

Biomaterials and Scaffolds that Promote Regenerative rather than Fibrotic Healing

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Abstract

Wound healing after dermal wounding is a major clinical problem and for adult skin, healing reverts to fibrotic repair, which involves an excess of collagen deposition and an activation of myofibroblasts. Embryonic skin, on the other hand, quickly regenerates without scarring, with tightly regulated immune responses and balanced cytokine signaling. The biomaterial scaffolds have been developed to become active therapeutic platforms that can alter the course of the wound from fibrosis to regeneration by mimicking essential microenvironmental signals. Scaffold design principles (architecture, porosity, stiffness, and surface topography) are discussed and natural and synthetic biomaterials are reviewed for their ability to induce regeneration associated phenotypes. We highlight immune-modulatory strategies which switch macrophages to pro-resolving phenotypes and inhibit fibrotic cascade. In addition to state of the art fabrication technologies like 3D bioprinting and electrospinning, advanced biofunctionalization strategies like sustained delivery of anti-fibrotic growth factors, miRNA therapeutics and cell-seeded constructs are also critically evaluated. Preliminary data have shown that strategically designed scaffolds can markedly decrease scar index and restore skin appendages. Lastly, we discuss translational issues and trends for personalized, phase-dependent responsive scaffolds. This analysis emphasizes that biomaterial-directed regeneration is a pedagogic therapeutic model that can revolutionize scar management in the clinical practice.

Keywords: scarless wound healing; biomaterial scaffolds; anti-fibrotic; immune modulation; regenerative medicine; tissue engineering; 3D bioprinting

1. Introduction

The process of wound healing in adult humans always results in scar formation, which is a fibrotic repair, and is unable to reproduce the structural and functional features of normal skin [1, 2]. The pathological extremes of this process are hypertrophic scars and keloids, which are a large burden physically, psychologically, and economically for millions of patients around the world [3]. Surgical revision, corticosteroid injection, laser therapy and silicone gel sheeting are still mainly palliative therapies in the treatment of current clinical management, which treat symptoms but not the pathophysiology [4]. The basic problem is that the adult wound healing paradigm is the one used, which is a fast,

inflammation mediated fibrotic response favoring wound closure over tissue quality [1].

A breakthrough came when the observation was made that skin wounds heal perfectly in early gestation mammalian embryos, which is without scarring and with complete restoration of skin appendages and function, which is indistinguishable from uninjured skin [1, 3]. Such a regenerative ability can be attributed to several intrinsic properties: a dampened inflammatory response; a predominant TGF- β 3 over TGF- β 1 signal; a high hyaluronic acid-rich extracellular matrix (ECM); and having a resident population of regenerative fibroblast lineages [5, 3]. These findings set a crucial foundation the adult wound microenvironment does not by default have to be regenerated, but is actively sent on the road to fibrosis. Thus,

biomaterial scaffolds offer a distinct viable approach to "reprogramming" this trajectory, by creating microenvironmental cues that replicate embryonic healing conditions [5, 6].

The traditional wound dressings simply serve as infection barriers and moisture barriers. The use of bioactive, instructive biomaterials, however, that interact dynamically with cells, modulate immune responses and deliver therapeutic cargo spatiotemporally controlled, has significantly changed over the last 20 years [7, 8, 9]. The design of modern scaffolds is aimed not just at filling the tissue defect, but at controlling the whole tissue healing process, from hemostasis to inflammation, proliferation, remodeling, to functional regeneration [10, 11].

The central hypothesis in this review is that the properties of a scaffold microenvironment (biochemical composition, architecture, mechanical properties and degradation kinetics) all play a role in determining the healing of the wound, either by fibrosis or by regeneration [12, 13]. These parameters can be systematically engineered to inhibit myofibroblast

activation, stimulate the organized deposition of collagen, encourage vascularization and even regenerate skin appendages, like hair follicles and sweat glands [14, 15].

This review covers all the biomaterial-directed approaches which aim at scarless regeneration of skin. We first review the mechanistic principles of fibrotic versus reparative healing and identify critical molecular targets that can be targeted by scaffolding. Then we critically review and discuss natural and synthetic biomaterial platforms, advanced architectural design parameters, and biofunctionalization strategies such as delivery of growth factors, gene therapeutics, and cell seeded constructs. The review will focus on fabrication technologies that allow for control of scaffold properties and then on the preclinical data from well-established animal models. Last, we discuss ongoing issues of clinical translation and future directions of personalized, phase-adaptive scaffold systems. This integrative analysis will set the foundation for evidence based design principles to move towards the development of clinically effective, scar preventing biomaterial therapies more quickly.

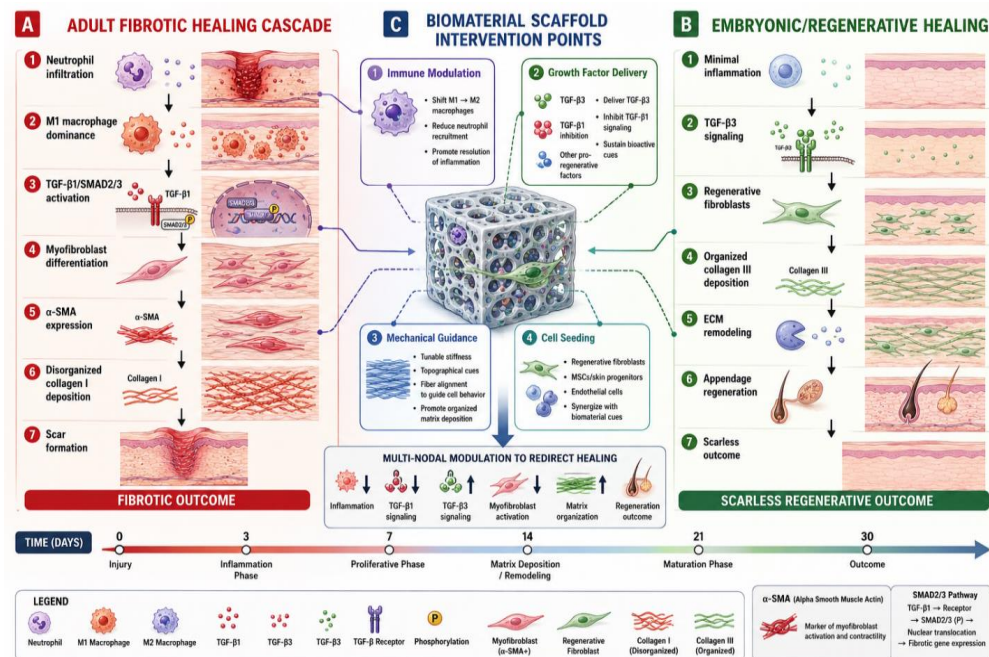


Figure 1. Wound healing trajectories and biomaterial intervention strategies are divergent. (A) In the adult fibrotic repair, there was strong inflammation, activation of myfibroblasts by TGF-β1 and collagen deposition in irregular pattern. (B) Embryo scarless healing: Attenuated inflammation, predominance of TGF-β3, organized tissue regeneration and functional restoration of the appendage. (C) Engineered scaffolds regulate several components of the fibrotic cascade to promote healing toward regeneration instead of fibrosis.

2. Mechanistic Foundations: Why Scaffolds Fail or Succeed in Preventing Scars

Biomaterials scaffolds may help to control the intricate interaction of growth factors, cytokines, and cellular mediators influencing the shift from acute wound healing to pathological

scarring [3, 16]. This process is mostly dependent on the TGF-β pathway and a change in the ratio of TGF-β1, which promotes the conversion of fibroblasts into myofibroblasts, collagen development, and wound contraction, and TGF-β3, which favors a regenerative healing with little scarring [5, 17]. TGF-β1 signals mostly through SMAD2/3-dependent pathways that cause alpha-smooth muscle actin (α-SMA) to

be expressed more and extracellular matrix (ECM) to be produced; TGF- β 3 signals mostly via SMAD2/3-independent routes that slow down fibrosis [3, 18]. A good scaffold-based technique to restore this crucial signaling balance is biomaterial-mediated sustained administration of the therapeutic agent TGF- β 3 or small-molecule inhibitors of TGF- β receptor I (T β RI), such SB431542 [19, 20].

An significant profibrotic mediator controlled after TGF- β 1, connective tissue development factor (CTGF) promotes collagen creation, angiogenesis, and tissue remodeling [16]. DPP4-positive zinc sulfide cellulose nanofiber (ZUCNF) scaffolds have been demonstrated to selectively target a subgroup of scar-forming cells therefore leading to scarless healing through DPP4 inhibition [21]. Mature scars also have an unorganized ECM and collagen cross-linking by lysyl oxidase (LOX) and matrix metalloproteinase (MMP) dysregulation [4, 16]. Therefore, LOX inhibitors or MMP activity modulation can be given via scaffolds to disrupt the mechanical feedback loop driving fibrosis [4].

Besides inhibiting fibrotic mediators, active induction of developmental and regenerative pathways is needed for successful scarless regeneration. The Wnt/beta-catenin pathway controls wound healing in a double way; activation drives transient proliferation and re-epithelialization and sustained fibrosis [16]. The modulation of Wnt signaling spatiotemporally, for example by sequestration of Wnt ligands, or Wnt inhibitors like Dickkopf-related protein 1 (DKK1), can influence tissue patterning to direct tissue regeneration [15, 16].

Angiogenesis, fibroblast proliferation and ECM synthesis are stimulated by members of the fibroblast growth factor (FGF) family, specifically basic fibroblast growth factor (bFGF/FGF-2), in ways that promote the orderly, physiologic remodeling rather than the chaotic deposition of scar tissue [22]. Immobilization of FGF-2 on collagen scaffolds using Heparan sulfate-mimetic improves stability and bioavailability, leading to vascularized granulation tissue formation and limiting both fibrotic processes and excessive scar tissue formation [22]. During the proliferative phase, adequate perfusion is maintained by gradients of vascular endothelial growth factor (VEGF) within the scaffolds that avoid activation of the fibroblasts by hypoxia [16].

Further targets for scaffold mediated delivery are anti-fibrotic cytokines, such as interleukin-10 (IL-10) and the small leucine-rich proteoglycan, decorin, which is a TGF- β 1 activity antagonist [5, 16]. The convergence of these pathways in a mechanistic way argues for the superiority of multi-modal

designs, that simultaneously inhibit fibrotic and promote regenerative signals [17, 23].

Healing following biomaterial implantation is determined by the innate immune response to biomaterial implantation. Neutrophils immediately enter the wound space, emitting reactive oxygen species (ROS), and pro-inflammatory cytokines which if sustained, create a fibrogenic environment [5, 24]. The surface chemistry, hydrophobicity and degradation products of scaffolds directly affect the lifespan and activation state of neutrophils [24].

Macrophages are the key players of the immune-scaffold interface. M1 macrophages are the classical activated phenotype, which produces inflammatory cytokines such as TNF, IL-1 and IL-6, that can activate fibroblasts and promote ECM production [5, 25]. Alternatively activated M2 macrophages mediate inflammation resolution by secreting IL-10 and TGF- β 3, and regulatory T cells (Tregs) also have an anti-inflammatory role and help to promote scarless healing [6, 26]. Biomaterial scaffolds can actively "educate" immune cells: hydrogel scaffolds designed to activate adaptive immune responses have been shown to impart regenerative wound healing by Treg polarization [6, 26]. An architectural study of immune cells around biomaterials during large-scale wound regeneration has been used to show that the scaffold structure influences spatial distribution and phenotypic polarization of immune cells [25].

The foreign body response is a continuous challenge for non-degradable or slow degrading materials. Chronic macrophage fusion into foreign body giant cells (FBGCs) and fibrous encapsulation are analogous to pathological scarring mechanisms [7,8]. The degradation kinetics of scaffolds need to therefore be carefully controlled: if it is too fast, there is an early inflammatory response and mechanical support is lost, and if it is too slow, there is chronic foreign body response [14, 27]. An alternative approach that is physiologically regulated is the use of enzyme-responsive degradation strategies that rely on endogenous MMP activity to break down the scaffold [14, 28].

The timing of immune modulation is also important. A new paradigm to be developed is the phase-adaptive scaffold that mimics the shift from pro- to anti-inflammatory towards physiological healing phases [28]. Recently, a dynamically phase-adaptive regulating hydrogel has been developed to sequentially deliver anti-inflammatory and pro-regenerative cargoes that selectively heal wounds through ultrafast anti-fibrotic wound healing according to microenvironmental cues at the wound [28]. This biomimetic strategy, which aims at mimicking the natural resolution process of inflammation that

is seen in the embryonic healing process, highlights the importance of creating scaffolds that can be dynamic and responsive rather than static matrices [5, 28].

3. Scaffold Design Strategies for Scarless Regeneration

Biomaterials derived from a natural source have intrinsic bioactivity, biocompatibility and structural resemblance to native ECM, and are especially appealing for scarless skin regeneration [7, 10]. The main structural protein of dermis, collagen, is the main scaffold material used in commercial products and experimental designs [22, 32]. However, native collagen scaffolds are not suitable for use in inhibiting the adhesion, migration, and physiological collagen remodeling of fibroblasts because they have to be cross-linked to optimize their degradation rate and mechanical strength [27]. In recent years, it has been shown that collagen scaffolds functionalized with heparan sulphate mimetics greatly improve the bioavailable delivery of FGF-2 and the regenerative healing response [22]. In addition, there has been a demonstration of better tissue regeneration and decreased scar formation in the preclinical models when using collagen-elastin composite dermal scaffolds, and recapitulating the native dermal ECM complexity is critical [32].

Hyaluronic acid (HA) is highly abundant in fetal wounds and scarless tissues, and shows unique immunomodulatory and pro-regenerative properties [3, 10]. The biological activity of HA is highly depends on its molecular weight with high molecular HA attenuating inflammation and low molecular HA fragments inducing angiogenesis and cell proliferation [10]. Hydrogel mixes for wound healing have been created using molecular weight-dependent characteristics that may be precisely changed chemically or by mixing several polymers together [10, 20]. These formulations do not leave scars.

Extracted from *Bombyx mori* silkworm cocoons, silk fibroin has exceptional mechanical characteristics, sluggish disintegration rate, and minimal immunogenicity [31]. A key advantage of faster degrading natural materials is the inability to control degradation rates and mechanical properties, which the tunable β -sheet crystallinity of this material is able to solve [31]. Bioengineered scaffolds using silk fibroin have been shown to promote hemostasis and skin regeneration in critical size full thickness heat induced burn wounds, promoting organized collagen deposition and a decrease in inflammatory infiltrate when compared with conventional wound dressings [31].

The most biomimetic approach is the use of decellularized extracellular matrix (dECM) scaffolds which retain native

tissue architecture, bioactive molecules and mechanical cues [1]. The dermal-specific matrices and small intestinal submucosa (SIS) have been studied to use as a wound healing agent, and they contain endogenous growth factors and basement membrane components that actively direct cell behaviour [1,7]. There are, however, also disadvantages for clinical translation, including batch-to-batch variability, the possibility of immunogenicity due to the presence of residual cellular material, and the problems of scale up [7].

Crustacean shell and brown algae derived chitosan and alginate possess intrinsic antimicrobial properties and hemostatic activity which is beneficial in treating contaminated or exuding wounds [10]. They are not particularly strong on their own, but as used in combination with other polymers, natural or synthetic, they create hybrid systems with improved functions [10, 11].

Synthetic polymers offer predictable and controllable characteristics that work well with the bioactivity of natural materials [8, 9]. The most frequently researched synthetic bases for skin tissue engineering are Poly(Lactic-co-Glycolic Acid) (PLGA) and its homopolymers Lactic Acid (LA) and Glycolic Acid (GA) [8, 14]. By changing the ratio of lactide to glycolide, the degradation rates may be completely regulated; increased glycolide content will accelerate the hydrolytic degradation [14]. Acidic degradation by-products, however, can trigger inflammation and may affect regeneration, which can be countered by the use of enzyme loaded systems to buffer the pH of the local environment or by using different polyester formulations [14].

Polycaprolactone (PCL) has very slow degradation rate (2-4 years), and is very useful for mechanical support of large or mechanically stressed wound sites [14, 29]. The enzyme PCL scaffolds have been shown to exhibit robust controlled degradation of scarless skin tissue regeneration, incorporating the enzymes into the scaffolds to speed up the degradation to match tissue remodeling time scales while maintaining the scaffold's structural integrity through critical healing periods [14]. Cell adhesion and nutrient transport can be improved by adding hydrophilic functionality to PCL by copolymerization or surface modification [29].

Polyethylene glycol (PEG) based hydrogels allow for fine control of mechanical properties, via changing the cross-linking density, covering mechanical moduli across orders of magnitude to match required tissue properties [12]. Incorporation of cell adhesive peptides (such as RGD) renders bioinert PEG interactive, and dynamic cross-linking chemistries allow stress relaxation properties of native ECM viscoelasticity [12, 20]. The photo-induced imine-crosslinking

hydrogels have been used to release therapeutic cargoes in a pulsatile manner, allowing for temporally programmed bioactivity that leads to scarless wound healing [20].

Polyurethane (PU) scaffolds have outstanding elasticity, which matches the elastic properties of native skin, and have proven beneficial in applications such as chronic wounds, where repeated mechanical stress can hinder wound healing [8]. But long-term biostability and possible inflammatory reaction to degradation products must be taken into account [8].

There are limitations of individual natural or synthetic materials and therefore the development of hybrid systems that combine bioactivity, mechanical performance with controlled degradation [11, 13]. Multigradient biomaterials have composition, porosity, and/or mechanical properties that change across space and are similar to the continuous transition seen in native tissue interfaces [13]. This type of designs is especially suitable for full thickness skin regeneration, where microenvironmental cues for the epidermal, dermal and hypodermal compartments are different [13, 15].

Single-unit functionally graded bioscaffolds have been implanted for the treatment of full-thickness skin wounds to promote seamless functional transition from the dense and mechanically durable substructures to the porous and cell-permissive upper layers, resulting in scar-free wounds [30]. Core-shell architectures allow for programmed delivery of drugs: the hydrophobic core provides the protection of sensitive drugs, while the hydrophilic shell releases the pro-regenerative factors at the start and provides sustained release of the anti-fibrotic drugs [20, 28]. Interpenetrating polymer networks (IPNs) are composed by mixing components that are both synthetic and natural and are used to create scaffolds that have high mechanical strength and cellular responsiveness [10].

The combination of NFS and MPs can be achieved in a single architectural framework, as NFS offer high surface area to volume ratio and MPs cargo loading capacity, allowing multi-factorial delivery of therapeutic agents [11, 29]. Nanofiber scaffolds that are aligned in the radial direction have been shown to support directed cell migration and wound healing, and alignment of fibers in the direction of a guidance gradient has been seen to facilitate oriented collagen deposition, which prevents wound contracture [29].

Alongside consideration of the properties of each individual component, the rational design of hybrid scaffolds should take into account emergent behaviors emerging from the interactions between the components. The differential

degradation rates, bonding and phase separation may create complex microenvironments that either synergistically stimulate regeneration or inadvertently initiate inflammatory cascades [11, 13]. This design complexity is increasingly overcome by means of computational modelling and high throughput screening platforms to optimise the hybrid formulation before in vivo validation [13, 25].

4. Architectural and Physical Design Parameters

In fact, the fundamental properties of scaffolds that influence their performance include cell infiltration, nutrient diffusion, removal of waste, and vascular ingrowth, which are all controlled by the scaffold's porosity [9, 13]. Optimal dermal regeneration occurs when pores are between 20-125 μm large, providing enough room for the migration of the fibroblasts and deposition of the ECM, while not too large to cause problems for cell adhesion [27]. Pores smaller than this limit will inhibit cell ingrowth and create fibrous encapsulation, similar to scar tissue, and pores larger than this limit will reduce mechanical integrity and slow epithelialisation [13, 27].

The interconnectivity between pores is also essential: pores that are completely isolated would allow the retention of only a few cells in small volumes of space, while completely interconnected pores would enable the organization of 3D tissues and the formation of vascular channels [9, 13]. Native skin stratification has been mimicked by gradient porosity designs, which are dense at the base of the wound to facilitate hemostasis and mechanical stability and increasingly open toward the surface to favor re-epithelialization, and which have shown better regenerative results [13, 30].

The role of pore geometry is not just one of size. Directional freezing, electrospinning, or 3D bioprinting techniques create anisotropic pores that promote cell alignment and organized ECM deposition, which is the opposite of the disorganized ECM architecture seen in scars [29, 30].

Cells are extremely sensitive to the topographical features at micro- and nanometer scales, which guide migration, proliferation and differentiation by contact guidance mechanisms [12, 29]. Sub-conventionally aligned nanofibers and nanogrooves guide keratinocyte and fibroblast migration in a defined direction and foster parallel organization of collagen fibrils that mimic the native dermal architecture and resist forces that promote the contraction of scar tissue [29]. Structured scaffolds comprising nanofibers aligned in a radial direction have been shown to promote organized tissue structure and/or directed cell migration from the wound periphery toward the center, promoting wound healing [29].

Random orientations, on the other hand, cause isotropic cell migration and random ECM deposition, which leads to predispositions for scar contracture [12]. Nanotopography of programmable immune-activating electrospun fibers directs cell behavior and modulates immune responses in a scarless fashion by means of integrated architectural and biochemical signaling [24]. The nanoscale surface topography also affects the adsorption of proteins, integrin clustering, and mechanotransduction pathways, which affect the activation state of the fibroblasts [12, 24].

The elastic modulus of native human dermis ranges from 0.1 to 0.5 MPa and varies from region to region depending on functional specialization [12, 14]. The stiffness of the scaffold has a significant effect on cell fate via mechanotransductive pathways involving the YAP/TAZ transcriptional co-activators, with substrates with a more native dermal compliance inducing quiescent fibroblast phenotypes and physiological ECM remodeling, while stiffer matrices ($>10\text{kPa}$) induce myofibroblast differentiation, α -SMA expression, and pathological collagen cross-linking [12, 16].

Mechanical tuning of biomaterials has been shown to promote scarless wound healing and regenerate functional skin appendages, leaving stiffness as an independent therapeutic parameter [12]. But static stiffness optimisation is not enough: the wound healing process goes through several stages that present different needs for mechanical properties, such as matrices that are relatively stiff during the initial hemostasis phase and compliant during remodeling, which allows tissue contraction and reorganization without triggering profibrotic signals [14, 28].

The enzymatically degradable cross-links, stress-relaxing viscoelastic materials, or external triggers for softening constitute critical advances called dynamic stiffness [12, 28]. Dynamically phase-adaptive wound healing regulating hydrogel can change between stiff, hemostasis inducing and soft, regeneration promoting matrix states according to cell endogenous enzyme activity, which triggers ultrafast anti-fibrotic wound healing [28]. The biomimetic approach mimics the natural mechanical evolution of healing wounds and highlights the importance of dynamically programmed instead of statically optimized scaffold characteristics.

The scaffold degradation process needs to be tightly controlled to offer mechanical support during the critical stages of healing, while not causing chronic foreign body reactions due to the scaffold's persistence [14, 27]. Excessive degradation (typical of uncross linked collagen or low molecular weight PLGA) leads to early scaffold failure, inflammatory reactions to degradation products, and

inadequate architectural support for scaffolding tissue regeneration [14, 27]. On the other hand, too fast a degradation rate leads to encapsulation of the implant by a dense fibrous tissue, producing a scar around the implant instead of preventing scar tissue formation [27].

Physiologically regulated alternatives to passive hydrolysis, such as enzyme-responsive degradation strategies, have been developed [14, 28]. To promote robust controlled degradation of the PCL-based fibrous scaffolds and simultaneously promote scarless skin tissue regeneration, the degradation of the scaffolds is coupled to the activity of MMPs present in the surrounding tissues. This results in the degradation of the scaffolds occurring as much as when the surrounding tissues are required to take over their mechanical load-bearing functions [14]. Likewise, cell-mediated degradation, in which infiltrating cells actively remodel the scaffold by secreting collagenases and other proteases, also produces degradation products which can have bioactive effects and further modulate healing outcomes [14, 28].

Synchronization of scaffold degradation with the remodeling timeline is a systems-level design challenge that needs to be addressed by material selection, architectural design and biofunctionalization strategies. One way to achieve this temporal complexity is to provide a multi-layered scaffold, characterised by different degradation rates - rapidly degrading surface layers to promote epithelialization on slowly degrading dermal compartments [13, 30].

5. Biofunctionalization Strategies: Active Cargo Delivery

Growth factors are the most well-studied bioactives to be delivered via a scaffold for scarless regeneration, and their delivery methods have been optimized to address their short half-lives, rapid diffusion, and supraphysiological doses when administered via bolus injection [16, 22]. The embryonic isoform of TGF- β (TGF- β 3) which is known to inhibit activation of myofibroblasts and to induce regenerative fibroblast phenotypes has been introduced into collagen scaffolds, fibrin hydrogels, and synthetic polymer matrices [3, 20]. However, TGF- β 3 is very sensitive in nature and requires approaches such as covalent attachment to a scaffold backbone, heparin binding or encapsulation in lipid nanoparticles to stabilize it in vitro and in vivo [22].

When given in sustained-release preparations, basic fibroblast growth factor (bFGF/FGF-2) has been shown to cause angiogenesis, fibroblast growth, and ordered ECM deposition [22]. With the glycosaminoglycan mimic also able to provide a conformationally active form to the growth factor and therefore shield it from proteolysis and present it to target

cell receptors [22], collagen scaffolds including heparan sulfate mimetics show an unexpectedly high ability for retaining and maintaining the bioactivity of FGF-2. Re-establishing the natural sequestration of FGF-2 by the basement membrane's HSPGs is a biomimetic strategy that is representative of the capacity of scaffold biofunctionalization to mimic physiological regulatory processes [22]. Quality of wound healing depends on the rate of re-epithelialization, which is stimulated by epidermal growth factor (EGF) and keratinocyte growth factor (KGF/FGF-7); delayed re-epithelialization allows hypergranulation and is a risk factor for hypertrophic scarring [16]. Pulsatile delivery platforms are platforms that provide a burst release of EGF/KGF in the early phase for rapid healing of the epidermis and then a continuous delivery of anti-fibrotic agents thereafter, as shown to have scarless wound healing in preclinical models [20]. Versatile photo-induced imine-crosslinking hydrogels allow temporal control of such release profiles by tuning the cross-linking densities and stimuli-responsive bond cleavage [20].

Pathological vascularization and inflammation is facilitated by excess of VEGF, which creates angiogenic gradients necessary for perfusion of regenerating tissue [16]. Scaffold mediated spatial control of VEGF delivery is found to lead to physiological, as opposed to chaotic, vascular patterns by restricting VEGF delivery to deeper layers of the scaffold while allowing exposure of the superficial layers to be kept low [16].

The new class of small molecule inhibitors that target profibrotic signaling pathways have translational benefits such as stability, scalability and regulatory experience [19, 21]. When delivered from 3D-printed biomimetic scaffolds, SB431542 is a powerful inhibitor of the TGF- β type I receptor (ALK5) and inhibits SMAD2/3 phosphorylation and myofibroblast differentiation [19]. The hydrophobic compound is protected from degradation during fabrication by extrusion and can be released over time that mimics the activation of the fibroblasts in the stroma during the printing process [19].

A recently discovered population of fibroblasts expressing the enzyme dipeptidyl peptidase-4 (DPP4) is the target of this class of inhibitors, known as DPP4 inhibitors. The small-molecule DPP4 inhibitor is slowly released from zinc sulfide cellulose nanofiber scaffolds, resulting in localized DPP4 inhibition that selectively blocks pathological subsets of fibroblasts while preserving regenerative subsets [21]. This cell-subtype specific design provides a good example of the precision that can be delivered by integrated biomaterial and pharmacological design.

Two clinically approved anti-fibrotics (pirfenidone and tranilast) have been evaluated for their effects on skin, with the scaffold delivery scheme to address systemic toxicity issue [16]. Local sustained release is a huge advantage in the management of keloids, especially when using corticosteroids and 5-fluorouracil (5-FU) which are mainstay drugs in the treatment of keloids [4].

Small leucine-rich proteoglycans, such as decorin, lumican and biglycan, which are naturally anti-fibrotic at low concentrations of TGF- β 1 and modulate collagen fibrillogenesis, are suitable candidates to be delivered as scaffolds [16]. They can be incorporated in biomaterial matrices to serve dual functions as structural components of the scaffold and as active modulators of ECM organization [16].

The potential for modulation of gene expression programs that underlie fibrotic versus regenerative outcomes from RNA-based therapeutics is unprecedented [16]. Fibroblast behaviour has been reprogrammed by delivery of anti-fibrotic miRNAs through scaffold platforms, such as miR-29 (which targets collagen synthesis), miR-145 (which suppresses TGF- β signaling), and the miR-200 family (which regulates EMT) [16]. RNA stability in the wound microenvironment, which is rich in nucleases, reactive oxygen species and pH variations, requires protection methods for the delivery of encapsulated RNA [16].

The potent sequence-specific knockdown of profibrotic gene expression with siRNA against TGF- β R1, CTGF, or collagen type I mRNA has been accomplished [16]. Several delivery vectors that are not viral, such as polyplexes (cationic polymer-siRNA complexes), lipid nanoparticles, and exosome-mediated delivery systems have also been incorporated into the architecture of scaffolds, which also provide protection from degradation and controlled release of siRNAs [16].

Due to the spatial organization of the gene delivery into the scaffolds, sophisticated therapeutic programming is possible: superficial layers are loaded with pro-epithelialization miRNAs, while deeper compartments are loaded with anti-fibrotic siRNAs, resulting in position-dependent gene regulatory environment mimicking the zonal organization of native skin [13, 16]. The precise integration of genetic, material and architectural design is exactly what the programmable artificial skins that perform multiple appendage regeneration do to achieve the healing of ant scars [15].

The techniques of cellular incorporation have promoted the transformation of scaffolds from passive delivery vehicles to

living tissue constructs with dynamic, responsive therapeutic action [16]. The anti-fibrotic effects of cells derived from adipose tissues, such as adipose-derived stem cells (ADSCs), are particularly exciting because they can be readily obtained from the patient, have low harvest morbidity and secrete exosomal miRNAs, growth factors, and immunomodulatory cytokines that inhibit fibrotic disease [16]. Scaffolds seeded with ADSC inhibit the activation of myofibroblasts, induce M2 macrophage polarization and improve angiogenesis via continuous paracrine signaling without replacing tissue [16].

Theoretically, induced pluripotent stem cells (iPSCs) and their derivatives can be propagated indefinitely and remain pluripotent; however, they have remained mostly confined to laboratory use due to the associated teratoma risk, differentiation heterogeneity, and regulatory complexity [16]. Scaffold-mediated differentiation guidance, using the presentation of lineage specific growth factors, stiffness cues, and topography cues, can overcome the problem of iPSC heterogeneity by restricting cell fate decisions to a targeted phenotypic trajectory [12, 16].

Seeded cell survival and engraftment in the unfriendly wound microenvironment, which is defined by hypoxia, inflammation, and proteolytic activity, is a major challenge [16]. Cell viability and therapeutic persistence is improved by scaffold designs that include oxygen-generating materials, anti-inflammatory coatings, and protease-resistant matrices [10, 16]. In addition, the architecture of the scaffolds affects their ability to retain cells: highly porous and interconnected networks allow for cells to infiltrate and vascularize, but may not necessarily be efficient at initial cell seeding, while denser networks can be more efficient in retaining cells, but may not allow for the infiltration and vascularization of cells.

6. Advanced Fabrication Technologies

Electrospinning is the most advanced and popular technique to generate fibrous scaffolds which have a nanofibrillar architecture similar to the native ECM [24, 29]. The parameters of the solution such as polymer concentration, the volatility of the solvents, and their electrical conductivity allow precise control of the fiber diameter, which is in the range of tens of nanometers to several micrometers [24, 29]. Randomly oriented electrospun mats have mechanical properties that are isotropic, and multidirectional cell migration properties, which are appropriate for applications that require relatively homogeneous tissue architecture [24]. For scarless dermal regeneration, however, where organized collagen bundles provide mechanical resilience and prevent

contracture, there is a growing preference for aligned fiber architectures [29].

Aligned nanofiber arrays are created by spinning parallel nanofibers using mandrel collectors and near-field electrospinning methods, which align cells, cell elongation, and collagen deposition in parallel [29]. Radially oriented nanofiber scaffolds containing engineered gradients of guidance signal promote cell migration in a specific direction, from the periphery to the center of the wound, to promote wound healing without scar contracture and retaining organized tissue structure [29]. These are further extended by co-axial electrospinning, where hydrophobic drug loaded cores are surrounded by hydrophilic shells to provide sustained release with burst release adjusted by shell thickness and porosity [24].

Compared with single-scale scaffolds, multi-scale scaffolds can overcome the intrinsic compromise between porosity and surface area by integrating both microfibers and nanofibers in a single construct to create highly porous scaffolds with a large surface area for bioactivity and protein adsorption [24, 30]. The single-unit functionally graded bioresorbable electrospun scaffolds can enable scar-free full-thickness skin wound healing by seamlessly transitioning from dense and mechanically robust base layer to porous and cell-permissive superficial layer [30].

The 3D bioprinting allows for spatiotemporal control, unprecedented geometric complexity and scaffold composition, as well as the placement of cells and therapeutic cargo [19]. On the other hand, systems based on extrusion extrude the cell-laden bioinks using programmable nozzles to construct tissue constructs layer-by-layer with high resolution of up to 100 μm [19]. Stratified constructs are enabled by multi-material printing for skin regeneration, such as epidermal compartments with keratinocytes on top of dermal layers with fibroblasts and endothelial progenitors, and hypodermal regions with adipocytes filling complete-thickness architecture. [19]

Rheological characteristics of bioinks, such as viscosity, shear-thinning and cross-linking kinetics, are crucial for achieving print fidelity and maintaining cell viability [19]. The biomimetic scaffolds are made by 3D-printing by a custom-built bio-plotter, and the incorporation of the therapeutic payload has been shown to be possible without hindering printability by using the liposome-encapsulated TGF- β inhibitor (SB431542), which is protected from degradation by the aqueous printing process and is released over time after printing [19]. A major challenge that has plagued the field of making nutrient channels to thick tissue constructs has been

addressed by "sacrificial printing" of a fugitive ink (e.g., Pluronic F127) that is removed after printing to form perfusable channels [19].

The digital light processing (DLP) and two-photon polymerization (TPP) light-based bioprinting technologies provide higher resolution (sub-micron to 50 μm) and faster fabrication rates with the limitation of material type selection due to the requirement of photocross-linking. Hybrid techniques such as the combination of extrusion-based deposition with light-based patterning are able to benefit from the best aspects of both techniques for more complex multi-scale tissue engineering approaches [19].

High throughput fabrication and screening of scaffold formulations can be achieved using microfluidic technologies, which can shorten conventional in vivo testing optimization cycles [25]. Wound-on-chip models combine biomaterial scaffolds with dynamic culture conditions, such as an interstitial fluid flow, cyclic strain, and controlled oxygen gradient, more faithfully recapitulating the in vivo microenvironment than well-plate static assays [25].

Scaffold-immune interactions, vascularization and tissue remodeling can be viewed in real time with organ-on-chip platforms that contain immune cells, endothelial cells and stromal populations in microfluidic channels [25]. In large-scale wound regeneration, tracing immune cells around biomaterials using spatial anchors has been used to uncover previously unappreciated spatial heterogeneity in macrophage polarization states, to guide scaffolds to be active regulators of immune cell localization [25]. These platforms are increasingly used for the in vivo design of these studies and are a more animal-free means of pre-screening scaffold formulations to gain mechanistic information [25].

Decellularization is a "gold standard" biomimetic method which deprives native tissues of their cellular constituents, while maintaining the architecture, mechanical properties and bioactive molecules present in the ECM, which are encoded to millions of years of evolution [1, 7]. A more complete removal of cells and the better preservation of 3D architecture is possible using perfusion decellularization methods that involve the circulation of detergents, enzymes and hyper/hypotonic solutions through tissue vasculature than by immersion methods [1]. Dermal matrices, small intestinal submucosa (SIS) and amniotic membranes have been decellularized and used successfully in wound healing, and dermal-specific matrices with high basement membrane content have been reconstituted into epidermal tissue in wound healing applications [1, 7].

Seeding density, selection of cell types and maturation protocols are important factors, which must be optimized for each application determining the functional success of decellularized scaffolds [1, 7]. The poor penetration and heterogeneous distribution of cell suspensions from simple pipetting onto scaffold surfaces is a drawback of the static seeding method. Dynamic seeding techniques such as spinner flask culture, perfusion bioreactor, or vacuum-assisted infiltration have been found to greatly enhance cellular distribution and viability, especially for thick constructs with severe diffusion limitations. Maturation period is another area where seeded cells regenerate and rearrange the decellularized matrix and build functional tissue architecture, which can take weeks to months to complete and is a major hurdle to clinical translation [1, 7].

7. In Vivo Evidence: Preclinical Models and Clinical Translation

A key factor in the success of scarless regeneration research that aims to understand the process of regeneration in a human tissue is the choice of the appropriate animal model for study [1, 3]. The Red Duroc pig is the gold standard of human-like scar formation and has hypertrophic scarring, prolonged inflammation and excessive ECM deposition after deep dermal injury [1]. This is because the skin of pigs is very similar to human skin in both anatomical and physiological characteristics with equivalent thicknesses of the epidermis, hair follicle density and wound healing kinetics, making it an essential model for pre-clinical testing of the efficacy of scaffolds [1]. But there are many factors such as high cost, housing, and ethical issues that restrict the throughput and accessibility [1].

The rabbit ear model is a more manageable model for hypertrophic scar induction and prevention studies [3]. The excisions of the ventral surface of the rabbit ear to leave a full-thickness skin defect always leave behind raised, erythematous scars with excessive collagen deposition which can be used as a platform for comparative efficacy assessment [3]. The small size of the wound allows for easy high-throughput screening of different scaffolds, but the thin dermis and lack of adnexal tissues are different from human skin [3].

Genetic manipulation of scaffold-cell interactions in murine models is unparalleled, allowing for the dissection of mechanisms with knockout, lineage tracing and reporter systems [6, 26]. But the primary difference between the healing process in mice, characterized by wound contraction (via panniculus carnosus muscle layer) and healing in humans (via re-epithelialization), makes it difficult to directly

transfer human wound healing results to mouse models [1, 3]. Limitations of this include the use of genetically modified mice (such as diabetic mice (db/db), immunodeficient mice) and splint wound (mechanical inhibition of contraction) models [3, 6].

Existing humanized models, such as the xenograft system that uses human skin onto immunodeficient mice, provide the best available models that closely mimic human wound healing in a genetically manipulable system, but are technically challenging and expensive [1, 6].

Full-thickness wounds are treated with standard-of-care techniques such as split-thickness skin grafts (STSG) to provide immediate coverage, but the STSG technique has several disadvantages, including donor site morbidity, inadequate cosmetic results, and functional deficits [1, 27]. Alternatives such as engineered skin substitutes, which can be acellular dermal matrices or multilayered constructs containing all cellular components, can reduce the need for harvesting from donors and may enhance cosmetic and functional results [1, 27].

The most clinically well-established skin substitutes are Apligraf® (Organogenesis) and Dermagraft® (Organogenesis/Advanced BioHealing), which are both effective for chronic wound healing, although there is not enough evidence to support their effectiveness in acute or surgical wound healing for scar prevention [1]. Integra® (Integra LifeSciences) is a bilayer product, made of bovine collagen and shark chondroitin-6-sulfate, which has been used extensively in clinical practice for burn reconstruction, and has been reported to have a lower impact on scar contracture than STSG alone [1]. But these commercial products were developed mainly for wound closure, and there remains a great unmet need for biomaterials specifically targeting the modulation of healing quality [1, 23].

Preliminary experiments show that optimized architectures can substantially improve a variety of outcome measures compared with traditional methods. Artificial skins that can be programmed to achieve a reduction of scar index greater than 50% in preclinical models, while re-establishing the function of the hair follicles and sweat glands, are also achieving multiple appendage regeneration, in conjunction with the treatment with dressings that are used as a standard treatment [15]. In a preclinical study, collagen-elastin dermal scaffolds were found to promote tissue regeneration and decrease scar formation, with organized collagen bundles and decreased α -SMA expression observed, along with restoration of the elastic fiber network when compared to collagen only dermal scaffolds [32]. The lipidsomes

encapsulated in 3D-printed biomimetic scaffolds can inhibit TGF- β signals continuously, leading to scar-free wound healing and tensile strength and elasticity values close to native skin [19].

Although not a scaffold, negative pressure wound therapy (NPWT) exerts a mechanical microenvironment which has been studied in the context of scaffold systems [4] and affects healing quality. NPWT and bioactive scaffolds could have a synergistic effect on promoting granulation tissue formation, and scaffold mediated biochemical cues could guide tissue organization toward regeneration instead of fibrosis [4].

Translating scaffold-based scar prevention strategies from bench to bedside is a daunting task regulatory, manufacturing and reimbursement hurdles. [1, 11] Combination products are products containing drugs, biologics or cells on a single scaffold subject to complex regulatory frameworks that may include requirements for the safety and efficacy of the components separately as well as together [1].

As clinical trials of scar prevention scaffolds start emerging, patient reported outcome measures (PROMs) are now being combined with objective measures such as the Vancouver Scar Scale (VSS), Patient and Observer Scar Assessment Scale (POSAS) and histomorphometric analysis [4, 23]. The functional endpoints, such as the tensile strength, elasticity and viscoelastic properties of the tissue (as evaluated by cutometry or ballistometry) have been more closely correlated with patient satisfaction than just aesthetic evaluation [12, 14].

The regulatory framework for personalized (patient-specific) scaffolds, especially those containing autologous cells or iPSC-derived tissues, is still not well developed and the existing regulatory pathways are crafted more for off-the-shelf scaffolds [1, 11]. Other translational hurdles that need to be overcome before it can be widely adopted clinically include manufacturing scalability, sterilization impact on bioactivity, and cold-chain logistics [11].

8. Challenges and Future Perspectives

The ultimate goal of scarless skin regeneration is the exact replication of the mechanisms involved in fetal wound healing in adult tissues, which requires the ability to modulate several interdependent biological processes [1, 3]. The hallmarks of embryonic healing are minimal inflammation, the presence of the predominant TGF- β 3 signaling, high hyaluronic acid, and no myofibroblast-mediated contraction [3, 5]. In contrast to child wounds, which show strong inflammatory responses, TGF- β 1 dominance, rapid collagen deposition, and contractile forces which all promote fibrotic outcomes, these inflammatory responses, TGF- β 1 dominance, the rapid

collagen deposition, and the contracting forces are all present in adult wounds and all contribute to the fibrotic outcome [3, 16].

One approach that may help fill this gap is to create "smart" responsive scaffolds that dynamically respond to the changing nature of wound healing over time [28]. Such a dynamically phase-adaptive regulating hydrogel may effectively 'rewind' the adult wound microenvironment to the embryonic state to promote very rapid anti-fibrotic wound healing, in accordance with the physiological time course of wound healing and the transition from pro-inflammatory to anti-inflammatory state [28]. Using enzymes responsive degradation, pH sensitive release or externally triggered actuation, scaffold properties can be manipulated in response to the endogenous healing needs over time [20, 28] to achieve temporal control of inflammation.

Along with passive reprogramming of the environment, there is active cellular reprogramming to the regenerative phenotypes of resident cell lineages [15, 16]. Programmable artificial skins can achieve multiple appendage regeneration by embedding the materials, biochemicals and genes into their structure, which shift the fate decision of fibroblasts away from myofibroblast differentiation and towards DPCs capable of supporting hair follicle neogenesis [15]. These strategies will greatly cross the traditional lines between biomaterial and gene therapy, creating new scientific and regulatory challenges that require interdisciplinary approaches [15, 16].

While standard scaffolds are available in a range of varieties, customized scaffolds are increasingly becoming a new frontier in regenerative medicine [13, 19]. In patient-specific 3D bioprinting, CT or MRI imaging data is used to reconstruct anatomical defects with a scaffold geometry that matches the topography of individual wounds [19]. While a major advantage of iPSC-derived autologous cells is their lack of immunogenicity, another is the potentially unlimited supply of cells, with the risk of differentiation heterogeneity and tumorigenicity remaining [16].

The use of AI-driven scaffold design optimization reduces the time-consuming formulation process that is traditionally done in an empirical way, predicting structure-property-function relationship from a large dataset [13]. In vitro and in vivo screening is used to train machine learning algorithms to find the best combination of material composition, architecture, and biofunctionalization to achieve the best regenerative results with the least fibrosis [13]. These computational methods are especially useful when dealing with complex design space, like the hybrid scaffold, where the emergent

behaviors resulting from the interactions of its different components cannot be predicted by intuition [13].

Combining biomaterial scaffolds with biosensors and wearable technology allows for monitoring a wound in real-time and modulating its therapeutic response in a closed-loop fashion [4, 28]. Biosensors embedded in the scaffolds are capable of detecting the healing process markers such as pH, temperature, oxygen tension and inflammatory cytokines, and thereby measuring the process objectively and continuously along with the intermittent clinical examination [4]. The next step is a closed loop system that autonomously controls therapeutic release based on sensor feedback; for instance, a wound sensed to be in the proliferative stage may receive an increased amount of pro-angiogenic factors, a wound undergoing excessive inflammation may receive an amount of anti-inflammatory factors [28].

The ability to monitor from a distance is especially beneficial in the care of chronic wounds as regular follow-up visits and dressing changes significantly affect the overall results of treatment [4]. The possibility of providing access to specialist wound care via telemedicine to underserved areas through the use of smart scaffold systems would be a great way to bring these services to a wider population [4].

Ultimately, the clinical importance of the advanced scaffold technologies will rely on production scale-up and cost-effectiveness [11]. Electrospinning and 3D bioprinting, although providing exquisite design control, are hampered by problems of batch to batch consistency, sterilization compatibility and production throughput, which are limiting factors to be overcome before they can be widely deployed [11, 29]. Complex capital expenditure and expertise are required for facilities that implement Good Manufacturing Practice (GMP) with cell-seeded constructs, limiting the availability of these centers to large academic medical centers [11].

However, off-the-shelf acellular scaffolds represent a pragmatic middle-ground approach, where manufacturing complexity is less and availability is greater, but with a compromise in the degree of personalization [11, 27]. Active research is underway on bioprinting and scaffold formulation that can accept patient-specific cells without complete redesign to be termed "universal" [19].

A major challenge with sterilization effects on scaffold bioactivity is that gamma irradiation, ethylene oxide and autoclaving can compromise the mechanical integrity of the scaffold, can alter the molecular weight distribution of the polymer and can degrade sensitive bioactive molecules [11]. These technologies are also gaining ground such as low-

temperature plasma, supercritical CO₂ and electron beam irradiation, which are all gentler, but not yet completely validated and approved by regulatory authorities [11].

However, reimbursement and health economics have a critical impact on clinical adoption, especially in resource-poor environments where the impact of scarring may be most severe [4, 11]. Cost-effectiveness, as measured by fewer revision surgeries, better quality-adjusted life years (QALYs), and fewer long-term complications, will be crucial for gaining payers' acceptance and support for the procedure and for ensuring equitable access [4].

9. Conclusions

This extensive survey has set the groundwork for recognizing the paradigm shift in wound healing from simple coverage to therapeutic intervention that is biomaterial-directed and, importantly, scarless. The findings from the mechanistic, design, fabrication and translational domains all converge to a few key principles that need to be followed in future development of scaffolds.

First, the properties of the microenvironment do not remain inert substrates but active modifiers of healing outcome. Collectively, the composition, architecture, mechanics, and degradation kinetics of biomaterial scaffolds drive the direction of wound healing — fibrotic or regenerative — trajectories [12, 13, 14]. The recognition requires an approach to scaffold design that is systems engineering, not materials selection, and optimization of each parameter in the context of interactions with biological systems [13].

Secondly, the key axis of scarless regeneration is immune modulation. It is the time course of polarization of macrophages, recruitment of Tregs and inflammatory resolution, and not any individual molecule, that dictates the fibrotic versus regenerative outcome [5, 6, 26]. Scaffolds that actively "educate" immune cells to pro-resolving phenotypes and not simply escape the foreign body reaction have better regenerative outcomes [6, 28].

Third, a phase adaptive function is critical for the reprogramming of wounds in adults. Static optimization of scaffold properties is not enough since wounds go through different biological stages, each having different requirements [14, 28]. The next wave of biomaterial design is towards dynamically responsive systems that can shift between pro- and anti-inflammatory, stiff and compliant mechanics, and fast and long therapeutic delivery [20, 28].

Fourth, there is the need for preclinical validation in the form of the rigorous, clinically relevant models. The translation of

promising in vitro findings to clinical applications is, in part, due to the reliance on the murine model that is dominated by wound contraction during wound healing [1, 3]. Although more expensive and complex, investment in porcine and humanized models is necessary for predictive validation of scar preventing interventions [1].

Significant gaps in knowledge remain and need to be explored. The long-term degradation products of scaffolds are not well understood, especially of synthetic polymers [14, 27]. The timing of scaffolds (immediate, delayed, and staged) has not been systematically compared to determine its optimum time of application relative to injury [4]. Patient-specific parameters such as age, diabetes, prior radiation, and genetic tendency to form keloid can greatly influence healing, but are not often taken into consideration during scaffold design [3, 16]. Lastly, there are new modalities that may be combined with scaffold-based therapies, such as exosome therapy, CRISPR-based gene editing and organoid-derived tissue constructs, which remain unexplored avenues of synergy [16].

With the field moving towards personalized, phase-adaptive, and digitally integrated scaffold systems, the dream of completely scarless wound healing that had been the realm of early life seems closer than ever to becoming reality. The biomaterials community is at a critical juncture and the promise of decades of basic science can be realized as a next generation of therapies capable of restoring function, aesthetics and psychological well-being that is so often lost as a result of scars.

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Conflict of Interest

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