ad7907.

[44] Di Francesco D, Di Varsavia C, Casarella S, Donetti E, Manfredi M, Mantovani D, *et al*. Characterisation of Matrix-Bound Nanovesicles (MBVs) Isolated from Decellularised Bovine Pericardium: New Frontiers in Regenerative Medicine. International Journal of Molecular Sciences. 2024; 25: 740. https://doi.org/10.3390/ijms25020740.

[45] Padma AM, Alshaikh AB, Song MJ, Akouri R, Oltean M, Brännström M, *et al*. Decellularization protocol-dependent damage-associated molecular patterns in rat uterus scaffolds differentially affect the immune response after transplantation. Journal of Tissue Engineering and Regenerative Medicine. 2021; 15: 674–685. https://doi.org/10.1002/term.3217.

[46] Smart I, Goecke T, Ramm R, Petersen B, Lenz D, Haverich A, *et al*. Dot blots of solubilized extracellular matrix allow quantification of human antibodies bound to epitopes present in decellularized porcine pulmonary heart valves. Xenotransplantation. 2021; 28: e12646. https://doi.org/10.1111/xen.12646.

[47] Hülsmann J, Grün K, El Amouri S, Barth M, Hornung K, Holzfuß C, *et al*. Transplantation material bovine pericardium: biomechanical and immunogenic characteristics after decellularization vs. glutaraldehyde-fixing. Xenotransplantation. 2012; 19: 286–297. https://doi.org/10.1111/j.1399-3089.2012.00719.x.

[48] Kasravi M, Ahmadi A, Babajani A, Mazloomnejad R, Hatamnejad MR, Shariatzadeh S, *et al*. Immunogenicity of decellularized extracellular matrix scaffolds: a bottleneck in tissue engineering and regenerative medicine. Biomaterials Research. 2023; 27: 10. https://doi.org/10.1186/s40824-023-00348-z.

[49] Willemse J, Verstegen MMA, Vermeulen A, Schurink IJ, Roest HP, van der Laan LJW, *et al*. Fast, robust and effective decellularization of whole human livers using mild detergents and pressure controlled perfusion. Materials Science & Engineering. C, Materials for Biological Applications. 2020; 108: 110200. https://doi.org/10.1016/j.msec.2019.110200.

[50] Struecker B, Butter A, Hillebrandt K, Polenz D, Reutzel-Selke A, Tang P, *et al*. Improved rat liver decellularization by arterial perfusion under oscillating pressure conditions. Journal of Tissue Engineering and Regenerative Medicine. 2017; 11: 531–541. https://doi.org/10.1002/term.1948.

[51] Zubarevich A, Osswald A, Amanov L, Arjomandi Rad A, Schmack B, Ruhparwar A, *et al*. Development and evaluation of a novel combined perfusion decellularization heart-lung model for tissue engineering of bioartificial heart-lung scaffolds. Artificial Organs. 2023; 47: 481–489. https://doi.org/10.1111/aor.14419.

[52] Jambar Nooshin B, Tayebi T, Babajani A, Khani MM, Niknejad H. Effects of Different Perfusing Routes through The Portal Vein, Hepatic Vein, and Biliary Duct on Whole Rat Liver Decellularization. Cell Journal. 2023; 25: 35–44. https://doi.org/10.22074/cellj.2022.557600.1081.

[53] Qu J, Van Hogezand RM, Zhao C, Kuo BJ, Carlsen BT. Decellularization of a Fasciocutaneous Flap for Use as a Perfusable Scaffold. Annals of Plastic Surgery. 2015; 75: 112–116. https://doi.org/10.1097/SAP.0000000000000157.

[54] Duisit J, Amiel H, Orlando G, Dedriche A, Behets C, Gianello P, *et al*. Face Graft Scaffold Production in a Rat Model. Plastic and Reconstructive Surgery. 2018; 141: 95–103. https://doi.org/10.1097/PRS.0000000000003910.

[55] Roth SP, Erbe I, Burk J. Decellularization of Large Tendon Specimens: Combination of Manually Performed Freeze-Thaw Cycles and Detergent Treatment. Methods in Molecular Biology. 2018; 1577: 227–237. https://doi.org/10.1007/7651_2017_49.

[56] Zhao F, Cheng J, Zhang J, Yu H, Dai W, Yan W, *et al*. Comparison of three different acidic solutions in tendon decellularized extracellular matrix bio-ink fabrication for 3D cell printing. Acta Biomaterialia. 2021; 131: 262–275. https://doi.org/10.1016/j.actbio.2021.06.026.

[57] Kao CY, Nguyen HQ, Weng YC. Characterization of Porcine Urinary Bladder Matrix Hydrogels from Sodium Dodecyl Sulfate Decellularization Method. Polymers. 2020; 12: 3007. https://doi.org/10.3390/polym12123007.

[58] Kasturi M, Vasanthan KS. Harvesting decellularized liver extracellular matrix from rodents for 3D scaffold fabrication. Artificial Cells, Nanomedicine, and Biotechnology. 2024; 52: 175–185. https://doi.org/10.1080/21691401.2024.2319893.

[59] Barthold JE, McCreery KP, Martinez J, Bellerjeau C, Ding Y, Bryant SJ, *et al*. Particulate ECM biomaterial ink is 3D printed and naturally crosslinked to form structurally-layered and lubricated cartilage tissue mimics. Biofabrication. 2022; 14: 25021. https://doi.org/10.1088/1758-5090/ac584c.

[60] Jeong W, Kim MK, Kang HW. Effect of detergent type on the performance of liver decellularized extracellular matrix-based bioinks. Journal of Tissue Engineering. 2021; 12: 2041731421997091. https://doi.org/10.1177/2041731421997091.

[61] Das P, Mishra R, Devi B, Rajesh K, Basak P, Roy M, *et al*. Decellularized xenogenic cartilage extracellular matrix (ECM) scaffolds for the reconstruction of osteochondral defects in rabbits. Journal of Materials Chemistry. B. 2021; 9: 4873–4894. https://doi.org/10.1039/d1tb00314c.

[62] Omid H, Abdollahi S, Bonakdar S, Haghighipour N, Shokrgozar MA, Mohammadi J. Biomimetic vascular tissue engineering by decellularized scaffold and concurrent cyclic tensile and shear stresses. Journal of Materials Science. Materials in Medicine. 2023; 34: 12. https://doi.org/10.1007/s10856-023-06716-4.

[63] Bera AK, Sriya Y, Pati F. Formulation of Dermal Tissue Matrix Bioink by a Facile Decellularization Method and Process Optimization for 3D Bioprinting toward Translation Research. Macromolecular Bioscience. 2022; 22: e2200109. https://doi.org/10.1002/mabi.202200109.

[64] Singh G, Satpathi S, Gopala Reddy BV, Singh MK, Sarangi S, Behera PK, *et al*. Impact of various detergent-based immersion and perfusion decellularization strategies on the novel caprine pancreas derived extracellular matrix scaffold. Frontiers in Bioengineering and Biotechnology. 2023; 11: 1253804. https://doi.org/10.3389/fbioe.2023.1253804.

[65] Belviso I, Sacco AM, Cozzolino D, Nurzynska D, Di Meglio F, Castaldo C, *et al*. Cardiac-derived extracellular matrix: A decellularization protocol for heart regeneration. PloS One. 2022; 17: e0276224. https://doi.org/10.1371/journal.pone.0276224.

[66] Meșină M, Mîndrilă I, Meșină-Botoran MI, Mîndrilă LA, Farhangee A, Pirici I. Optimization Techniques of Single-Detergent Based Protocols for Heart Tissue Decellularization. Current Health Sciences Journal. 2023; 49: 156–162. https://doi.org/10.12865/CHSJ.49.02.156.

[67] Bae JY, Park SY, Shin YH, Choi SW, Kim JK. Preparation of human decellularized peripheral nerve allograft using amphoteric detergent and nuclease. Neural Regeneration Research. 2021; 16: 1890–1896. https://doi.org/10.4103/1673-5374.306091.

[68] Singh A, Singh SK, Kumar V, Gupta J, Kumar M, Sarma DK, *et al.* Derivation and Characterization of Novel Cytocompatible Decellularized Tissue Scaffold for Myoblast Growth and Differentiation. Cells. 2023; 13: 41. https://doi.org/10.3390/cells13010041.

[69] Zhang J, Xiang Y, Yang Q, Chen J, Liu L, Jin J, *et al*. Adipose-derived stem cells derived decellularized extracellular matrix enabled skin regeneration and remodeling. Frontiers in Bioengineering and Biotechnology. 2024; 12: 1347995. https://doi.org/10.3389/fbioe.2024.1347995.

[70] Nyambat B, Manga YB, Chen CH, Gankhuyag U, Pratomo Wp A, Kumar Satapathy M, *et al*. New Insight into Natural Extracellular Matrix: Genipin Cross-Linked Adipose-Derived Stem Cell Extracellular Matrix Gel for Tissue Engineering. International Journal of Molecular Sciences. 2020; 21: 4864. https://doi.org/10.3390/ijms21144864.

[71] Antarianto RD, Pragiwaksana A, Septiana WL, Mazfufah NF, Mahmood A. Hepatocyte Differentiation from iPSCs or MSCs in Decellularized Liver Scaffold: Cell-ECM Adhesion, Spatial Distribution, and Hepatocyte Maturation Profile. Organogenesis. 2022; 18: 2061263. https://doi.org/10.1080/15476278.2022.2061263.

[72] Batista VF, de Sá Schiavo Matias G, Carreira ACO, Smith LC, Rodrigues R, Araujo MS, *et al*. Recellularized rat testis scaffolds with embryoid bodies cells: a promising approach for tissue engineering. Systems Biology in Reproductive Medicine. 2022; 68: 44–54. https://doi.org/10.1080/19396368.2021.2007554.

[73] Ebner-Peking P, Krisch L, Wolf M, Hochmann S, Hoog A, Vári B, *et al*. Self-assembly of differentiated progenitor cells facilitates spheroid human skin organoid formation and planar skin regeneration. Theranostics. 2021; 11: 8430–8447. https://doi.org/10.7150/thno.59661.

[74] Eminli S, Kwieder B, Yi K, Huang CJZ, Moon JI, Chang CH, *et al*. Clinically compatible advances in blood-derived endothelial progenitor cell isolation and reprogramming for translational applications. New Biotechnology. 2021; 63: 1–9. https://doi.org/10.1016/j.nbt.2021.02.001.

[75] Reinders MEJ, Groeneweg KE, Hendriks SH, Bank JR, Dreyer GJ, de Vries APJ, *et al*. Autologous bone marrow-derived mesenchymal stromal cell therapy with early tacrolimus withdrawal: the randomized prospective, single-center, open-label TRITON study. American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2021; 21: 3055–3065. https://doi.org/10.1111/ajt.16528.

[76] Avila-Portillo LM, Aristizabal F, Riveros A, Abba MC, Correa D. Modulation of Adipose-Derived Mesenchymal Stem/Stromal Cell Transcriptome by G-CSF Stimulation. Stem Cells International. 2020; 2020: 5045124. https://doi.org/10.1155/2020/5045124.

[77] Ahn SY, Maeng YS, Kim YR, Choe YH, Hwang HS, Hyun YM. *In vivo* monitoring of dynamic interaction between neutrophil and human umbilical cord blood-derived mesenchymal stem cell in mouse liver during sepsis. Stem Cell Research & Therapy. 2020; 11: 44. https://doi.org/10.1186/s13287-020-1559-4.

[78] Liu J, Hanson A, Yin W, Wu Q, Wauthier E, Diao J, *et al*. Decellularized liver scaffolds for constructing drug-metabolically functional *ex vivo* human liver models. Bioactive Materials. 2024; 43: 162–180. https://doi.org/10.1016/j.bioactmat.2024.09.029.

[79] Smith MJ, Dempsey SG, Veale RW, Duston-Fursman CG, Rayner CAF, Javanapong C, *et al*. Further structural characterization of ovine forestomach matrix and multi-layered extracellular matrix composites for soft tissue repair. Journal of Biomaterials Applications. 2022; 36: 996–1010. https://doi.org/10.1177/08853282211045770.

[80] Kim BS, Kwon YW, Kong JS, Park GT, Gao G, Han W, *et al*. 3D cell printing of *in vitro* stabilized skin model and *in vivo* pre-vascularized skin patch using tissue-specific extracellular matrix bioink: a step towards advanced skin tissue engineering. Biomaterials. 2018; 168: 38–53. https://doi.org/10.1016/j.biomaterials.2018.03.040.

[81] Chandika P, Khan F, Heo SY, Kim YM, Yi M, Jung WK. Enhanced wound-healing capability with inherent antimicrobial activities of usnic acid incorporated poly(ε-caprolactone)/decellularized extracellular matrix nanofibrous scaffold. Biomaterials Advances. 2022; 140: 213046. https://doi.org/10.1016/j.bioadv.2022.213046.

[82] Bhar B, Ranta P, Samudrala PK, Mandal BB. Omentum Extracellular Matrix-Silk Fibroin Hydroscaffold Promotes Wound Healing through Vascularization and Tissue Remodeling in the Diabetic Rat Model. ACS Biomaterials Science & Engineering. 2024; 10: 1090–1105. https://doi.org/10.1021/acsbiomaterials.3c01877.

[83] Lee J, Rabbani CC, Gao H, Steinhart MR, Woodruff BM, Pflum ZE, *et al*. Hair-bearing human skin generated entirely from pluripotent stem cells. Nature. 2020; 582: 399–404. https://doi.org/10.1038/s41586-020-2352-3.

[84] Sumathy B, Velayudhan S. Fabrication and evaluation of a bilayered gelatin based scaffold with arrayed micro-pits for full-thickness skin construct. International Journal of Biological Macromolecules. 2023; 251: 126360. https://doi.org/10.1016/j.ijbiomac.2023.126360.

[85] Jackson R, Eade S, Zehbe I. An epithelial organoid model with Langerhans cells for assessing virus-host interactions. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 2019; 374: 20180288. https://doi.org/10.1098/rstb.2018.0288.

[86] Böttcher-Haberzeth S, Klar AS, Biedermann T, Schiestl C, Meuli-Simmen C, Reichmann E, *et al*. "Trooping the color": restoring the original donor skin color by addition of melanocytes to bioengineered skin analogs. Pediatric Surgery International. 2013; 29: 239–247. https://doi.org/10.1007/s00383-012-3217-0.

[87] Chen Z, Zhang B, Shu J, Wang H, Han Y, Zeng Q, *et al*. Human decellularized adipose matrix derived hydrogel assists mesenchymal stem cells delivery and accelerates chronic wound healing. Journal of Biomedical Materials Research. Part A. 2021; 109: 1418–1428. https://doi.org/10.1002/jbm.a.37133.

[88] Chang H, Wen X, Li Z, Ling Z, Zheng Y, Xu C. Co-delivery of dendritic cell vaccine and anti-PD-1 antibody with cryomicroneedles for combinational immunotherapy. Bioengineering & Translational Medicine. 2023; 8: e10457. https://doi.org/10.1002/btm2.10457.

[89] Suriyaamporn P, Pornpitchanarong C, Charoenying T, Dechsri K, Ngawhirunpat T, Opanasopit P, *et al*. Artificial intelligence-driven hydrogel microneedle patches integrating 5-fluorouracil inclusion complex-loaded flexible pegylated liposomes for enhanced non-melanoma skin cancer treatment. International Journal of Pharmaceutics. 2025; 669: 125072. https://doi.org/10.1016/j.ijpharm.2024.125072.

[90] Anbazhagan G, Suseela SB, Sankararajan R. Design, analysis and fabrication of solid polymer microneedle patch using CO_2 laser and polymer molding. Drug Delivery and Translational Research. 2023; 13: 1813–1827. https://doi.org/10.1007/s13346-023-01296-w.

[91] Aldawood FK, Andar A, Desai S. A Comprehensive Review of Microneedles: Types, Materials, Processes, Characterizations and Applications. Polymers. 2021; 13: 2815. https://doi.org/10.3390/polym13162815.

[92] Hartmann XH, van der Linde P, Homburg EF, van Breemen LC, de Jong AM, Luttge R. Insertion Process of Ceramic Nanoporous Microneedles by Means of a Novel Mechanical Applicator Design. Pharmaceutics. 2015; 7: 503–522. https://doi.org/10.3390/pharmaceutics7040503.

[93] Kim MK, Jeong W, Kang HW. Liver dECM-Gelatin Composite Bioink for Precise 3D Printing of Highly Functional Liver Tissues. Journal of Functional Biomaterials. 2023; 14: 417. https://doi.org/10.3390/jfb14080417.

[94] Kim MK, Jeong W, Jeon S, Kang HW. 3D bioprinting of dECM-incorporated hepatocyte spheroid for simultaneous promotion of cell-cell and -ECM interactions. Frontiers in Bioengineering and Biotechnology. 2023; 11: 1305023. https://doi.org/10.3389/fbioe.2023.1305023.

Editor's note: The Scientific Editor responsible for this paper was Bo Lei.

Received: 22nd January 2025; **Accepted**: 10th July 2025; **Published**: 31st October 2025