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Biomaterials in tissue repair and regeneration: key insights from extracellular matrix biology

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The extracellular matrix (ECM) serves as a dynamic biological framework that orchestrates cellular behavior through biomechanical and biochemical cues, playing a pivotal role in tissue homeostasis and repair. Despite significant advancements in biomaterial design, current regenerative strategies often fail to fully replicate the ECM's complexity, leading to suboptimal healing outcomes. This review comprehensively examines ECM biology and its application in biomaterial engineering, highlighting structural-functional relationships, integrin-mediated signaling, and ECM remodeling mechanisms in wound healing. We analyze diverse biomaterial classes—including ECM-based scaffolds, synthetic polymers, natural biomaterials, bioceramics, and composites—focusing on their design principles, fabrication techniques, degradation profiles, and clinical applications. Key challenges such as immunogenicity, vascularization, mechanical mismatch, and regulatory hurdles are critically evaluated. Innovations in decellularization, biofunctionalization, and advanced manufacturing (e.g., 3D bioprinting, electrospinning) are discussed as promising avenues to enhance biomimicry and therapeutic efficacy. Furthermore, we explore clinically approved ECM-derived products and underscore the need for standardized protocols to bridge translational gaps. By integrating emerging research with clinical perspectives, this review provides a roadmap for developing next-generation ECM-inspired biomaterials that address unmet needs in regenerative medicine, emphasizing interdisciplinary collaboration to optimize safety, functionality, and patient outcomes.

KEYWORDS

extracellular matrix, tissue engineering, regenerative medicine, biomaterials, decellularization, 3D bioprinting, integrin signaling, wound healing

1 Introduction

The extracellular matrix (ECM) represents a highly sophisticated biological framework that transcends its conventional role as a passive structural scaffold (1, 2). Comprising a dynamic network of proteins, glycosaminoglycans, and signaling molecules, the ECM actively orchestrates fundamental cellular processes—including adhesion, migration, proliferation, and differentiation—through integrated biomechanical and biochemical cues (3–5). This regulatory capacity arises from its tissue-specific composition and architecture, making it indispensable for physiological homeostasis and a critical blueprint for biomaterial design in regenerative medicine (6, 7). The rising global burden of chronic wounds, degenerative diseases, and organ failure has intensified the

demand for advanced therapeutic strategies that address the limitations of conventional treatments (8). While current biomaterials often fail to recapitulate the ECM's dynamic reciprocity with cells (9)—leading to suboptimal outcomes such as fibrosis or functional deficits (10)—recent innovations have yielded ECM-inspired platforms with enhanced biomimicry (11). These span natural polymers (e.g., collagen, hyaluronic acid) (12), synthetic systems (e.g., PLGA, PEG) (13), and hybrid constructs, each offering tunable biocompatibility, mechanics, and bioactivity (14). Concurrent advances in fabrication technologies—such as 3D bioprinting (15), electrospinning (16), and microfluidic patterning (17)—now enable precise replication of the ECM's hierarchical architecture, further augmented by biofunctionalization with peptides (18), glycosaminoglycan mimetics (19), and nanostructured coatings (20). Stimuli-responsive biomaterials exemplify particular promise, dynamically interfacing with host tissues through controlled growth factor release (21) or adaptive mechanical properties (22).

Central to the ECM's therapeutic relevance is its dual role in tissue repair: as a structural scaffold and a signaling hub. Following injury, it directs hemostasis, inflammation, proliferation, and remodeling by spatially coordinating cellular responses (23). Key components like fibronectin and collagen engage integrin receptors (24, 25), activating FAK/ERK pathways to drive migration (26, 27) while sequestered growth factors (e.g., TGF-β, PDGF) are released to modulate proliferation (26, 28–32). This synchronized regulation of adhesion, motility, and cell cycle progression creates an optimized microenvironment for regeneration (33–36) (Figure 1).

Despite these advances, critical translational challenges persist. Gaps remain in understanding how engineered ECM analogs influence regenerative outcomes (37), particularly in mimicking dynamic remodeling (38). Immune responses (39), mechanical mismatches (40), and inadequate vascularization (41) further complicate clinical implementation. This review systematically examines ECM biology and its biomaterial applications, analyzing: (i) structure-function relationships governing cell fate; (ii) molecular signaling mechanisms; (iii) comparative advantages of biomaterial classes; and (iv) strategies to overcome immunological, manufacturing, and regulatory barriers. By integrating these perspectives, we aim to accelerate the development of ECM-inspired therapies that bridge the gap between bench innovation and clinical impact.

2 Integrin-mediated signaling in tissue repair and regeneration

Integrins serve as fundamental mediators of bidirectional communication between cells and their ECM microenvironment, playing indispensable roles in tissue repair and regeneration. These transmembrane receptors, composed of α and β subunits, recognize specific ECM components including collagen, fibronectin, and laminin, thereby orchestrating essential cellular processes such as adhesion, migration, proliferation, and survival (Figure 2) (42). The dynamic interplay between integrins and their ECM ligands forms the molecular foundation for tissue regeneration, with distinct subunit combinations conferring specificity to these critical interactions (43).

The activation of integrin signaling initiates with ECM ligand binding, which induces conformational changes that promote receptor clustering and the assembly of focal adhesion complexes (44). These specialized structures serve as mechanical and biochemical signaling hubs, recruiting adaptor proteins including talin, vinculin, and paxillin to bridge the connection between integrins and the actin cytoskeleton. The formation of focal adhesions triggers the activation of multiple downstream signaling pathways that collectively coordinate the cellular response to tissue injury (45).

Central to this signaling network is the focal adhesion kinase (FAK) pathway, which, upon activation at Tyr397, recruits Src family kinases to regulate cytoskeletal dynamics and promote cell migration (46, 47). Parallel MAPK/ERK pathway activation regulates gene expression for proliferation and differentiation, while the PI3K/Akt pathway promotes cell survival in stressful, injured tissue microenvironments (48–50). These interconnected pathways function synergistically to ensure appropriate cellular responses during the repair process (51).

The mechanical properties of the ECM exert a profound influence on integrin signaling dynamics. Substrate stiffness, topography, and ligand density collectively modulate the spatial organization and activation state of integrin clusters (44, 52). This mechanosensitive regulation of integrin function has inspired innovative biomaterial design strategies aimed at recapitulating key aspects of native ECM signaling. Engineered matrices incorporating RGD peptide sequences demonstrate enhanced capacity to promote cell adhesion and migration through selective engagement of αvβ3 and α5β1 integrins (53, 54).

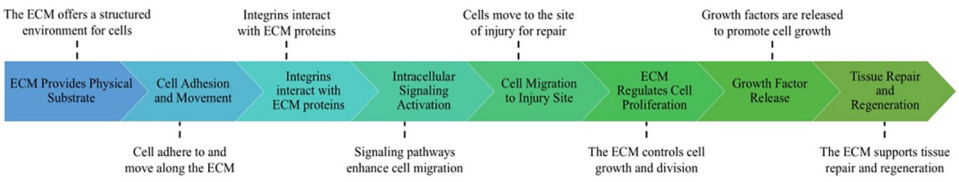

FIGURE 1
The ECM supports cell migration and proliferation in tissue repair by creating a structured environment and interacting with integrin receptors, while growth factors promote cell proliferation and influence the cell cycle, enhancing tissue regeneration.

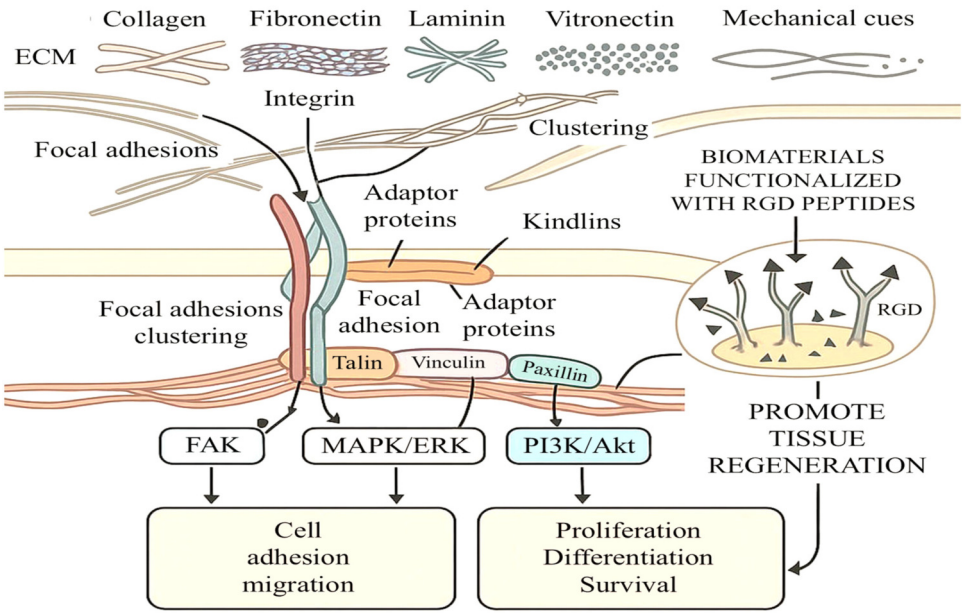

FIGURE 2
Integrin-mediated signaling in tissue repair and regeneration: integrins, transmembrane receptors binding to ECM components, undergo conformational changes and form focal adhesions. This activates FAK, MAPK/ERK, and PI3K/Akt pathways, regulating cell adhesion, migration, proliferation, and survival. ECM mechanical properties and bioengineered materials modulate integrin signaling to enhance tissue regeneration.

Recent advances in regenerative medicine have yielded sophisticated biomaterial systems capable of dynamic interaction with integrin receptors. Mineralized scaffolds functionalized with integrin-binding peptides promote osteogenic differentiation of mesenchymal stem cells, while cardiac-specific matrices improve tissue integration following myocardial injury (55, 56). Particularly promising are stimuli-responsive platforms that adapt their presentation of integrin ligands in response to local mechanical or biochemical cues, thereby providing temporal control over regenerative processes (57).

Deciphering integrin signaling pathways enables advanced biomaterial design for regenerative medicine. Targeted modulation of these pathways enhances cellular responses, tissue integration, and therapeutic efficacy while reducing side effects. Key innovations involve nanostructured materials for enhanced integrin clustering, multi-ligand systems for simultaneous integrin engagement, and responsive biomaterials that adapt to physiological cues. These approaches advance regenerative therapies beyond structural mimicry to active biological control, enabling complex tissue restoration (58, 59).

3 Dynamic ECM remodeling in wound healing

ECM remodeling is a dynamic, tightly regulated process essential for wound healing, involving degradation of the provisional matrix and deposition of new ECM components critical for tissue restoration (60, 61). Shortly after injury, a fibrin-rich provisional matrix forms, offering structural support and enabling cellular infiltration that initiates repair (62, 63). This matrix also modulates the inflammatory response by recruiting fibroblasts and endothelial cells (64, 65). Matrix metalloproteinases (MMPs) become pivotal during the remodeling phase by degrading the provisional matrix and facilitating fibroblast migration and ECM synthesis (66, 67). MMPs ensure a balanced transition from matrix degradation to new ECM formation, which is essential for effective healing (68). A hallmark of this phase is the replacement of type III collagen with type I collagen, enhancing tissue tensile strength and restoring structural integrity (69–71); see Figure 3. Moreover, remodeling involves upregulation of matricellular proteins like fibronectin and tenascin-C, which modulate cell-ECM interactions and influence cell behavior, including adhesion, migration, and differentiation (72, 73). Precise regulation of ECM turnover is crucial; dysregulation can lead to pathological scarring, such as hypertrophic scars or keloids (74, 75). Overall, ECM remodeling supports both early repair and later tissue normalization through coordinated synthesis and degradation (61).

4 ECM-inspired biomaterials

ECM-inspired biomaterials have emerged as a significant advancement in the field of tissue engineering, presenting promising approaches for the repair and regeneration of damaged tissues (76). These biomaterials are engineered to replicate both the structural and biochemical characteristics of the natural ECM, providing an optimal environment conducive to cellular activities critical for healing (77). The inherent

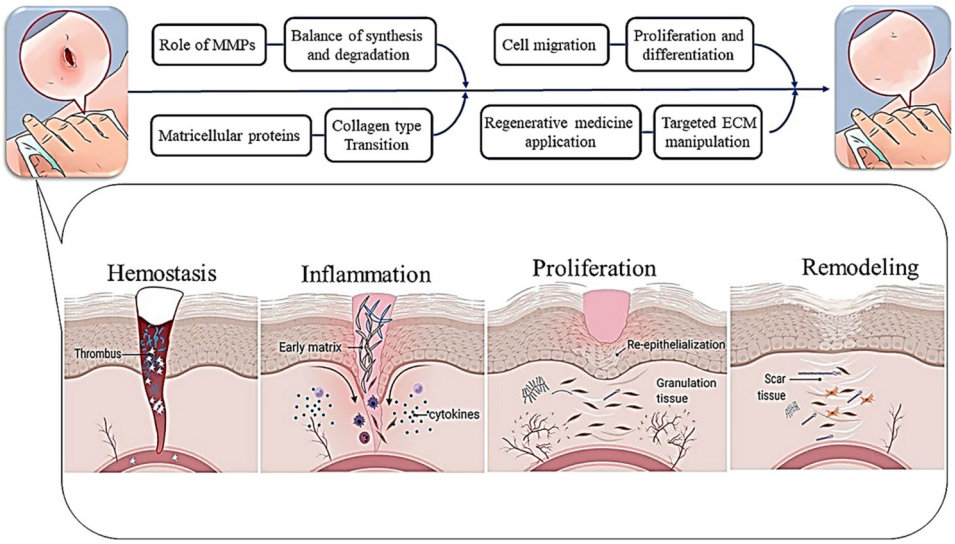

FIGURE 3
The dynamic process of ECM remodeling during wound healing, highlighting its key phases and components. Following an injury, a fibrin-rich provisional matrix is quickly established, providing structural support and facilitating cellular infiltration to initiate healing. As healing progresses, MMPs degrade this provisional matrix, enabling fibroblast migration and the synthesis of new ECM components. A significant transition occurs from type III to type I collagen deposition, enhancing tissue strength. The remodeling phase is characterized by increased matricellular proteins like fibronectin and tenascin-C, which influence cell-ECM interactions. Maintaining a balance between ECM synthesis and degradation is crucial to prevent complications such as hypertrophic scars.

properties of the ECM are being investigated in efforts to develop scaffolds that promote cell attachment and proliferation while also enhancing the intricate processes of tissue repair and remodeling (78). The creation of these biomaterials is underpinned by a comprehensive understanding of the ECM's functions in physiological processes, thus positioning them as essential tools within the realm of regenerative medicine (79).

4.1 Design principles and material selection of ECM-inspired biomaterials

The design principles underlying ECM-inspired biomaterials focus on the precise replication of the architecture, composition, and mechanical properties characteristic of the native ECM (80). Critical factors in material selection involve the origin of ECM components, the techniques employed for decellularization, and the integration of bioactive molecules enhancing cell signaling and facilitating tissue integration (81). Commonly utilized materials, such as collagen, gelatin, fibrin, and hyaluronic acid, are favored not only for their inherent biocompatibility but also for their capacity to support fundamental cellular processes, including adhesion, migration, and proliferation (Table 1) (82). Among these, collagen is particularly prominent due to its abundance in mammalian ECM and its ability to impart tensile strength and structural integrity to engineered tissues (83).

The methods of decellularization are crucial in the synthesis of ECM-based biomaterials, as these techniques strive to eliminate cellular components while preserving the structural integrity and bioactive properties of the native matrix (84). Various techniques, including chemical treatments, enzymatic digestion, and physical approaches such as freeze-thaw cycles, can be effectively utilized to achieve successful decellularization (85). The selection of a specific decellularization method significantly influences the resulting material's properties, affecting mechanical strength, porosity, and degradation kinetics. Furthermore, subsequent processing steps—such as crosslinking and sterilization—are essential to enhance the stability, durability, and overall functionality of these biomaterials (86).

In addition to selection and processing methods, the incorporation of spatial patterning techniques further enhances the functionality of ECM-inspired biomaterials. These techniques facilitate the design of scaffolds with specific microarchitectures that accurately replicate the native tissue environment (87). Techniques such as photolithography and electrospinning allow for precise manipulation of ECM component distribution at the micro- and nanoscale (88, 89). This spatial control is crucial for promoting proper organization and alignment of cells within the scaffold, ultimately improving tissue integration and enhancing the overall functionality of the engineered tissue constructs.

5 Biomaterial classes, properties, fabrication techniques, and degradation profiles in tissue repair and regeneration

Biomaterials used in tissue engineering are broadly classified into five main categories based on their composition,

TABLE 1 The diversity of ECM-inspired biomaterials, their compositions, architectures, mechanical properties, and applications.

Type of ECM-Inspired Biomaterial	Composition	Architecture	Mechanical Properties	Applications
Decellularized Tissues	Natural ECM proteins (collagen, elastin)	Retains native tissue structure	Variable stiffness, mimics native tissue	Tissue engineering, regenerative medicine (90)
		3D structure reflects original organ architecture		Organ transplantation, vascular grafts (90)
Synthetic Hydrogels	Polyethylene glycol (PEG), hyaluronic acid	3D porous networks	Tunable mechanical properties, adjustable viscosity	Drug delivery, cell culture, wound healing (91)
		Hydrophilic networks facilitate nutrient transport		Soft tissue repair, tissue engineering (91)
Self-Assembled Peptide Scaffolds	Peptides designed to mimic ECM components	Nanofibrous structures	Adjustable stiffness and elasticity	Tissue repair, 3D cell culture (92)
		Self-assembly can be tuned for specific applications		Bone regeneration, guided tissue regeneration (92)
Composite Biomaterials	Combination of natural and synthetic polymers	Layered or hybrid structures	Enhanced mechanical strength and flexibility	Bone regeneration, soft tissue repair (93)
	Often include bioactive glass or ceramics	Interconnected porosity promotes cell infiltration		Cartilage repair, orthopedic applications (93)
Electrospun Fibers	Collagen, gelatin, or synthetic polymers	Fibrous mats with high surface area	High tensile strength and flexibility	Nerve regeneration, wound healing (94)
	Can include blended polymers for enhanced properties	Mimics the structure of native ECM		Drug delivery vehicles, tissue scaffolding (94)
Bio-inks for 3D Printing	Natural polymers (alginate, gelatin)	Customizable structures based on design	Varies based on formulation	Organ-on-chip models, personalized tissue scaffolds (95)
	Often combined with cells for bioprinting	Controlled architecture enables multi-layering		Custom prosthetics, tissue mimicry (95)
Nanoparticle-Integrated Biomaterials	Biodegradable polymers with nanoparticles	3D or 2D structures	Variable stiffness due to integration of nanoparticles	Drug delivery, cancer therapy (96)
	Can include gold, silver, or silica particles	Enhanced mechanical and bioactivity properties		Imaging and diagnosis tools (96)
Conductive Biomaterials	Polymers with conductive properties (e.g., PEDOT: PSS)	Scaffold frameworks for cell adhesion	Electrical conductivity enhances cellular responses	Neural tissue engineering, cardiac tissue repair (97)
	Often incorporated with growth factors	Can be made 3D-printed or electrospun		Bioelectronics, sensors within the body (97)
Responsive Hydrogels	Stimuli-responsive polymers (e.g., pH or temperature-sensitive)	Swell and shrink upon stimulus	Mechanical properties change with environmental conditions	Drug delivery systems, smart wound dressings (98)
	Often includes additives for responsiveness	Dynamic architecture can enhance function		Diagnostic applications, environmental sensing (98)

physicochemical properties, and biological functions: (1) ECM-based biomaterials, (2) synthetic polymers, (3) natural biomaterials, (4) bioceramics, and (5) composites. Each class exhibits unique physical, chemical, and biological characteristics that determine its suitability for specific regenerative applications (99).

A pivotal factor influencing biomaterial efficacy is their degradation profile. Effective biomaterials degrade at rates synchronized with tissue formation, maintaining scaffold integrity during healing. Additionally, their degradation products must be non-toxic, readily cleared, and supportive of the regenerative environment, ensuring optimal scaffold performance without adverse effects (100).

A comprehensive understanding of these materials' properties alongside their fabrication methods is essential for designing scaffolds and devices that optimize cell–material interactions, mechanical stability, and degradation kinetics, all critical to successful tissue regeneration. The subsequent sections detail the composition, functionalities, and manufacturing techniques associated with these biomaterial classes (Table 2).

TABLE 2 Summary of physical/chemical properties and fabrication techniques of biomaterial classes.

Biomaterial Class	Key Properties	Common Fabrication Techniques
ECM-based	Native composition, high bioactivity, porous	Decellularization, lyophilization, 3D bioprinting (90)
Synthetic polymers	Tunable, reproducible, controlled degradation	Electrospinning, 3D printing, solvent casting (101)
Natural biomaterials	Biocompatible, biodegradable, variable strength	Gelation, crosslinking, freeze-drying (102)
Bioceramics	Osteoconductive, strong, brittle	Sintering, sol-gel, 3D printing (103)
Composites	Synergistic, customizable, multifunctional	Co-electrospinning, particulate leaching (104)

5.1 ECM-based biomaterials

ECM-based biomaterials comprise decellularized tissue matrices, ECM-derived hydrogels, and self-assembled scaffolds engineered to replicate the biochemical and biophysical

properties of the native ECM. These materials are inherently bioactive, containing crucial biological cues such as growth factors, glycosaminoglycans, and adhesive motifs (e.g., RGD peptides), which regulate cellular behaviors including adhesion, migration, proliferation, and differentiation via integrin-mediated and other signaling pathways (105). Structurally, ECM scaffolds exhibit a porous, fibrillar architecture that promotes cell infiltration and nutrient diffusion, essential for effective tissue regeneration. However, their mechanical properties vary with tissue origin and decellularization methods, often necessitating reinforcement for load-bearing applications (106, 107).

Fabrication approaches include physical, chemical, or enzymatic decellularization, enzymatic digestion to produce hydrogels, and lyophilization for porous constructs. Advanced techniques such as electrospinning yield nanofibrous matrices mimicking native microarchitecture, while 3D bioprinting allows precise spatial deposition of ECM components, enabling complex, organ-specific scaffold fabrication with enhanced reproducibility (101, 108). Innovations in decellularization focus on preserving ECM ultrastructure and bioactivity to support stem cell incorporation and growth factor delivery, with tissue-specific hydrogels demonstrating potential for minimally invasive therapies due to their injectability and remodeling capacity (81, 109). Clinically, ECM-based scaffolds are applied in cardiac repair, vascular grafts, wound healing, and ligament reconstruction, with several products achieving regulatory approval or undergoing clinical trials, underscoring their translational relevance (110).

ECM biomaterials primarily degrade *via* enzymatic pathways involving MMPs, collagenases, and other proteases targeting collagen, elastin, and glycosaminoglycans. This tightly regulated remodeling mirrors natural tissue turnover and wound healing processes (111). Importantly, degradation by-products are generally biocompatible and may actively enhance regeneration by releasing bioactive peptides that stimulate cell migration, proliferation, angiogenesis, and matrix synthesis. For example, collagen-derived peptides can serve as chemotactic factors to guide cell infiltration. Nonetheless, the degradation rate must be carefully balanced: excessively rapid breakdown can undermine scaffold integrity and tissue formation, whereas overly slow degradation may hinder tissue remodeling and integration (112).

5.2 Synthetic polymers

Synthetic polymers, including polylactic acid (PLA), polyglycolic acid (PGA), poly lactic-co-glycolic acid (PLGA), and polycaprolactone (PCL), have become widely utilized scaffolding materials in regenerative medicine due to their tunable mechanical properties, controlled degradation rates, and ease of processing (113, 114). These polymers offer high reproducibility, scalability, and well-defined chemical structures, enabling precise modulation of key physical and chemical characteristics such as hydrophilicity, stiffness, and degradation kinetics. Such versatility renders them suitable for diverse tissue engineering applications spanning cartilage, bone, nerve, and soft tissue regeneration (115).

To augment bioactivity and enhance functional integration, extensive research has focused on modifying polymer architecture through variations in copolymer ratios and molecular weights, and implementing surface engineering strategies such as plasma treatment, peptide grafting, and biomimetic coatings. These approaches mimic biological cues or facilitate the incorporation of growth factors, thereby promoting cell adhesion, proliferation, and differentiation (116). Fabrication techniques, including solvent casting, melt extrusion, and electrospinning, allow the generation of films, fibers, and nanofibrous matrices that replicate ECM features, while 3D printing enables the creation of anatomically precise scaffolds with customizable porosity and spatial patterning (101, 117).

Degradation of synthetic polymers primarily occurs via hydrolysis of ester bonds in the polymer backbone, with the degradation rate modulated by factors such as copolymer composition, molecular weight, crystallinity, and scaffold geometry. This predictable and tunable degradation is advantageous for synchronizing scaffold resorption with tissue formation. However, hydrolysis generates acidic by-products—lactic and glycolic acids—that can lower local pH, potentially induce inflammation or cytotoxic effects if not adequately buffer by surrounding tissues or scaffold design (118). Therefore, balancing degradation kinetics with biocompatibility through careful polymer selection and scaffold architecture is essential to maintain a conducive microenvironment for cell viability and tissue regeneration.

5.3 Natural biomaterials

Natural biomaterials—such as collagen, gelatin, chitosan, alginate, and hyaluronic acid—are extensively utilized in tissue engineering owing to their inherent biocompatibility, biodegradability, and capacity to closely mimic native ECM components (119, 120). These polymers inherently contain bioactive motifs that facilitate cellular adhesion, proliferation, and differentiation, making them particularly suitable for regenerative applications across cartilage, skin, nerve, and soft tissues (121).

Despite these biological advantages, natural polymers often exhibit mechanical limitations, including relatively low stiffness and significant batch-to-batch variability, which can compromise reproducibility and long-term scaffold stability (122). To overcome these constraints, chemical and physical modification strategies have been applied to enhance mechanical properties and tailor biofunctional characteristics. Fabrication methods commonly employed include ionic or covalent crosslinking to induce gelation, freeze-drying to create porous scaffolds, electrospinning to produce fibrous structures, and photo-crosslinking to fine-tune mechanical stiffness and degradation kinetics in response to cellular needs (123, 124). These techniques enable the formation of versatile scaffold architectures, such as hydrogels, sponges, and films, which are frequently blended with synthetic polymers to improve mechanical strength and control degradation profiles (125).

Recent advances highlight the potential of crosslinked collagen hydrogels in enhancing mechanical stability and directing stem cell differentiation within cartilage and skin regeneration models. Gelatin meth acryloyl (GelMA) has emerged as a prominent biomaterial due to its tunable rheological properties and compatibility with 3D bioprinting technologies, facilitating the fabrication of vascularized tissue constructs (126, 127). Similarly, chitosan derivatives with improved solubility and functionalization have demonstrated efficacy in nerve and cartilage tissue engineering, while RGD-modified alginate scaffolds have shown enhanced mesenchymal stem cell adhesion and osteochondral differentiation. Hyaluronic acid-based hydrogels with engineered stiffness have been successfully applied in wound healing, synovial joint repair, and neural regeneration (128, 129).

In terms of degradation, natural polymers typically undergo enzymatic breakdown or hydrolysis at rates generally faster than synthetic polymers. Enzymes such as collagenases and lysozymes secreted by cells mediate scaffold resorption. The resulting degradation products—oligosaccharides, peptides, and amino acids—are largely non-toxic and well-integrated within cellular metabolic pathways, often facilitating tissue remodeling and integration. However, excessively rapid degradation can undermine scaffold mechanical integrity prematurely, potentially compromising support during critical phases of tissue regeneration.

5.4 Bioceramics

Bioceramics, including hydroxyapatite (HA), tricalcium phosphate (TCP), and bioactive glasses, are pivotal materials in bone and dental tissue engineering due to their remarkable osteoconductivity, chemical stability, and high compressive strength, which collectively confer suitability for load-bearing applications (130, 131). These ceramics facilitate direct bonding with native bone tissue, providing essential structural support during the regenerative process. However, their inherent brittleness and limited mechanical flexibility constrain their applicability in soft tissue engineering, while their relatively slow degradation rates may impede complete tissue remodeling unless carefully tailored.

To enhance their bioactivity and regenerative potential, extensive research has focused on nanostructuring bioceramics to increase surface area, thereby promoting improved cellular adhesion, proliferation, and osteogenic differentiation (132). Ion-doping approaches—such as substitution with strontium (Sr^{2+}) or silicon (Si^{4+}) ions—have been demonstrated to stimulate osteogenesis, angiogenesis, and exhibit anti-resorptive properties *in vivo*, further augmenting the therapeutic efficacy of these materials (133).

Composite scaffolds that integrate bioceramics with biodegradable polymers, growth factors, or stem cells exhibit synergistic effects, accelerating bone healing and enabling controlled resorption, particularly advantageous for large or complex osseous defects (134). Advances in additive manufacturing, including 3D printing technologies, have facilitated the fabrication of patient-specific ceramic implants with precisely engineered porosity and mechanical properties. These innovations optimize vascular infiltration and promote robust integration with host tissue (135, 136).

Clinically, bioceramics are widely employed in dental implants, craniofacial reconstruction, and orthopedic devices, where they have demonstrated long-term biocompatibility, mechanical durability, and effective osseointegration (137). Fabrication techniques such as sintering, sol-gel processing, and surface modifications—including micro topographical roughening and bioactive coatings—are employed to enhance cellular attachment, vascularization, and implant stability, thereby improving functional outcomes.

Bioceramics predominantly undergo degradation via slow dissolution in physiological fluids and active cellular resorption by osteoclast-like cells. The rate of degradation is influenced by parameters including material porosity, crystallinity, and surface chemistry (138).

The gradual resorption profile of bioceramics ensures sustained mechanical support during critical phases of bone regeneration. As degradation proceeds, released calcium and phosphate ions contribute to new mineralized tissue formation. Nevertheless, incomplete resorption or accumulation of ceramic debris may impede full tissue remodeling or elicit inflammatory responses if degradation kinetics and scaffold design are not properly controlled.

5.5 Composites

Composite biomaterials represent a strategic amalgamation of diverse material classes—such as synthetic polymers, bioceramics, and biological macromolecules—engineered to synergistically enhance mechanical strength, bioactivity, and biodegradability to address the complex demands of tissue regeneration (139). By combining the advantageous properties of each component, these hybrid systems overcome the intrinsic limitations of individual materials, enabling the development of scaffolds with precisely tailored physicochemical and biological characteristics.

For instance, polymer-ceramic composites like PCL blended with HA have demonstrated improved osteogenic differentiation and mineral deposition, making them particularly effective in bone tissue engineering (140). The ceramic component contributes essential mechanical reinforcement and osteoconductivity, while the polymer matrix imparts flexibility and facilitates manufacturability. This compositional synergy also allows fine-tuning of degradation kinetics, thereby aligning scaffold resorption with the temporal progression of tissue regeneration.

Advancements in fabrication techniques, especially additive manufacturing and layer-by-layer assembly, have facilitated the production of gradient or stratified scaffolds that closely replicate complex tissue interfaces such as the osteochondral junction (141, 142). The precise spatial control afforded by these technologies supports the recreation of native tissue anisotropy and zonal heterogeneity, which enhances structural integration and promotes functional restoration.

Moreover, the integration of bioactive agents—including bone morphogenetic protein-2 (BMP-2) and vascular endothelial

growth factor (VEGF)—within composite scaffolds further stimulates angiogenesis, stem cell recruitment, and tissue repair in critical-sized defects (143, 144). These biofunctional constructs are engineered for controlled, localized, and sustained release of therapeutic factors, optimizing the regenerative microenvironment.

A critical aspect of composite biomaterials is their tailored degradation behavior, which results from the interplay between their constituent components. Degradable polymers typically undergo hydrolytic or enzymatic cleavage, bioceramics degrade via dissolution or cellular resorption, and natural ECM -derived materials are enzymatically broken down. By combining these components, composite scaffolds can be designed to exhibit synergistic or sequential degradation profiles that closely match the tissue healing timeline, ensuring mechanical support is maintained during early regeneration and progressively replaced by newly formed tissue (145).

The biological performance of these composites depends heavily on the compatibility and degradation synchrony of the integrated materials. Properly balanced degradation kinetics prevent premature scaffold fragmentation and promote uniform cellular infiltration and tissue ingrowth, which are essential for effective remodeling. Conversely, mismatched degradation rates or material incompatibility can lead to scaffold instability or heterogeneous regeneration, ultimately compromising functional outcomes.

Composite biomaterials engineered for complex tissue interfaces—such as tendon-to-bone entheses, vascular grafts, and nerve conduits—illustrate the necessity of integrating mechanical robustness with controlled bioactive delivery. Such multifunctional systems meet the dual demands of biomechanical support and localized biological modulation, thereby advancing regenerative therapies toward more predictable and durable clinical success (146, 147).

6 Advantages and limitations of biomaterial classes in tissue engineering

The strategic selection of biomaterials for tissue engineering requires careful evaluation of their inherent advantages and limitations across multiple functional parameters. As shown in Table 3, the five principal biomaterial classes—ECM-based, synthetic polymers, natural biomaterials, bioceramics, and composites—each present distinct profiles of biocompatibility, bioactivity, mechanical properties, and manufacturability that dictate their clinical suitability.

ECM-derived and natural biomaterials excel in biological recognition and cellular signaling but face challenges with immunogenicity (particularly in xenogeneic formulations), batch-to-batch variability, and insufficient mechanical strength for load-bearing applications. Synthetic polymers offer superior reproducibility and tunable properties, though their frequent lack of intrinsic bioactivity and potential for cytotoxic degradation byproducts (e.g., acidic monomers from PLGA hydrolysis) remain significant concerns (148). Bioceramics provide exceptional osteoconductivity and structural stability in bone regeneration, yet their inherent brittleness and processing limitations constrain wider application. Composite systems strategically combine material classes to achieve synergistic performance, though this introduces fabrication complexity and potential interfacial incompatibilities (149).

Beyond class-specific limitations, four fundamental challenges persist across all biomaterial categories (Table 4). First, immune compatibility remains problematic, with ECM-based and natural materials particularly prone to provoking inflammatory responses or rejection through residual xenogeneic antigens. Second, cytotoxic effects may emerge from either degradation byproducts (synthetics) or residual crosslinking agents (natural/ECM materials). Third, physiological integration is frequently compromised by mechanical mismatches or asynchronous degradation kinetics, leading to fibrotic encapsulation or incomplete tissue remodeling. Fourth, long-term safety profiles require further validation, especially regarding late-stage inflammatory responses, mineralization anomalies, or stress-shielding effects from mechanical property disparities.

The risk of infection presents additional translational hurdles, particularly for biological materials that may harbor pathogens or support biofilm formation despite sterilization protocols. Furthermore, the dynamic interplay between scaffold degradation and tissue formation necessitates precise temporal control—overly rapid resorption can compromise structural support, while

TABLE 3 Clinically approved biomaterial-based systems for tissue repair and regeneration.

Product Name	Composition	Clinical Indication	Regulatory Status	Manufacturer
Integra® Dermal Regeneration Template	Bovine collagen + glycosaminoglycan	Skin regeneration, burn treatment	FDA approved, CE marked	Integra LifeSciences (195)
AlloDerm®	Decellularized human dermis	Soft tissue reconstruction, burns	FDA cleared (HCT/P)	LifeCell Corporation (196)
Bio-Gide®	Collagen membrane (porcine)	Guided bone regeneration	CE marked	Geistlich Pharma (197)
Infuse® Bone Graft	Recombinant human BMP-2 + collagen	Spinal fusion, bone defects	FDA approved	Medtronic (198)
GraftJacket®	Acellular human dermis	Chronic wound repair	FDA cleared (HCT/P)	Wright Medical (199)
OsteoCel®	Cellular allograft (bone matrix + MSCs)	Bone regeneration	FDA cleared (HCT/P)	NuVasive (200)
EpiFix®	Dehydrated amniotic membrane	Chronic wound healing	FDA cleared (HCT/P)	MiMedx (201)
Actifuse®	Silicate-substituted calcium phosphate	Bone void filler	FDA cleared, CE marked	Baxter (202)
Chondro-Gide®	Collagen type I/III membrane	Cartilage repair (knee)	CE marked	Geistlich Pharma (203)
Permacol™	Porcine dermal collagen	Soft tissue repair	FDA cleared, CE marked	Medtronic (204)

FDA, U.S. food and drug administration; CE, European conformity; HCT/P, human cells, tissues, and cellular and tissue-based products.

TABLE 4 Comparative Performance Matrix of Tissue Engineering Biomaterials.

Biomaterial Class	Key Advantages	Primary Limitations	Cross-Cutting Challenges
ECM-based	High bioactivity, native cell signaling, excellent biocompatibility	Immunogenicity, source variability, low mechanical strength	Immune responses (xenogeneic antigens), infection risk, complex sterilization (5)
Synthetic polymers	Highly tunable properties, excellent reproducibility, scalable production	Limited bioactivity, cytotoxic degradation products	Mechanical mismatch, acidic degradation microenvironment (150)
Natural biomaterials	Innate biocompatibility, biodegradability, bioactive motifs	Rapid degradation, immunogenicity, weak mechanics	Batch variability, pathogen risk, crosslinker toxicity (151)
Bioceramics	Superior osteoconductivity, high compressive strength, stability	Brittleness, difficult processing, slow degradation	Stress shielding, poor interfacial integration (152)
Composites	Tailorable properties, synergistic performance, multifunctionality	Complex fabrication, interfacial incompatibility, regulatory hurdles	Phase separation, inconsistent degradation profiles (153)

excessively persistent materials may impede functional tissue maturation.

7 Applications of biomaterials in tissue engineering

ECM-inspired biomaterials have been extensively applied in tissue engineering due to their ability to promote repair and regeneration across multiple tissues (154). Notably, in vascular grafts, these materials provide a supportive microenvironment that enhances endothelial cell proliferation and angiogenesis. These biomaterials mimic the mechanical properties of native blood vessels and enhance graft patency. Examples include decellularized vascular tissues and synthetic hydrogels (155–157). Similarly, ECM-derived cardiac patches enhance myocardial repair post-infarction by promoting cell survival, tissue regeneration, and endothelial cell growth, thereby improving angiogenesis. These patches support cardiac cell function and integration, with key examples including decellularized cardiac matrices and elastin-based scaffolds (158, 159). Beyond cardiovascular applications, ECM scaffolds are employed in regenerating skin, bone, cartilage, and nerve tissues (160). Moreover, ECM-based materials have advanced organ-on-a-chip technologies leverage ECM-derived microenvironments to replicate physiological conditions for real-time monitoring of cellular responses, with ECM-derived hydrogels and peptide-composite biomaterials proving particularly effective and enhancing drug testing and disease modeling (161, 162).

7.1 Bone tissue regeneration

Bone regeneration research utilizes ECM-derived materials that enhance osteogenic differentiation of stem cells and support bone healing by incorporating bioactive cues and mimicking natural bone structure, such as decellularized bone matrices and HA composites (163). Scaffold design focuses on creating osteoconductive environments that promote osteoinduction through stem cell differentiation and host tissue integration. Bioactive ceramics like biphasic calcium phosphate (BCP) and HA composites enhance osteointegration (164), while emerging 3D-printed scaffolds with bioactive nanoparticles improve *in vivo* osteogenic differentiation (165, 166). Controlled bone formation is achieved via growth factor delivery (e.g., BMP-2, BMP-7) in biodegradable carriers (167). Composite scaffolds combining natural polymers (collagen, chitosan) with ceramics demonstrate superior mechanical and cellular outcomes (168), and surface modifications (nanotopography, biofunctional peptides) further enhance stem cell adhesion and mineralization (169). Key challenges include vascularizing large defects, ensuring long-term growth factor safety, and addressing regulatory and cost barriers for clinical translation.

7.2 Cartilage tissue regeneration

Cartilage repair remains challenging due to tissue avascularity and limited self-renewal capacity. Biomaterials designed for cartilage regeneration aim to replicate native mechanical properties while supporting chondrocyte function, with examples including chitosan-based scaffolds and elastin-like polypeptides (170). Hydrogels based on hyaluronic acid, gelatin, or alginate mimic the native ECM to promote chondrogenesis (171), while ECM-derived scaffolds preserve biochemical cues to enhance cell attachment and differentiation (78). Advanced strategies employ composite systems for sustained delivery of growth factors (TGF-β, IGF-1) to stimulate hyaline cartilage formation (172), as well as MSC-laden biomimetic scaffolds and 3D bioprinting to achieve precise spatial architecture (173). Despite progress, key challenges persist in generating durable hyaline cartilage, scaling up manufacturing, and ensuring integration with subchondral bone.

7.3 Skin tissue regeneration

Wound healing employs natural and synthetic biomaterials to accelerate closure, reduce scarring, and restore function, especially in chronic wounds and burns. Decellularized dermal matrices and collagen scaffolds improve closure and revascularization (77) and also facilitate keratinocyte migration and re-epithelialization in skin healing (174). Incorporation of

bioactive molecules like VEGF enhances angiogenesis (175). Electrospun synthetic polymers (e.g., PCL) support cell infiltration tailored to wound environments (176). Advanced templates incorporating stem cells or exosomes promote superior regeneration (177), while antimicrobial wound dressings mitigate infection risk (178). Balancing bioactivity, degradation, and regulatory approval remains critical.

7.4 Nerve tissue regeneration

ECM-inspired scaffolds play a pivotal role in nerve regeneration by providing structural support and essential biochemical signals that enhance neuronal survival and growth while mimicking the natural nerve environment, as demonstrated by decellularized nerve grafts and peptide-based hydrogels (179). Peripheral and central nerve repair strategies focus on axonal guidance, neurogenesis, and functional restoration through multiple approaches. Biodegradable nerve conduits made from PCL, PLA, or ECM-mimetic materials support regeneration (180), with electroactive polymers further enhancing neurotrophic signaling (181). Decellularized nerve scaffolds effectively preserve bioactive cues to facilitate Schwann cell migration (182), while composite conduits incorporating neurotrophic factors (NGF, BDNF) delivered via microspheres or hydrogels show improved regenerative outcomes (183). Advanced 3D bioprinted nerve interfaces with aligned microchannels offer promising solutions for bridging critical nerve gaps (184). Despite these advances, key challenges remain in optimizing scaffold design, ensuring proper vascularization, and navigating regulatory pathways for bioactive conduit approval.

7.5 Liver tissue regeneration

Liver regeneration research focuses on replicating architecture, metabolic function, and transplantation alternatives. Decellularized liver matrices retain vascular and biliary structures for hepatocyte recellularization (185). 3D bioprinted liver constructs with multicellular components enhance hepatocyte function (186). Bioartificial liver systems in modular bioreactors serve as bridging therapies for acute failure (187), complemented by microfluidic platforms for viability assessment (188). Major obstacles include vascularization, immune compatibility, and scalable off-the-shelf graft production.

7.6 Vascular tissue regeneration

Vascular engineering targets grafts for damaged vessels, from small-diameter grafts to arteries. Decellularized vessels preserve native cues promoting endothelialization (189, 190). Electrospun polymers and elastomers enable compliant, hemocompatible grafts (191). EPC seeding and preconditioning improve patency and thrombogenicity (192). Incorporation of anticoagulants and nitric oxide donors enhances durability (193). Bioprinting vascular networks with hierarchical microchannels advances complex vasculature engineering (194). Challenges include ensuring long-term patency, mechanical compliance, and evolving regulatory frameworks.

7.7 Other tissues

Emerging biomaterial applications include muscle (injectable hydrogels), tendon (aligned nanofibers), and lung (decellularized matrices, vascularized bioprinted constructs). Smart biomaterials responsive to mechanical, electrical, or biochemical stimuli and gene delivery systems show promise in enhancing regeneration.

8 Clinically approved biomaterial-based systems for tissue repair and regeneration

The transition from laboratory to clinical application represents a critical step in advancing tissue engineering. Successful clinical translation of biomaterials affirms their safety, efficacy, and therapeutic potential. Over recent decades, multiple biomaterial-based systems have gained regulatory approval for various tissue regeneration applications. Table 3 summarizes approved biomaterial products, highlighting their diverse compositions, clinical uses, and regulatory statuses.

The progression of these biomaterials into clinical practice reflects significant advancements in biomaterial science, manufacturing scalability, and understanding of tissue-specific regenerative cues. Notably, many approved systems incorporate natural components that mimic native ECM, fostering integration and functional tissue regeneration.

Moreover, the regulatory landscape reveals a growing acceptance of advanced biological products, such as decellularized tissues (AlloDerm®) and cellular allografts (OsteoCel®), which offer superior bioactivity. The inclusion of growth factors (e.g., recombinant BMP-2 in Infuse®) demonstrates the increasing reliance on bioactive molecules to stimulate regenerative processes.

9 Regulatory considerations for ECM-based biomaterials

Regulatory considerations for ECM-based biomaterials involve a variety of factors, including the selection of source tissues, decellularization techniques, and subsequent processing methods (205). The origin of the tissue—whether allogeneic or xenogeneic—can significantly influence the immunogenicity and biocompatibility of the resultant product (206). Regulatory authorities mandate a thorough evaluation of these materials to ensure compliance with stringent safety standards, which includes assessments of potential inflammatory responses and long-term biocompatibility (207). For example, effective decellularization is essential for removing cellular components that could trigger an immune response (208); however,

existing guidelines lack standardized criteria for evaluating the sufficiency of decellularization processes (209). This lack of standardization can result in inconsistencies in clinical outcomes, as some commercially available ECM scaffolds may not fully adhere to established criteria, yet still show favorable results in practice (210).

Furthermore, the manufacturing process of ECM-based biomaterials is complex and typically involves multiple steps that can modify their physical and biochemical characteristics (211). These alterations can affect cellular behavior and tissue integration following implantation. Consequently, regulatory agencies must evaluate not only the final product but also the entire manufacturing process when assessing ECM-based biomaterials (212). This comprehensive approach is vital to ensure that these materials achieve their intended therapeutic objectives while minimizing associated risks. As research in this field progresses, the establishment of clear guidelines and standardized protocols will be essential for streamlining the regulatory approval process for ECM-inspired biomaterials.

10 Innovations in ECM biomaterials research

Advancements in ECM biomaterials research are crucial for overcoming current challenges and enhancing their functionality in tissue engineering applications (213). Recent developments have concentrated on enhancing the mechanical properties and bioactivity of ECM-derived materials through various strategies (214). Researchers are exploring innovative decellularization methods that preserve the structural integrity and biological functionality of ECM components while effectively removing cellular debris (84). Furthermore, incorporating bioactive molecules, such as growth factors or peptides, into ECM scaffolds shows potential in promoting specific cellular responses that aid tissue regeneration (5).

Another promising area of research involves the creation of hybrid biomaterials that combine ECM components with synthetic polymers or other materials, resulting in scaffolds with customized properties (14). These hybrid systems capitalize on the benefits of both natural and synthetic materials, providing enhanced mechanical strength while preserving critical bioactive characteristics necessary for cell signaling and tissue integration (14). Furthermore, Advancements in fabrication techniques, such as 3D bioprinting and electrospinning, allow for the creation of complex scaffold architectures that better replicate native tissue environments, enhancing cellular behavior and improving healing outcomes (88).

11 Translational gaps in ECM-inspired biomaterials

Despite significant advances in ECM-inspired biomaterials for tissue repair and regeneration, several scientific and translational gaps persist. Addressing these challenges is essential for the successful clinical translation and optimization of biomaterial-based therapies (Table 5).

TABLE 5 Key gaps and challenges.

Gap/ Challenge	Concrete Example (s)	Ongoing Efforts/ Recent Advances
Immunogenicity	Decellularized ECM from animal sources can trigger immune responses and fibrosis in host tissue.	Improved decellularization protocols; use of human-derived ECM (215).
Integration with Host Tissue	Synthetic scaffolds often fail to integrate, leading to encapsulation or poor vascularization.	Surface modification with bioactive peptides; co-delivery of angiogenic factors (216).
Vascularization	Large engineered constructs lack sufficient blood vessel ingrowth, limiting nutrient diffusion.	Incorporation of pro-angiogenic cues; pre-vascularized scaffolds (217).
Batch-to-Batch Variability	ECM-derived materials show inconsistent mechanical and biochemical properties due to source variation.	Standardized processing and quality control protocols (218).
Long-Term Safety and Degradation	Unpredictable degradation rates or toxic byproducts (e.g., acidic degradation of PLGA) can harm tissue.	Development of tunable, bioresorbable polymers with safe byproducts (219).
Distinction Between ECM Types	Decellularized ECM and ECM-inspired synthetics are often conflated, obscuring their unique properties.	Clearer classification and reporting standards in research (220).
Limited Mechanistic Insight	Many studies report outcomes without elucidating the underlying cell-ECM signaling mechanisms.	Advanced imaging, omics, and mechanobiology studies (221).
Regulatory and Translational Barriers	Complex compositions and variability complicate regulatory approval for clinical use.	Collaboration with regulatory agencies; development of standards (222).

Future research directions in ECM biomaterials should also emphasize the exploration of interactions between these materials and host tissues at the molecular level. Identifying how various ECM compositions influence cellular responses will produce crucial insights for optimizing scaffold design tailored for specific applications (223). Additionally, employing advanced imaging techniques and *in vivo* models will develop a deeper comprehension of ECM remodeling processes post-implantation and their effects on long-term tissue regeneration (224). Innovative research methodologies can address these challenges, advancing the development of more effective ECM-inspired biomaterials to significantly improve patient outcomes in regenerative medicine.

12 Conclusion

ECM-inspired biomaterials have significantly advanced tissue repair and regeneration by mimicking native ECM's biochemical and biophysical properties, promoting cell migration,

proliferation, and differentiation, and improving healing. However, clinical translation faces scientific and translational challenges.

A key scientific limitation is the incomplete understanding of how specific ECM components and their spatial arrangements collectively regulate cell behavior. While molecules like collagen, fibronectin, and laminin influence cell adhesion, their complex interactions with growth factors and signaling molecules require further elucidation to rationally design biomaterials that faithfully recreate the native ECM microenvironment.

Immunogenicity remains a concern, with residual immunogenic molecules in decellularized ECM or immune reactions to synthetic materials potentially causing chronic inflammation, fibrosis, or graft failure. Research focuses on improving decellularization, developing immunomodulatory biomaterials, and engineering safer degradation profiles. Achieving effective host tissue integration and vascularization are major translational barriers. Synthetic scaffolds often struggle to support sufficient cell infiltration or blood vessel formation. Strategies like incorporating pro-angiogenic factors or creating pre-vascularized constructs are being explored, but robust vascularization in large or complex tissues remains challenging.

Batch-to-batch variability, especially in ECM-derived materials, hinders reproducibility, quality assurance, and regulatory approval. Standardizing sourcing, processing, and characterization is crucial. Furthermore, the distinction between decellularized ECM scaffolds and ECM-inspired synthetic materials needs clarification for accurate interpretation and tailored therapeutic strategies. Long-term safety and efficacy data are limited, necessitating longitudinal investigations and well-designed clinical trials to evaluate durability, degradation, and biological integration *in vivo*.

Overcoming these hurdles requires interdisciplinary collaboration, integrating advanced biomaterial engineering, high-throughput screening, and systems biology. This will accelerate the development of safe, effective, and innovative ECM-inspired biomaterials.

In conclusion, ECM-inspired biomaterials offer a transformative approach to regenerative therapies. Continued interdisciplinary research is essential to overcome current challenges and engineer intelligent, adaptable, and biocompatible systems for personalized and highly effective regenerative solutions.

Author contributions

SA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YA: Data curation, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. YR: Data curation, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. EB: Methodology, Resources, Writing – original draft, Writing – review & editing. DF: Data curation, Investigation, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declare that Generative AI was used in the creation of this manuscript. The authors confirm the ethical application of artificial intelligence (AI) tools in drafting, editing, and proofreading this manuscript, particularly for enhancing clarity and refining the scientific language. AI-generated content was thoroughly reviewed and validated by the authors to ensure accuracy, adherence to academic standards, and the integrity of the research.

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References

1. Dzobo K, Dandara C. The extracellular matrix: its composition, function, remodeling, and role in tumorigenesis. *Biomimetics*. (2023) 8(2):146. doi: 10.3390/biomimetics8020146

2. Shawky JH, Balakrishnan UL, Stuckenholz C, Davidson LA. Multiscale analysis of architecture, cell size and the cell cortex reveals cortical F-actin density and composition are major contributors to mechanical properties during convergent extension. *Development*. (2018) 145(19):dev161281. doi: 10.1242/dev.161281

3. Lu J, Gao Y, Cao C, Wang H, Ruan Y, Qin K, et al. 3D Bioprinted scaffolds for osteochondral regeneration: advancements and applications. *Mater Today Bio*. (2025) 32:101834. doi: 10.1016/j.mtbio.2025.101834

4. Koka P, Chandramohan Y, Perumal E, Kavarthapu A, Dhanasekaran A, Chandran A, et al. Fabrication of ECM mimicking bioactive scaffold: a regenerative approach for MSC mediated applications. *Stem Cells Int*. (2023) 2023(1):6282987. doi: 10.1155/2023/6282987

5. Sharma P, Roy S. Designing ECM-inspired supramolecular scaffolds by utilizing the interactions between a minimalistic neuroactive peptide and heparin. *Nanoscale*. (2023) 15(16):7537–58. doi: 10.1039/D2NR06221F

6. Hussey GS, Dziki JL, Badylak SF. Extracellular matrix-based materials for regenerative medicine. *Nat Rev Mater*. (2018) 3(7):159–73. doi: 10.1038/s41578-018-0023-x

7. Rowley AT, Nagalla RR, Wang SW, Liu WF. Extracellular matrix-based strategies for immunomodulatory biomaterials engineering. *Adv Healthcare Mater*. (2019) 8(8):1801578. doi: 10.1002/adhm.201801578

8. Potekaev NN, Borzykh OB, Medvedev GV, Pushkin DV, Petrova MM, Petrov AV, et al. The role of extracellular matrix in skin wound healing. *J Clin Med*. (2021) 10(24):5947. doi: 10.3390/jcm10245947

9. Jia X, Chen J, Lv W, Li H, Ariga K. Engineering dynamic and interactive biomaterials using material nanoarchitectonics for modulation of cellular behaviors. *Cell Rep Phys Sci*. (2023) 4(2):101251. doi: 10.1016/j.xcrp.2023.101251

10. Dolan CP, Motherwell JM, Franco SR, Janakiram NB, Valerio MS, Goldman SM, et al. Evaluating the potential use of functional fibrosis to facilitate improved outcomes following volumetric muscle loss injury. *Acta Biomater*. (2022) 140:379–88. doi: 10.1016/j.actbio.2021.11.032

11. Yan X, Bethers B, Chen H, Xiao S, Lin S, Tran B, et al. Recent advancements in biomimetic 3D printing materials with enhanced mechanical properties. *Front Mater*. (2021) 8:518886. doi: 10.3389/fmats.2021.518886

12. Wu L, Kang Y, Shi X, Yuezhen B, Qu M, Li J, et al. Natural-wood-inspired ultrastrong anisotropic hybrid hydrogels targeting artificial tendons or ligaments. *ACS Nano*. (2023) 17(14):13522–32. doi: 10.1021/acsnano.3c01976

13. Duskey JT, Baraldi C, Gamberini MC, Ottonelli I, Da Ros F, Tosi G, et al. Investigating novel syntheses of a series of unique hybrid PLGA-chitosan polymers for potential therapeutic delivery applications. *Polymers (Basel)*. (2020) 12(4):823. doi: 10.3390/polym12040823

14. Casarin M, Todesco M, Fontanella CG, Morlacco A, Dal Moro F, Bagno A. Hybrid materials for tissue repair and replacement: another frontier in biomaterial exploitation focusing on cardiovascular and urological fields. *Processes*. (2023) 11(7):2013. doi: 10.3390/pr11072013

15. Singh G, Mehta S, Saini A, Pabla B. Advances in additive manufacturing techniques for bioprinting. *ECS Trans*. (2022) 107(1):6273. doi: 10.1149/10701.6273ecst

16. Chen S, Li R, Li X, Xie J. Electrospinning: an enabling nanotechnology platform for drug delivery and regenerative medicine. *Adv Drug Delivery Rev*. (2018) 132:188–213. doi: 10.1016/j.addr.2018.05.001

17. Park D, Kang M, Choi JW, Paik S-M, Ko J, Lee S, et al. Microstructure guided multi-scale liquid patterning on an open surface. *Lab Chip*. (2018) 18(14):2013–22. doi: 10.1039/C7LC01288H

18. Song J, Zhang Q, Li G, Zhang Y. Constructing ECM-like structure on the plasma membrane via peptide assembly to regulate the cellular response. *Langmuir*. (2022) 38(29):8733–47. doi: 10.1021/acs.langmuir.2c00711

19. Hoffmann M, Snyder NL, Hartmann L. Glycosaminoglycan mimetic precision glycomacromolecules with sequence-defined sulfation and rigidity patterns. *Biomacromolecules*. (2022) 23(9):4004–14. doi: 10.1021/acs.biomac.2c00829

20. Farooq SA, Raina A, Mohan S, Arvind Singh R, Jayalakshmi S, Irfan Ul Haq M. Nanostructured coatings: review on processing techniques, corrosion behaviour and tribological performance. *Nanomaterials*. (2022) 12(8):1323. doi: 10.3390/nano12081323

21. Shi H, Wang C, Ma Z. Stimuli-responsive biomaterials for cardiac tissue engineering and dynamic mechanobiology. *APL Bioeng*. (2021) 5(1):011506. doi: 10.1063/5.0025378

22. Liu Z, Zhang Y, Zhang M, Tan G, Zhu Y, Zhang Z, et al. Adaptive structural reorientation: developing extraordinary mechanical properties by constrained flexibility in natural materials. *Acta Biomater*. (2019) 86:96–108. doi: 10.1016/j.actbio.2019.01.010

23. Pastar I, Marjanovic J, Stone RC, Chen V, Burgess JL, Mervis JS, et al. Epigenetic regulation of cellular functions in wound healing. *Exp Dermatol*. (2021) 30(8):1073–89. doi: 10.1111/exd.14325

24. Fierro Morales JC, Xue Q, Roh-Johnson M. An evolutionary and physiological perspective on cell-substrate adhesion machinery for cell migration. *Front Cell Dev Biol*. (2022) 10:943606. doi: 10.3389/fcell.2022.943606

25. Park EJ, Myint PK, Ito A, Appiah MG, Darkwah S, Kawamoto E, et al. Integrin-ligand interactions in inflammation, cancer, and metabolic disease: insights into the multifaceted roles of an emerging ligand irisin. *Front Cell Dev Biol*. (2020) 8:588066. doi: 10.3389/fcell.2020.588066

26. Katoh K. Signal transduction mechanisms of focal adhesions: src and FAK-mediated cell response. *Front Biosci Landmark*. (2024) 29(11):392. doi: 10.31083/j.fbl2911392

27. Thomas JR, Paul NR, Morgan MR. Adhesion and growth factor receptor crosstalk mechanisms controlling cell migration. *Essays Biochem*. (2019) 63(5):553–67. doi: 10.1042/EBC20190025

28. Gupta VK, Chaudhuri O. Mechanical regulation of cell-cycle progression and division. *Trends Cell Biol*. (2022) 32(9):773–85. doi: 10.1016/j.tcb.2022.03.010

29. de Lucas B, Pérez LM, Gálvez BG. Importance and regulation of adult stem cell migration. *J Cell Mol Med*. (2018) 22(2):746–54. doi: 10.1111/jcmm.13422

30. Radithia D, Yuliana Y, Puspitasari Y, Sismiyanti R, Pratiwi AS. An *in vivo* study of effects of platelet-rich plasma on transforming growth factor-β1 and matrix metalloprotein 9 expression in traumatic ulcers with diabetes mellitus. *Eur J Dent*. (2024) 18(01):214–8. doi: 10.1055/s-0043-1764429

31. Abdelwahab MM, Abohashema DM, Abdelwahab MS, Fayed MT, Ghanem A, Mohamed OA. The role of the extracellular matrix (ECM) in wound healing [IE, matrix metalloproteinases (MMPs) and growth factors]. In: Ahmed MG, Ashique S, Farid A, Zengin G, editors. *Nanotechnology in Wound Healing*. Boca Raton, FL: CRC Press (2025). p. 124–48.

32. Abolhasani S, Fattahi D, Ahmadi Y, Valipour B, Ghasemian M, Rajabibazl M, et al. Synergistic effects of micropatterned substrates and transforming growth factor-β1 on differentiation of human mesenchymal stem cells into vascular smooth muscle cells through modulation of Krüppel-like factor 4. *In Vitro Cell Dev Biol Anim*. (2025) 61:644–55. doi: 10.1007/s11626-025-01033-2

33. Zhao M, Rolandi M, Isseroff RR. Bioelectric signaling: role of bioelectricity in directional cell migration in wound healing. *Cold Spring Harbor Perspect Biol*. (2022) 14(10):a041236. doi: 10.1101/cshperspect.a041236

34. Mayya C, Kharbhanda S, Haque A, Bhatia D. Mechanisms of collective cell migration in wound healing: physiology and disease. In: Kumar P, Kothari V, editors. *Wound Healing Research*. Singapore: Springer (2021). p. 55–74. doi: 10.1007/978-981-16-2677-7_2

35. Zheng Y, Nan H, Liu Y, Fan Q, Wang X, Liu R, et al. Modeling cell migration regulated by cell extracellular-matrix micromechanical coupling. *Phys Rev E*. (2019) 100(4):043303. doi: 10.1103/PhysRevE.100.043303

36. Yamada KM, Doyle AD, Lu J. Cell–3D matrix interactions: recent advances and opportunities. *Trends Cell Biol*. (2022) 32(10):883–95. doi: 10.1016/j.tcb.2022.03.002

37. Arcuri S, Pennarossa G, De Iorio T, Gandolfi F, Brevini TA. 3D ECM-based scaffolds boost young cell secretome-derived EV rejuvenating effects in senescent cells. *Int J Mol Sci*. (2023) 24(9):8285. doi: 10.3390/ijms24098285

38. Shou Y, Teo XY, Wu KZ, Bai B, Kumar AR, Low J, et al. Dynamic stimulations with bioengineered extracellular matrix-mimicking hydrogels for mechano cell reprogramming and therapy. *Adv Sci*. (2023) 10(21):2300670. doi: 10.1002/advs.202300670

39. Kiboneka AN, Mwesigwa R. A primer on immune responses and mechanisms. *World J Adv Res Rev*. (2023) 18(2):233–43. doi: 10.30574/wjarr.2023.18.2.0814

40. Kim D, Fishel R, Lee J-B. Coordinating multi-protein mismatch repair by managing diffusion mechanics on the DNA. *J Mol Biol*. (2018) 430(22):4469–80. doi: 10.1016/j.jmb.2018.05.032

41. Hosseini M, Brown J, Shafiee A. Strategies to induce blood vessel ingrowth into skin grafts and tissue-engineered substitutes. *Tissue Eng Part C*. (2022) 28(3):113–26. doi: 10.1089/ten.tec.2021.0213

42. Nieuwenhuis B, Haenzi B, Andrews MR, Verhaagen J, Fawcett JW. Integrins promote axonal regeneration after injury of the nervous system. *Biol Rev*. (2018) 93(3):1339–62. doi: 10.1111/brv.12398

43. Serratos IN, Olayo R, Millán-Pacheco C, Morales-Corona J, Vicente-Escobar JO, Soto-Estrada AM, et al. Modeling integrin and plasma-polymerized pyrrole interactions: chemical diversity relevance for cell regeneration. *Sci Rep*. (2019) 9(1):7009. doi: 10.1038/s41598-019-43286-4

44. Yu J, Huang J, Jansen JA, Xiong C, Walboomers XF. Mechanochemical mechanism of integrin clustering modulated by nanoscale ligand spacing and rigidity of extracellular substrates. *J Mech Behav Biomed Mater*. (2017) 72:29–37. doi: 10.1016/j.jmbbm.2017.04.018

45. Revach O-Y, Grosheva I, Geiger B. Biomechanical regulation of focal adhesion and invadopodia formation. *J Cell Sci*. (2020) 133(20):jcs244848. doi: 10.1242/jcs.244848

46. Su B, Gao L, Meng F, Guo L, Rothschild J, Gelman IH. Adhesion-mediated cytoskeletal remodeling is controlled by the direct scaffolding of Src from FAK complexes to lipid rafts by SSeCKS/AKAP12. *Oncogene*. (2013) 32(16):2016–26. doi: 10.1038/onc.2012.218

47. Wang W, Liu Y, Liao K. Tyrosine phosphorylation of cortactin by the FAK-Src complex at focal adhesions regulates cell motility. *BMC Cell Biol*. (2011) 12:1–15. doi: 10.1186/1471-2121-12-49

48. Zhao J, Zhu L, Wijesekera N, Jones C. Specific Akt family members impair stress-mediated transactivation of viral promoters and enhance neuronal differentiation: important functions for maintaining latency. *J Virol*. (2020) 94(21):10–1128. doi: 10.1128/JVI.00901-20

49. Liu S, Jin R, Xiao AY, Chen R, Li J, Zhong W, et al. Induction of neuronal PI3Kγ contributes to endoplasmic reticulum stress and long-term functional impairment in a murine model of traumatic brain injury. *Neurotherapeutics*. (2019) 16(4):1320–34. doi: 10.1007/s13311-019-00748-x

50. Zuo L, Zhu Y, Hu L, Liu Y, Wang Y, Hu Y, et al. PI3-kinase/Akt Pathway-regulated membrane transportation of acid-sensing ion channel 1a/calcium ion influx/endoplasmic reticulum stress activation on PDGF-induced HSC activation. *J Cell Mol Med*. (2019) 23(6):3940–50. doi: 10.1111/jcmm.14275

51. Sanchez A, Lee D, Kim DI, Miller KM. Making connections: integrative signaling mechanisms coordinate DNA break repair in chromatin. *Front Genet*. (2021) 12:747734. doi: 10.3389/fgene.2021.747734

52. Gaikwad HK, Jaswandkar SV, Katti KS, Haage A, Katti DR. Molecular basis of conformational changes and mechanics of integrins. *Philos Trans R Soc A*. (2023) 381(2250):20220243. doi: 10.1098/rsta.2022.0243

53. Ahn S, Sharma U, Kasuba KC, Strohmeyer N, Müller DJ. Engineered biomimetic fibrillar fibronectin matrices regulate cell adhesion initiation, migration, and proliferation via α5β1 integrin and syndecan-4 crosstalk. *Adv Sci*. (2023) 10(24):2300812. doi: 10.1002/advs.202300812

54. Koss KM, Sereda TJ, Kumirov VK, Wertheim JA. A class of peptides designed to replicate and enhance the receptor for hyaluronic acid mediated motility binding domain. *Acta Biomater*. (2023) 167:293–308. doi: 10.1016/j.actbio.2023.05.009

55. Lyu R, Chen Y, Shuai Y, Wang J, Lu L, Cheng Q, et al. Novel biomaterial-binding/osteogenic bi-functional peptide binds to silk fibroin membranes to effectively induce osteogenesis *in vitro* and *in vivo*. *ACS Appl Mater Interfaces*. (2023) 15(6):7673–85. doi: 10.1021/acsami.2c17554

56. Xiao Y, Donnelly H, Sprott M, Luo J, Jayawarna V, Lemgruber L, et al. Material-driven fibronectin and vitronectin assembly enhances BMP-2 presentation and osteogenesis. *Mater Today Bio*. (2022) 16:100367. doi: 10.1016/j.mtbio.2022.100367

57. Zhang J, Wong SHD, Wu X, Lei H, Qin M, Shi P, et al. Engineering photoresponsive ligand tethers for mechanical regulation of stem cells. *Adv Mater*. (2021) 33(48):2105765. doi: 10.1002/adma.202105765

58. Maynard SA, Winter CW, Cunnane EM, Stevens MM. Advancing cell-instructive biomaterials through increased understanding of cell receptor spacing and material surface functionalization. *Regen Eng Transl Med*. (2021) 7:533–47. doi: 10.1007/s40883-020-00180-0

59. Zhao J, Santino F, Giacomini D, Gentilucci L. Integrin-targeting peptides for the design of functional cell-responsive biomaterials. *Biomedicines*. (2020) 8(9):307. doi: 10.3390/biomedicines8090307

60. Park HJ, Rouabhia M, Lavertu D, Zhang Z. Electrical stimulation modulates the expression of multiple wound healing genes in primary human dermal fibroblasts. *Tissue Eng, Part A*. (2015) 21(13-14):1982–90. doi: 10.1089/ten.tea.2014.0687

61. Ghilardi SJ, O'Reilly BM, Sgro AE. Intracellular signaling dynamics and their role in coordinating tissue repair. *Wiley Interdiscip Rev*. (2020) 12(3):e1479. doi: 10.1002/wsbm.1479

62. Das SL, Bose P, Lejeune E, Reich DH, Chen C, Eyckmans J. Extracellular matrix alignment directs provisional matrix assembly and three dimensional fibrous tissue closure. *Tissue Eng, Part A*. (2021) 27(23-24):1447–57. doi: 10.1089/ten.tea.2020.0332

63. Nandi S, Sommerville L, Nellenbach K, Mihalko E, Erb M, Freytes DO, et al. Platelet-like particles improve fibrin network properties in a hemophilic model of provisional matrix structural defects. *J Colloid Interface Sci*. (2020) 577:406–18. doi: 10.1016/j.jcis.2020.05.088

64. Nicu R, Ciolacu DE, Petrovici A-R, Rusu D, Avadanei M, Mihaila AC, et al. 3D Matrices for enhanced encapsulation and controlled release of anti-inflammatory bioactive compounds in wound healing. *Int J Mol Sci*. (2023) 24(4):4213. doi: 10.3390/ijms24044213

65. Witherel CE, Sao K, Brisson BK, Han B, Volk SW, Petrie RJ, et al. Regulation of extracellular matrix assembly and structure by hybrid M1/M2 macrophages. *Biomaterials*. (2021) 269:120667. doi: 10.1016/j.biomaterials.2021.120667

66. Kandhwal M, Behl T, Singh S, Sharma N, Arora S, Bhatia S, et al. Role of matrix metalloproteinase in wound healing. *Am J Transl Res*. (2022) 14(7):4391.

67. Barker TH, Engler AJ. The provisional matrix: setting the stage for tissue repair outcomes. *Matrix Biol*. (2017) 60:1–4. doi: 10.1016/j.matbio.2017.04.003

68. Nguyen TT, Mobashery S, Chang M. Roles of matrix metalloproteinases in cutaneous wound healing. In: Alexandrescu V, editor. *Wound Healing-new Insights into Ancient Challenges*. Rijeka: InTechOpen (2016). p. 10.

69. Susilo ME, Paten JA, Sander EA, Nguyen TD, Ruberti JW. Collagen network strengthening following cyclic tensile loading. *Interface Focus*. (2016) 6(1):20150088. doi: 10.1098/rsfs.2015.0088

70. Chen K, Henn D, Januszyk M, Barrera JA, Noishiki C, Bonham CA, et al. Disrupting mechanotransduction decreases fibrosis and contracture in split-thickness skin grafting. *Sci Transl Med*. (2022) 14(645):eabj9152. doi: 10.1126/scitranslmed.abj9152

71. Chang P, Li S, Sun Q, Guo K, Wang H, Li S, et al. Large full-thickness wounded skin regeneration using 3D-printed elastic scaffold with minimal functional unit of skin. *J Tissue Eng*. (2022) 13:20417314211063022. doi: 10.1177/20417314211063022

72. Imanaka-Yoshida K, Aoki H. Tenascin-C and mechanotransduction in the development and diseases of cardiovascular system. *Front Physiol*. (2014) 5:283. doi: 10.3389/fphys.2014.00283

73. Midwood KS, Chiquet M, Tucker RP, Orend G. Tenascin-C at a glance. *J Cell Sci*. (2016) 129(23):4321–7. doi: 10.1242/jcs.190546

74. Jeon YJ, Kim YH, Jeon YJ, Lee WW, Bae IG, Yi KW, et al. Increased synthesis of hyaluronic acid by enhanced penetration of CTP-EGF recombinant in human keratinocytes. *J Cosmet Dermatol*. (2019) 18(5):1539–45. doi: 10.1111/jocd.12855

75. Voegeli R, Monneuse JM, Schoop R, Summers B, Rawlings A. The effect of photodamage on the female Caucasian facial stratum corneum corneome using mass spectrometry-based proteomics. *Int J Cosmet Sci*. (2017) 39(6):637–52. doi: 10.1111/ics.12426

76. Guan Y, Yang B, Xu W, Li D, Wang S, Ren Z, et al. Cell-derived extracellular matrix materials for tissue engineering. *Tissue Eng Part B*. (2022) 28(5):1007–21. doi: 10.1089/ten.teb.2021.0147

77. Ilomuanya MO, Cardoso-Daodu IM, Ubani-Ukoma UN, Adebona AC. Polymeric biomaterials for wound healing incorporating plant extracts and extracellular matrix components. In: Aghaei S, editor. *Recent Advances in Wound Healing*. London: IntechOpen (2021). p. 1–15. doi: 10.5772/intechopen.98556

78. Morwood AJ, El-Karim IA, Clarke SA, Lundy FT. The role of extracellular matrix (ECM) adhesion motifs in functionalised hydrogels. *Molecules*. (2023) 28(12):4616. doi: 10.3390/molecules28124616

79. Najman S, Stojanović S, Živković J, Najdanović J, Radenković M, Vasiljević P, et al. Applications of biomaterials in regenerative medicine and tissue engineering–concepts and perspective. *Contemp Mater*. (2023) 14(1):1–12. doi: 10.7251/COMEN2301001N

80. Xing Y, Varghese B, Ling Z, Kar AS, Reinoso Jacome E, Ren X. Extracellular matrix by design: native biomaterial fabrication and functionalization to boost tissue regeneration. *Regen Eng Transl Med*. (2022) 8(1):55–74. doi: 10.1007/s40883-021-00210-5

81. Biehl A, Martins AMG, Davis ZG, Sze D, Collins L, Mora-Navarro C, et al. Towards a standardized multi-tissue decellularization protocol for the derivation of extracellular matrix materials. *Biomater Sci*. (2023) 11(2):641–54. doi: 10.1039/D2BM01012G

82. Krüger-Genge A, Tondera C, Hauser S, Braune S, Görs J, Roch T, et al. Immunocompatibility and non-thrombogenicity of gelatin-based hydrogels. *Clin Hemorheol Microcirc*. (2021) 77(3):335–50. doi: 10.3233/CH-201028

83. Martinez ATT, Buitrago-Sierra R, Aponte AG. Collagen: a promising molecule in biomedical applications. *J Biomimetics Biomater Biomed Eng*. (2023) 60:11–28. doi: 10.4028/p-v5a3hl

84. Wu H, Yin G, Pu X, Wang J, Liao X, Huang Z. Preliminary study on the antigen-removal from extracellular matrix via different decellularization. *Tissue Eng Part C*. (2022) 28(6):250–63. doi: 10.1089/ten.tec.2022.0025

85. Rabbani M, Zakian N, Alimoradi N. Contribution of physical methods in decellularization of animal tissues. *J Med Signals Sens*. (2021) 11(1):1–11. doi: 10.4103/jmss.JMSS_2_20

86. Xu C, Chen Y, Lin J, Liu HH. Direct and indirect culture methods for studying biodegradable implant materials *in vitro*. *J Visualized Exp*. (2022) 182:e63065. doi: 10.3791/63065-v

87. Pedram P, Mazio C, Imparato G, Netti PA, Salerno A. Spatial patterning of PCL μ-scaffolds directs 3D vascularized bio-constructs morphogenesis *in vitro*. *Biofabrication*. (2022) 14(4):045007. doi: 10.1088/1758-5090/ac8620

88. Kennedy KM, Bhaw-Luximon A, Jhurry D. Cell-matrix mechanical interaction in electrospun polymeric scaffolds for tissue engineering: implications for scaffold design and performance. *Acta Biomater*. (2017) 50:41–55. doi: 10.1016/j.actbio.2016.12.034

89. Abolhasani S, Rajabibazl M, Khani M-M, Parandakh A, Hoseinpoor R. The cooperative effects of micro-grooved topography and TGF-β1 on the vascular smooth muscle cell contractile protein expression of the mesenchymal stem cells. *Differentiation*. (2020) 115:22–9. doi: 10.1016/j.diff.2020.06.003

90. Kort-Mascort J, Flores-Torres S, Peza-Chavez O, Jang JH, Pardo LA, Tran SD, et al. Decellularized ECM hydrogels: prior use considerations, applications, and opportunities in tissue engineering and biofabrication. *Biomater Sci*. (2023) 11(2):400–31. doi: 10.1039/D2BM01273A

91. Godesky MD, Shreiber DI. Hyaluronic acid-based hydrogels with independently tunable mechanical and bioactive signaling features. *Biointerphases*. (2019) 14(6):061005. doi: 10.1063/1.5126493

92. Sever M, Tansik G, Arslan E, Yergoz F, Ozkan AD, Tekinay AB, et al. Self-assembled peptide nanostructures and their gels for regenerative medicine applications. In: Azevedo HS, da Silva RMP, editors. *Self-Assembling Biomaterials*. Duxford: Elsevier (2018). p. 455–73. doi: 10.1016/B978-0-08-102015-9.00022-8

93. Ismail YMB, Reinwald Y. Hybrid composite for orthopedic applications. In: Siddiquee S, Hong MGJ, Rahman MM, editors. *Composite Materials: Applications in Engineering, Biomedicine and Food Science*. Cham: Springer. (2020). p. 319–31. doi: 10.1007/978-3-030-45489-0_14

94. Zha F, Chen W, Lv G, Wu C, Hao L, Meng L, et al. Effects of surface condition of conductive electrospun nanofiber mats on cell behavior for nerve tissue engineering. *Mater Sci Eng C*. (2021) 120:111795. doi: 10.1016/j.msec.2020.111795

95. Ali S, Majeed S. Advancement of bio inks in three dimensional bioprinting. *Biomed J Sci Tech Res*. (2018) 11:4. doi: 10.26717/bjstr.2018.11.002129

96. Cao D, Chen L, Zhang Z, Luo Y, Zhao L, Yuan C, et al. Biodegradable nanomaterials for diagnosis and therapy of tumors. *J Mater Chem B*. (2023) 11(9):1829–48. doi: 10.1039/D2TB02591D

97. Lee S, Ozlu B, Eom T, Martin DC, Shim BS. Electrically conducting polymers for bio-interfacing electronics: from neural and cardiac interfaces to bone and artificial tissue biomaterials. *Biosens Bioelectron*. (2020) 170:112620. doi: 10.1016/j.bios.2020.112620

98. Chopra L, Chohan JS. Stimuli responsive bio-based hydrogels: potential employers for biomedical applications. In: Babbar A, Kumar R, Dhawan V, Ranjan N, Sharma A, editors. *Additive Manufacturing of Polymers for Tissue Engineering*. Boca Raton: Taylor & Francis (2022). p. 79–99.

99. Agrawal R, Singh S, Saxena KK, Buddhi D. A role of biomaterials in tissue engineering and drug encapsulation. *Proc Inst Mech Eng Part E*. (2023) 227:09544089221150740. doi: 10.1177/09544089221150740

100. Wang L, Wang C, Wu S, Fan Y, Li X. Influence of the mechanical properties of biomaterials on degradability, cell behaviors and signaling pathways: current progress and challenges. *Biomater Sci*. (2020) 8(10):2714–33. doi: 10.1039/D0BM00269K

101. Bansal J, Neuman K, Greene VK Jr, Rubenstein DA. Development of 3D printed electrospun scaffolds for the fabrication of porous scaffolds for vascular applications. *3D Print Addit Manuf*. (2022) 9(5):380–8. doi: 10.1089/3dp.2020.0337

102. Troy E, Tilbury MA, Power AM, Wall JG. Nature-based biomaterials and their application in biomedicine. *Polymers (Basel)*. (2021) 13(19):3321. doi: 10.3390/polym13193321

103. Ly M, Spinelli S, Hays S, Zhu D. 3D Printing of ceramic biomaterials. *Eng Regen*. (2022) 3(1):41–52. doi: 10.1016/j.engreg.2022.01.006

104. Passaro J, Imparato C, Parida D, Bifulco A, Branda F, Aronne A. Electrospinning of PVP-based ternary composites containing SiO2 nanoparticles and hybrid TiO2 microparticles with adsorbed superoxide radicals. *Compos B Eng*. (2022) 238:109874. doi: 10.1016/j.compositesb.2022.109874

105. Cramer MC, Badylak SF. Extracellular matrix-based biomaterials and their influence upon cell behavior. *Ann Biomed Eng*. (2020) 48(7):2132–53. doi: 10.1007/s10439-019-02408-9

106. Xu Y, Shi G, Tang J, Cheng R, Shen X, Gu Y, et al. ECM-inspired micro/nanofibers for modulating cell function and tissue generation. *Sci Adv*. (2020) 6(48):eabc2036. doi: 10.1126/sciadv.abc2036

107. Elmashhady HH, Kraemer BA, Patel KH, Sell SA, Garg K. Decellularized extracellular matrices for tissue engineering applications. *Electrospinning*. (2017) 1(1):87–99. doi: 10.1515/esp-2017-0005

108. Erben J, Jirkovec R, Kalous T, Klicova M, Chvojka J. The combination of hydrogels with 3D fibrous scaffolds based on electrospinning and meltblown technology. *Bioengineering*. (2022) 9(11):660. doi: 10.3390/bioengineering9110660

109. Lee JS, Choi YS, Lee JS, Jeon EJ, An S, Lee MS, et al. Mechanically-reinforced and highly adhesive decellularized tissue-derived hydrogel for efficient tissue repair. *Chem Eng J*. (2022) 427:130926. doi: 10.1016/j.cej.2021.130926

110. Khanna A, Zamani M, Huang NF. Extracellular matrix-based biomaterials for cardiovascular tissue engineering. *J Cardiovasc Dev Dis*. (2021) 8(11):137. doi: 10.3390/jcdd8110137

111. Bracaglia LG, Winston S, Powell DA, Fisher JP. Synthetic polymer coatings diminish chronic inflammation risk in large ECM-based materials. *J Biomed Mater Res Part A*. (2019) 107(3):494–504. doi: 10.1002/jbm.a.36564

112. Martin JR, Gupta MK, Page JM, Yu F, Davidson JM, Guelcher SA, et al. A porous tissue engineering scaffold selectively degraded by cell-generated reactive oxygen species. *Biomaterials*. (2014) 35(12):3766–76. doi: 10.1016/j.biomaterials.2014.01.026

113. Capuana E, Lopresti F, Ceraulo M, La Carrubba V. Poly-l-lactic acid (PLLA)-based biomaterials for regenerative medicine: a review on processing and applications. *Polymers (Basel)*. (2022) 14(6):1153. doi: 10.3390/polym14061153

114. Ranganathan N, Mugeshwaran A, Joseph Bensingh R, Abdul Kader M, Nayak SK. Biopolymeric scaffolds for tissue engineering application. In: Paul A, editor. *Biomedical Engineering and Its Applications in Healthcare*. Singapore: Springer (2019). p. 249–74. doi: 10.1007/978-981-13-3705-5_11

115. Duijvelshoff R, Cabrera MS, Sanders B, Dekker S, Smits AI, Baaijens FP, et al. Transcatheter-delivered expandable bioresorbable polymeric graft with stenting capacity induces vascular regeneration. *Basic Transl Sci*. (2020) 5(11):1095–110. doi: 10.1016/j.jacbts.2020.09.005

116. Punet X, Mauchauffe R, Rodríguez-Cabello JC, Alonso M, Engel E, Mateos-Timoneda MA. Biomolecular functionalization for enhanced cell–material interactions of poly (methyl methacrylate) surfaces. *Regen Biomater*. (2015) 2(3):167–75. doi: 10.1093/rb/rbv014

117. Romero-Araya P, Pino V, Nenen A, Cárdenas V, Pavicic F, Ehrenfeld P, et al. Combining materials obtained by 3D-printing and electrospinning from commercial polylactide filament to produce biocompatible composites. *Polymers (Basel)*. (2021) 13(21):3806. doi: 10.3390/polym13213806

118. Zhang T, Gao Y, Zhu L, Zeng Q, Zhou M. Degradation modeling of degradable copolymers for biomimetic scaffolds. *Friction*. (2020) 8:594–603. doi: 10.1007/s40544-019-0291-5

119. Farshidfar N, Iravani S, Varma RS. Alginate-based biomaterials in tissue engineering and regenerative medicine. *Mar Drugs*. (2023) 21(3):189. doi: 10.3390/md21030189

120. Serafin A, Culebras M, Collins MN. Synthesis and evaluation of alginate, gelatin, and hyaluronic acid hybrid hydrogels for tissue engineering applications. *Int J Biol Macromol*. (2023) 233:123438. doi: 10.1016/j.ijbiomac.2023.123438

121. Iovene A, Zhao Y, Wang S, Amoako K. Bioactive polymeric materials for the advancement of regenerative medicine. *J Funct Biomater*. (2021) 12(1):14. doi: 10.3390/jfb12010014

122. Kerwald J, De Mitri AG, de Moura Delezuk JA, de Castilho GJ, Beppu MM. Natural polymers and their processing: bottlenecks to overcome their limitations in medical applications. *Biomed Mater Devices*. (2023) 1(1):213–33. doi: 10.1007/s44174-022-00021-4

123. Ghaleh H, Alizadehaghdam M, Abbasi F. Quality of protein fibers assembly impacts biofunctional characteristics of a tissue engineering scaffold. *Mater Today Commun*. (2022) 33:104636. doi: 10.1016/j.mtcomm.2022.104636

124. Tai Y, Banerjee A, Goodrich R, Jin L, Nam J. Development and utilization of multifunctional polymeric scaffolds for the regulation of physical cellular microenvironments. *Polymers (Basel)*. (2021) 13(22):3880. doi: 10.3390/polym13223880

125. Ishikawa S, Iijima K, Matsukuma D, Iijima M, Osawa S, Otsuka H. An interpenetrating polymer network hydrogel with biodegradability through controlling self-assembling peptide behavior with hydrolyzable cross-linking networks. *Mater Today Adv*. (2021) 9:100131. doi: 10.1016/j.mtadv.2021.100131

126. Kirsch M, Birnstein L, Pepelanova I, Handke W, Rach J, Seltsam A, et al. Gelatin-methacryloyl (GelMA) formulated with human platelet lysate supports mesenchymal stem cell proliferation and differentiation and enhances the hydrogel's mechanical properties. *Bioengineering*. (2019) 6(3):76. doi: 10.3390/bioengineering6030076

127. Liu C, Yu Q, Yuan Z, Guo Q, Liao X, Han F, et al. Engineering the viscoelasticity of gelatin methacryloyl (GelMA) hydrogels via small "dynamic bridges" to regulate BMSC behaviors for osteochondral regeneration. *Bioact Mater*. (2023) 25:445–59. doi: 10.1016/j.bioactmat.2022.07.031

128. Escalante S, Rico G, Becerra J, San Román J, Vázquez-Lasa B, Aguilar MR, et al. Chemically crosslinked hyaluronic acid-chitosan hydrogel for application on cartilage regeneration. *Front Bioeng Biotechnol*. (2022) 10:1058355. doi: 10.3389/fbioe.2022.1058355

129. Wang M, Deng Z, Guo Y, Xu P. Designing functional hyaluronic acid-based hydrogels for cartilage tissue engineering. *Mater Today Bio*. (2022) 17:100495. doi: 10.1016/j.mtbio.2022.100495

130. Lim K-T, Patel DK, Dutta SD, Choung H-W, Jin H, Bhattacharjee A, et al. Human teeth-derived bioceramics for improved bone regeneration. *Nanomaterials*. (2020) 10(12):2396. doi: 10.3390/nano10122396

131. Fernandes HR, Gaddam A, Rebelo A, Brazete D, Stan GE, Ferreira JM. Bioactive glasses and glass-ceramics for healthcare applications in bone regeneration and tissue engineering. *Materials (Basel)*. (2018) 11(12):2530. doi: 10.3390/ma11122530

132. Li X, Liu M, Chen F, Wang Y, Wang M, Chen X, et al. Design of hydroxyapatite bioceramics with micro-/nano-topographies to regulate the osteogenic activities of bone morphogenetic protein-2 and bone marrow stromal cells. *Nanoscale*. (2020) 12(13):7284–300. doi: 10.1039/C9NR10561A

133. Kim H-W, Kim Y-J. Effect of silicon or cerium doping on the anti-inflammatory activity of biphasic calcium phosphate scaffolds for bone regeneration. *Prog Biomater*. (2022) 11(4):421–30. doi: 10.1007/s40204-022-00206-6

134. Bag S. Biodegradable composite scaffold for bone tissue regeneration. In: Paul S, editor. *Biomedical Engineering and its Applications in Healthcare*. Singapore: Springer (2019). p. 657–79. doi: 10.1007/978-981-13-3705-5_27

135. Coulter FB, Levey RE, Robinson ST, Dolan EB, Deotti S, Monaghan M, et al. Additive manufacturing of multi-scale porous soft tissue implants that encourage vascularization and tissue ingrowth. *Adv Healthcare Mater*. (2021) 10(14):2100229. doi: 10.1002/adhm.202100229

136. Paxton NC, Dinoro J, Ren J, Ross MT, Daley R, Zhou R, et al. Additive manufacturing enables personalised porous high-density polyethylene surgical

implant manufacturing with improved tissue and vascular ingrowth. *Appl Mater Today*. (2021) 22:100965. doi: 10.1016/j.apmt.2021.100965

137. Liu Y, Li T, Sun M, Cheng Z, Jia W, Jiao K, et al. ZIF-8 modified multifunctional injectable photopolymerizable GelMA hydrogel for the treatment of periodontitis. *Acta Biomater*. (2022) 146:37–48. doi: 10.1016/j.actbio.2022.03.046

138. Askaria S, Yazdani E, Arabuli L, Goldadi H, Marnani S, Emami M. *In vitro* and *in vivo* examination for bioceramics degradation. *J Compos Compd*. (2022) 4:169–77.

139. Zarrintaj P, Seidi F, Azarfam MY, Yazdi MK, Erfani A, Barani M, et al. Biopolymer-based composites for tissue engineering applications: a basis for future opportunities. *Compos B Eng*. (2023) 258:110701. doi: 10.1016/j.compositesb.2023.110701

140. Murugan S, Parcha SR. Fabrication techniques involved in developing the composite scaffolds PCL/HA nanoparticles for bone tissue engineering applications. *J Mater Sci: Mater Med*. (2021) 32(8):93. doi: 10.1007/s10856-021-06564-0

141. Chen L, Wei L, Su X, Qin L, Xu Z, Huang X, et al. Preparation and characterization of biomimetic functional scaffold with gradient structure for osteochondral defect repair. *Bioengineering*. (2023) 10(2):213. doi: 10.3390/bioengineering10020213

142. Jia S, Wang J, Zhang T, Pan W, Li Z, He X, et al. Multilayered scaffold with a compact interfacial layer enhances osteochondral defect repair. *ACS Appl Mater Interfaces*. (2018) 10(24):20296–305. doi: 10.1021/acsami.8b03445

143. Vater C, Hetz M, Quade M, Lode A, Gelinsky M, Rammelt S, et al. Combined application of BMP-2 and naturally occurring bioactive factor mixtures for the optimized therapy of segmental bone defects. *Acta Biomater*. (2023) 157:162–74. doi: 10.1016/j.actbio.2022.11.064

144. Rady AA, Hamdy SM, Abdel-Hamid MA, Hegazy MG, Fathy SA, Mostafa AA. The role of VEGF and BMP-2 in stimulation of bone healing with using hybrid bio-composite scaffolds coated implants in animal model. *Bull Natl Res Cent*. (2020) 44:1–9. doi: 10.1186/s42269-020-00369-x

145. Zhang F, King MW. Biodegradable polymers as the pivotal player in the design of tissue engineering scaffolds. *Adv Healthcare Mater*. (2020) 9(13):1901358. doi: 10.1002/adhm.201901358

146. No YJ, Castilho M, Ramaswamy Y, Zreiqat H. Role of biomaterials and controlled architecture on tendon/ligament repair and regeneration. *Adv Mater*. (2020) 32(18):1904511. doi: 10.1002/adma.201904511

147. Hou J, Yang R, Vuong I, Li F, Kong J, Mao H-Q. Biomaterials strategies to balance inflammation and tenogenesis for tendon repair. *Acta Biomater*. (2021) 130:1–16. doi: 10.1016/j.actbio.2021.05.043

148. Jangid AK, Kim S, Kim K. Polymeric biomaterial-inspired cell surface modulation for the development of novel anticancer therapeutics. *Biomater Res*. (2023) 27(1):59. doi: 10.1186/s40824-023-00404-8

149. ID A, Satria GAP, Dewi AH, Ardhani R. Bioceramics for clinical application in regenerative dentistry. In: Chun HJ, Park K, Kim C-H, Khang G, editors. *Novel Biomaterials for Regenerative Medicine*. Singapore: Springer (2018). p. 309–16. doi: 10.1007/978-981-13-0947-2_16

150. Seggiani M, Cinelli P, Mallegni N, Balestri E, Vannini C, Vallerini F, et al. Biocomposites based on PHBs and natural fibers for commodity applications in different environments: processing, performance in soil, compost and sea water. *J Chem Eng Process Technol*. (2018) 9:44–5.

151. Insuasti-Cruz E, Suárez-Jaramillo V, Mena Urresta KA, Pila-Varela KO, Fiallos-Ayala X, Dahoumane SA, et al. Natural biomaterials from biodiversity for healthcare applications. *Adv Healthcare Mater*. (2022) 11(1):2101389. doi: 10.1002/adhm.202101389

152. Pina S, Rebelo R, Correlo VM, Oliveira JM, Reis RL. Bioceramics for osteochondral tissue engineering and regeneration. In: Oliveira JM, Pina S, Reis RL, Roman JS, editors. *Osteochondral Tissue Engineering: Nanotechnology, Scaffolding-Related Developments and Translation*. Cham: Springer (2018). p. 53–75. doi: 10.1007/978-3-319-76711-6_3

153. Burela RG, Kamineni JN, Harursampath D. Multifunctional polymer composites for 3D and 4D printing. In: Sadasivuni KK, Deshmukh K, Almaadeed MA, editors. *3D and 4D Printing of Polymer Nanocomposite Materials*. Amsterdam: Elsevier (2020). p. 231–57. doi: 10.1016/b978-0-12-816805-9.00008-9

154. Chouhan D, Kaushik S, Arora D. Trends in bio-derived biomaterials in tissue engineering. In: Bhaskar B, Sreenivasa Rao P, Kasoju N, Nagarjuna V, Baadhe RR, editors. *Biomaterials in Tissue Engineering and Regenerative Medicine: From Basic Concepts to State of the Art Approaches*. Singapore: Springer (2021). p. 163–213. doi: 10.1007/978-981-16-0002-9_6

155. Alasvand N, Behnamghader A, Milan PB, Simorgh S, Mobasheri A, Mozafari M. Tissue-engineered small-diameter vascular grafts containing novel copper-doped bioactive glass biomaterials to promote angiogenic activity and endothelial regeneration. *Mater Today Bio*. (2023) 20:100647. doi: 10.1016/j.mtbio.2023.100647

156. Snyder Y, Lasley Q, Jana S. Vascular graft with native-like mechanical properties. *Mater Lett*. (2023) 333:133568. doi: 10.1016/j.matlet.2022.133568

157. Jiang B, Suen R, Wang JJ, Zhang ZJ, Wertheim JA, Ameer GA. Mechanocompatible polymer-extracellular-matrix composites for vascular tissue engineering. *Adv Healthcare Mater*. (2016) 5(13):1594–605. doi: 10.1002/adhm.201501003

158. Hao Y, Zhang W, Qin J, Tan L, Luo Y, Chen H. Biological cardiac patch based on extracellular vesicles and extracellular matrix for regulating injury-related microenvironment and promoting cardiac tissue recovery. *ACS Appl Bio Mater*. (2022) 5(11):5218–30. doi: 10.1021/acsabm.2c00659

159. Yao Y, Li A, Wang S, Lu Y, Xie J, Zhang H, et al. Multifunctional elastomer cardiac patches for preventing left ventricle remodeling after myocardial infarction *in vivo*. *Biomaterials*. (2022) 282:121382. doi: 10.1016/j.biomaterials.2022.121382

160. Liu K, Li L, Chen J, Li Y, Wen W, Lu L, et al. Bone ECM-like 3D printing scaffold with liquid crystalline and viscoelastic microenvironment for bone regeneration. *ACS Nano*. (2022) 16(12):21020–35. doi: 10.1021/acsnano.2c08699

161. Calejo I, Heinrich MA, Zambito G, Mezzanotte L, Prakash J, Moreira Teixeira L. Advancing tumor microenvironment research by combining organs-on-chips and biosensors. In: Caballero D, Kundu SC, Reis RL, editors. *Microfluidics and Biosensors in Cancer Research: Applications in Cancer Modeling and Theranostics*. Cham: Springer (2022). p. 171–203. doi: 10.1007/978-3-031-04039-9_7

162. Gheorghiu M, Stănică L, Tegla MGG, Polonschii C, Bratu D, Popescu O, et al. Cellular sensing platform with enhanced sensitivity based on optogenetic modulation of cell homeostasis. *Biosens Bioelectron*. (2020) 154:112003. doi: 10.1016/j.bios.2019.112003

163. Miar S, Pearson J, Montelongo S, Zamilpa R, Betancourt AM, Ram B, et al. Regeneration enhanced in critical-sized bone defects using bone-specific extracellular matrix protein. *J Biomed Mater Res Part B*. (2021) 109(4):538–47. doi: 10.1002/jbm.b.34722

164. Xu X, Wang H, Zhang S, Mei X, Ying B, Li R, et al. ECM-inspired 3D printed polyetherimide scaffold with Arg-Gly-Asp peptides for the improvement of bioactivity and osteogenic differentiation of osteoblasts. *Mater Today Commun*. (2022) 30:103166. doi: 10.1016/j.mtcomm.2022.103166

165. Liu X, Miao Y, Liang H, Diao J, Hao L, Shi Z, et al. 3D-printed Bioactive ceramic scaffolds with biomimetic micro/nano-HAp surfaces mediated cell fate and promoted bone augmentation of the bone–implant interface *in vivo*. *Bioactive Mater*. (2022) 12:120–32. doi: 10.1016/j.bioactmat.2021.10.016

166. Abolhasani S, Ahmadi Y, Rostami Y, Zendeh MB, Fattahi D. Therapeutic applications of miRNA in the management of obesity and osteoporosis. *J Diabetes Metab Dis*. (2025) 24(1):75. doi: 10.1007/s40200-025-01589-6

167. De Witte T-M, Wagner AM, Fratila-Apachitei LE, Zadpoor AA, Peppas NA. Degradable poly (methyl methacrylate)-co-methacrylic acid nanoparticles for controlled delivery of growth factors for bone regeneration. *Tissue Eng, Part A*. (2020) 26(23-24):1226–42. doi: 10.1089/ten.tea.2020.0010

168. Vukajlovic D, Parker J, Bretcanu O, Novakovic K. Chitosan based polymer/bioglass composites for tissue engineering applications. *Mater Sci Eng C*. (2019) 96:955–67. doi: 10.1016/j.msec.2018.12.026

169. Li R, Li S, Zhang Y, Jin D, Lin Z, Tao X, et al. Titanium surfaces with biomimetic topography and copper incorporation to modulate behaviors of stem cells and oral bacteria. *Front Bioeng Biotechnol*. (2023) 11:1223339. doi: 10.3389/fbioe.2023.1223339

170. Jacob G, Shimomura K, Hart DA, Fujie H, Nakamura N. Mechanical and biologic properties of articular cartilage repair biomaterials. In: Koh J, Zaffagnini S, Kuroda R, Longo UG, Amirouche F, editors. *Orthopaedic Biomechanics in Sports Medicine*. Cham: Springer (2021). p. 57–71. doi: 10.1007/978-3-030-81549-3_5

171. Kuth S, Karakaya E, Reiter N, Schmidt L, Paulsen F, Teßmar J, et al. Oxidized hyaluronic acid-gelatin-based hydrogels for tissue engineering and soft tissue mimicking. *Tissue Eng, Part C*. (2022) 28(7):301–13. doi: 10.1089/ten.tec.2022.0004

172. Askari M, Bonakdar S, Anbouhi MH, Shahsavarani H, Kargozar S, Khalaj V, et al. Sustained release of TGF-β1 via genetically-modified cells induces the chondrogenic differentiation of mesenchymal stem cells encapsulated in alginate sulfate hydrogels. *J Mater Sci*. (2019) 30:1–11. doi: 10.1007/s10856-018-6203-9

173. Perez MR, Masri NZ, Walters-Shumka J, Kahale S, Willerth SM. Protocol for 3D bioprinting mesenchymal stem cell-derived neural tissues using a fibrin-based bioink. *Bio Protoc*. (2023) 13(9):1250. doi: 10.21769/bioprotoc.4663

174. Solarte David VA, Güiza-Argüello VR, Arango-Rodríguez ML, Sossa CL, Becerra-Bayona SM. Decellularized tissues for wound healing: towards closing the gap between scaffold design and effective extracellular matrix remodeling. *Front Bioeng Biotechnol*. (2022) 10:821852. doi: 10.3389/fbioe.2022.821852

175. Ghalehbandi S, Yuzugulen J, Pranjol MZI, Pourgholami MH. The role of VEGF in cancer-induced angiogenesis and research progress of drugs targeting VEGF. *Eur J Pharmacol*. (2023) 949:175586. doi: 10.1016/j.ejphar.2023.175586

176. Mai Z, Liu Q, Bian Y, Wang P, Fu X, Lin D, et al. PCL/Collagen/UA composite biomedical dressing with ordered microfiberous structure fabricated by a 3D near-field electrospinning process. *Polymers (Basel)*. (2022) 15(1):223. doi: 10.3390/polym15010223

177. Kim H, Kim D, Kim W, Lee S, Gwon Y, Park S, et al. Therapeutic strategies and enhanced production of stem cell-derived exosomes for tissue regeneration. *Tissue Eng Part B Rev*. (2023) 29(2):151–66. doi: 10.1089/ten.teb.2022.0118

178. Halstead FD, Rauf M, Bamford A, Wearn CM, Bishop JR, Burt R, et al. Antimicrobial dressings: comparison of the ability of a panel of dressings to prevent biofilm formation by key burn wound pathogens. *Burns*. (2015) 41(8):1683–94. doi: 10.1016/j.burns.2015.06.005

179. Kellaway SC, Roberton V, Jones JN, Loczenski R, Phillips JB, White LJ. Engineered neural tissue made using hydrogels derived from decellularised tissues for the regeneration of peripheral nerves. *Acta Biomater*. (2023) 157:124–36. doi: 10.1016/j.actbio.2022.12.003

180. Perrelle JM, Boreland AJ, Gamboa JM, Gowda P, Murthy NS. Biomimetic strategies for peripheral nerve injury repair: an exploration of microarchitecture and cellularization. *Biomedical Materials & Devices*. (2023) 1(1):21–37. doi: 10.1007/s44174-022-00039-8

181. Zhang Q, Esrafilzadeh D, Crook JM, Kapsa R, Stewart EM, Tomaskovic-Crook E, et al. Electrical stimulation using conductive polymer polypyrrole counters reduced neurite outgrowth of primary prefrontal cortical neurons from NRG1-KO and DISC1-LI mice. *Sci Rep*. (2017) 7(1):42525. doi: 10.1038/srep42525

182. Rao Z, Lin Z, Song P, Quan D, Bai Y. Biomaterial-based Schwann cell transplantation and Schwann cell-derived biomaterials for nerve regeneration. *Front Cell Neurosci*. (2022) 16:926222. doi: 10.3389/fncel.2022.926222

183. Sandoval-Castellanos AM, Claeyssens F, Haycock JW. Bioactive 3D scaffolds for the delivery of NGF and BDNF to improve nerve regeneration. *Front Mater*. (2021) 8:734683. doi: 10.3389/fmats.2021.734683

184. Huang L, Gao J, Wang H, Xia B, Yang Y, Xu F, et al. Fabrication of 3D scaffolds displaying biochemical gradients along longitudinally oriented microchannels for neural tissue engineering. *ACS Appl Mater Interfaces*. (2020) 12(43):48380–94. doi: 10.1021/acsami.0c15185

185. Sibuea CV. Liver decellularization as liver organoid reconstruction scaffold. *Buletin Farmatera*. (2021) 6(1):6–10. doi: 10.30596/bf.v6i1.4560

186. He J, Wang J, Pang Y, Yu H, Qin X, Su K, et al. Bioprinting of a hepatic tissue model using human-induced pluripotent stem cell-derived hepatocytes for drug-induced hepatotoxicity evaluation. *Int J Bioprint*. (2022) 8(3):581. doi: 10.18063/ijb.v8i3.581

187. Damania A, Hassan M, Shirakigawa N, Mizumoto H, Kumar A, Sarin SK, et al. Alleviating liver failure conditions using an integrated hybrid cryogel based cellular bioreactor as a bioartificial liver support. *Sci Rep*. (2017) 7(1):40323. doi: 10.1038/srep40323

188. Eades J, Audiffred JF, Fincher M, Choi J-W, Soper SA, Monroe WT. A simple micromilled microfluidic impedance cytometer with vertical parallel electrodes for cell viability analysis. *Micromachines (Basel)*. (2023) 14(2):283. doi: 10.3390/mi14020283

189. Wang X, Chan V, Corridon PR. Decellularized blood vessel development: current state-of-the-art and future directions. *Front Bioeng Biotechnol*. (2022) 10:951644. doi: 10.3389/fbioe.2022.951644

190. Abolhasani S, Ahmadi Y, Rostami Y, Fattahi D. The role of MicroRNAs in mesenchymal stem cell differentiation into vascular smooth muscle cells. *Cell Div*. (2025) 20(1):1–9. doi: 10.1186/s13008-025-00146-0

191. Fusaro L, Gualandi C, Antonioli D, Soccio M, Liguori A, Laus M, et al. Elastomeric electrospun scaffolds of a biodegradable aliphatic copolyester containing PEG-like sequences for dynamic culture of human endothelial cells. *Biomolecules*. (2020) 10(12):1620. doi: 10.3390/biom10121620

192. Rytter N, Carter H, Piil P, Sørensen H, Ehlers T, Holmegaard F, et al. Ischemic preconditioning improves microvascular endothelial function in remote vasculature by enhanced prostacyclin production. *J Am Heart Assoc*. (2020) 9(15):e016017. doi: 10.1161/JAHA.120.016017

193. Wang Y, Wu H, Zhou Z, Maitz MF, Liu K, Zhang B, et al. A thrombin-triggered self-regulating anticoagulant strategy combined with anti-inflammatory capacity for blood-contacting implants. *Sci Adv*. (2022) 8(9):eabm3378. doi: 10.1126/sciadv.abm3378

194. Wang D, Maharjan S, Kuang X, Wang Z, Mille LS, Tao M, et al. Microfluidic bioprinting of tough hydrogel-based vascular conduits for functional blood vessels. *Sci Adv*. (2022) 8(43):eabq6900. doi: 10.1126/sciadv.abq6900

195. Heimbach D, Luterman A, Burke J, Cram A, Herndon D, Hunt J, et al. Artificial dermis for major burns. A multi-center randomized clinical trial. *Ann Surg*. (1988) 208(3):313. doi: 10.1097/00000658-198809000-00008

196. Wainwright D. Use of an acellular allograft dermal matrix (AlloDerm) in the management of full-thickness burns. *Burns*. (1995) 21(4):243–8. doi: 10.1016/0305-4179(95)93866-I

197. Hämmerle CH, Jung RE. Bone augmentation by means of barrier membranes. *Periodontol 2000*. (. 2003) 33(1):36–53. doi: 10.1046/j.0906-6713.2003.03304.x

198. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *Clin Spine Surg*. (2002) 15(5):337–49. doi: 10.1097/00024720-200210000-00001

199. Brigido SA. The use of an acellular dermal regenerative tissue matrix in the treatment of lower extremity wounds: a prospective 16-week pilot study. *Int Wound J*. (2006) 3(3):181–7. doi: 10.1111/j.1742-481X.2006.00209.x

200. Eastlack RK, Garfin SR, Brown CR, Meyer SC. Osteocel plus cellular allograft in anterior cervical discectomy and fusion: evaluation of clinical and radiographic outcomes from a prospective multicenter study. *Spine*. (2014) 39(22):E1331–E7. doi: 10.1097/BRS.0000000000000557

201. Zelen CM, Serena TE, Denoziere G, Fetterolf DE. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. *Int Wound J*. (2013) 10(5):502–7. doi: 10.1111/iwj.12097

202. Wheeler DL, Jenis LG, Kovach ME, Marini J, Turner AS. Efficacy of silicated calcium phosphate graft in posterolateral lumbar fusion in sheep. *Spine J*. (2007) 7(3):308–17. doi: 10.1016/j.spinee.2006.01.005

203. Behrens P, Bitter T, Kurz B, Russlies M. Matrix-associated autologous chondrocyte transplantation/implantation (MACT/MACI)—5-year follow-up. *Knee*. (2006) 13(3):194–202. doi: 10.1016/j.knee.2006.02.012

204. Parker DM, Armstrong PJ, Frizzi JD, North JH. Porcine dermal collagen (permacol) for abdominal wall reconstruction. *Curr Surg*. (2006) 63(4):255–8. doi: 10.1016/j.cursur.2006.05.003

205. Liu W, Lin H, Zhao P, Xing L, Li J, Wang Z, et al. A regulatory perspective on recombinant collagen-based medical devices. *Bioact Mater*. (2022) 12:198–202. doi: 10.1016/j.bioactmat.2021.10.031

206. Casós K, Sommaggio R, Pérez-Cruz M, Costa C. Cell-based assays for modeling xenogeneic immune responses. In: Costa C, editor. *Xenotransplantation: Methods and Protocols*. New York: Springer (2020). p. 99–113. doi: 10.1007/978-1-0716-0255-3_7

207. Joyce K, Buljovcic Z, Rosic G, Kaszkin-Bettag M, Pandit A. Issues with tissues: trends in tissue-engineered products in clinical trials in the European union. *Tissue Eng Part B Rev*. (2023) 29(1):78–88. doi: 10.1089/ten.teb.2022.0094

208. Tan J, Zhang Q-Y, Huang L-P, Huang K, Xie H-Q. Decellularized scaffold and its elicited immune response towards the host: the underlying mechanism and means of immunomodulatory modification. *Biomater Sci*. (2021) 9(14):4803–20. doi: 10.1039/D1BM00470K

209. Naso F, Gandaglia A. Can heart valve decellularization be standardized? A review of the parameters used for the quality control of decellularization processes. *Front Bioeng Biotechnol*. (2022) 10:830899. doi: 10.3389/fbioe.2022.830899

210. Miller WG, Myers G, Cobbaert CM, Young IS, Theodorsson E, Wielgosz RI, et al. Overcoming challenges regarding reference materials and regulations that influence global standardization of medical laboratory testing results. *Clin Chem Lab Med (CCLM)*. (2023) 61(1):48–54. doi: 10.1515/cclm-2022-0943

211. Ramakrishna M, Rao SV. Fabrication of ECM and study of its parameters in NaCl electrolyte. *Mater Today Proc*. (2021) 46:934–9. doi: 10.1016/j.matpr.2021.01.181

212. Song X, Tang Z, Liu W, Chen K, Liang J, Yuan B, et al. Biomaterials and regulatory science. *J Mater Sci Technol*. (2022) 128:221–7. doi: 10.1016/j.jmst.2022.04.018

213. Singh AK, Sundram S, Malviya R. Human-derived biomaterials for biomedical and tissue engineering applications. *Curr Pharm Des*. (2023) 29(8):584–603. doi: 10.2174/1381612829666230320103412

214. Zhou R, Wu Y, Chen K, Zhang D, Chen Q, Zhang D, et al. A polymeric strategy empowering vascular cell selectivity and potential application superior to extracellular matrix peptides. *Adv Mater*. (2022) 34(42):2200464. doi: 10.1002/adma.202200464

215. Banerjee D, Nayakawde NB, Antony D, Deshmukh M, Ghosh S, Sihlbom C, et al. Characterization of decellularized implants for extracellular matrix integrity and immune response elicitation. *Tissue Eng, Part A*. (2022) 28(13-14):621–39. doi: 10.1089/ten.tea.2021.0146

216. Sarkar B, Nguyen PK, Gao W, Dondapati A, Siddiqui Z, Kumar VA. Angiogenic self-assembling peptide scaffolds for functional tissue regeneration. *Biomacromolecules*. (2018) 19(9):3597–611. doi: 10.1021/acs.biomac.8b01137

217. Pattanaik S, Arbra C, Bainbridge H, Dennis SG, Fann SA, Yost MJ. Vascular tissue engineering using scaffold-free prevascular endothelial–fibroblast constructs. *Biores Open Access*. (2019) 8(1):1–15. doi: 10.1089/biores.2018.0039

218. Salah B, Radouane D, Jurgen B. Variability analysis using hybrid intelligent methods and sequential Monte Carlo simulation: application to quality control of material. *Int J Adv Manuf Technol*. (2019) 104:1133–44. doi: 10.1007/s00170-019-03712-3

219. Xu Z, Mangas-Sanjuán V, Merino-Sanjuán M, Merino V, García-Arieta A. Influence of inter-and intra-batch variability on the sample size required for demonstration of equivalent microstructure of semisolid dosage forms. *Pharmaceutics*. (2020) 12(12):1159. doi: 10.3390/pharmaceutics12121159

220. Nellinger S, Mrsic I, Keller S, Heine S, Southan A, Bach M, et al. Cell-derived and enzyme-based decellularized extracellular matrix exhibit compositional and structural differences that are relevant for its use as a biomaterial. *Biotechnol Bioeng*. (2022) 119(4):1142–56. doi: 10.1002/bit.28047

221. Xu X-P, Anderson KL, Swift MF, Volkmann N, Hanein D. Unraveling the molecular details of the cell-ECM interface: 3D structures of membrane-embedded integrin complexes. *Microsc Microanal*. (2017) 23(S1):1102–3. doi: 10.1017/S1431927617006171

222. Agrahari V, Agrahari V. Facilitating the translation of nanomedicines to a clinical product: challenges and opportunities. *Drug Discov Today*. (2018) 23(5):974–91. doi: 10.1016/j.drudis.2018.01.047

223. Barberio C, Saez J, Withers A, Nair M, Tamagnini F, Owens RM. Conducting polymer-ECM scaffolds for human neuronal cell differentiation. *Adv Healthcare Mater*. (2022) 11(20):2200941. doi: 10.1002/adhm.202200941

224. Long J, Qin Z, Chen G, Song B, Zhang Z. Decellularized extracellular matrix (d-ECM): the key role of the inflammatory process in pre-regeneration after implantation. *Biomater Sci*. (2023) 11(4):1215–35. doi: 10.1039/D2BM01204A