June 2025
Volume 5
Issue 1

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.1.1282

A Primer on Fabricating Bioactive Regenerative Scaffolds – From Materials and Surface Properties to Microenvironment

Mai M. Ali

Department of Pharmaceutics, Division of Pharmaceutical Sciences, College of Pharmacy, Arab Academy for Science, Technology and Maritime Transport, Alexandria.

Email: drmaiali@aast.edu

Received on, 28 March 2025 - Accepted on, 14 April 2025 - Published on, 29 April 2025

ABSTRACT:

Scaffold-based regenerative medicine is based on the creation of biomaterial constructs that effectively mimic the native tissue extracellular matrix (ECM), guiding cell behavior and enhancing functional tissue regeneration. Achieving this requires a multifaceted approach that includes careful material selection, control over scaffold architecture, enhancement of bioactivity, and the application of appropriate fabrication techniques. This review offers a comprehensive exploration of these core design principles, equipping researchers with the knowledge to engineer successful scaffolds for a range of regenerative applications. The review examines a spectrum of biocompatible materials and their surface characteristics like roughness, topography, and wettability, carefully weighing their strengths and limitations with respect to mechanical properties, degradation kinetics, potential immunogenicity, and bioactivity. Furthermore, scaffold architecture—encompassing pore size, interconnectivity, and fiber alignment—that plays a crucial role in mediating cell infiltration, nutrient transport, and tissue organization will be discussed. The review also covers the different aspects of increasing scaffold bioactivity, like functionalization with cell adhesion motifs, incorporation of encapsulated growth factors, phytoconstituents, and immunomodulation to create a pro-regenerative microenvironment. Finally, the review discusses the application of various techniques like 3D printing and electrospinning, among others, in scaffold fabrication. By effectively integrating these elements, researchers can design scaffolds that not only provide structural support but also actively orchestrate the regenerative process for better treatment outcomes.

Keywords: ***scaffold, biopolymer, regenerative medicine, drug loading, mechanical properties, porosity, immunomodulation, degradation, surface topography, bioactivity.***

1. Introduction

Regenerative medicine, once considered "a dream," is now a fast-developing scientific area aiming to restore, maintain, or improve damaged tissues and organs affected by disease, injury, or congenital conditions [1]. It combines various knowledge disciplines, including cell biology, materials science, and engineering principles, to offer treatment options that traditional methods lack [2]. Within regenerative medicine, tissue engineering is a strategy that makes use of scaffolds as temporary 3D frameworks similar to native tissue extracellular matrices (ECMs) that facilitate cell attachment, proliferation, differentiation, and the formation of functional tissue [3]. In the last 20 years, an increase in the number of relevant publications on the Scopus Database (Figure 1) has been noted, which indicates its importance.

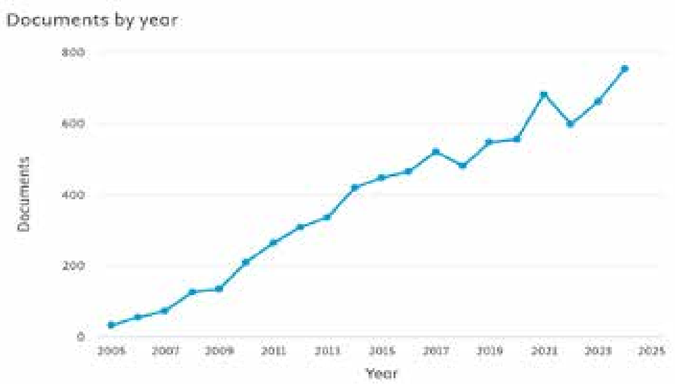

Figure 1: Number of publications over the past 20 years related to the terms "Regenerative medicine" and "Tissue engineering" and "Scaffold" on the Scopus Database.

Engineering of a successful regenerative scaffold is complex and relies on the scaffold's ability to mimic the native tissue extracellular matrix (ECM) microenvironment. This necessitates careful consideration of key design principles (like material selection, scaffold design, bioactivity, and suitable fabrication technique) that influence cellular responses and tissue development [1, 4]. Failure to properly balance these aspects can ultimately lead to scaffold failure.

This review aims to help junior researchers explore the core design principles that govern scaffold performance in regenerative medicine. By analyzing the interplay of materials, structure, and biological activity, the review underscores the need for an integrated, interdisciplinary approach to engineer a successful scaffold. This review further explores the latest trends in material research and fabrication, aligning them with the evolving needs of regenerative strategies to address the development of scalable and cost-effective manufacturing techniques for complex scaffold designs, an area requiring further attention. Ultimately, this understanding will empower researchers to effectively develop more clinically relevant scaffolds to address tissue and organ damage.

2. Key Design Considerations

A. *Material Properties:*

1. Material Biocompatibility

Materials selection for scaffolds depends on the application and desired tissue properties [5]. The chosen materials dictate mechanical properties, degradation kinetics, and, critically, the host scaffold interactions through cell adhesion, and immune response [6]. Inappropriate materials selection can trigger inflammatory immune responses, that ultimately leads to scaffold rejection and treatment failure.

Materials used in any scaffold fabrication can be generally grouped into polymers (natural and synthetic), bio-ceramics, and biodegradable metals, [7] each with unique biocompatibility profiles and application suitability. Using combinations of these biomaterials in composites can open an avenue for properly tailoring scaffold properties to intended applications [8]. A summary of the popular materials used in scaffold fabrication is presented in Table 1.

a. Polymers

Polymeric biomaterials can be derived from both natural and synthetic sources. Natural polymers used in scaffolds encompass carbohydrates like alginate and hyaluronic acid alongside proteins like collagen and elastin alone or in combinations [9]. These biopolymers are widely available, generally non-toxic, and highly biocompatible due to their close resemblance to ECM [10] and provide excellent support for cell adhesion, proliferation, and differentiation [11]. However, natural polymers often suffer from sensitivity and degradation at elevated temperatures, necessitating purification to prevent immunological responses after implantation, and poor mechanical properties. Crosslinking, both chemical and physical, remains a primary method to address the mechanical limitations of natural polymers in scaffold fabrication. Chemical crosslinking, using agents like genipin (favored for its lower cytotoxicity compared to glutaraldehyde) or enzymatic methods, increases polymer network density and enhances mechanical properties. Physical crosslinking, methods like dehydrothermal treatment (DHT) or ionic crosslinking with multivalent ions, offers improvements while often maintaining better biocompatibility [12, 13].

In contrast to natural polymers, synthetic polymers provide enhanced control over scaffold properties such as mechanical properties, degradation rates, and minimized immunogenicity [14, 15]. However, they often lack inherent bioactivity, requiring surface modification or mixing with other natural polymers to facilitate cell attachment [15]. Common synthetic polymers used in tissue engineering and scaffold fabrication include PCL [16] and PLA [17], as well as PLGA [18], PEG [19], and emerging materials like poly(hydroxyalkanoates) (PHAs) [20].

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.1.1282

Table 1: A summary of the popular materials used in scaffold fabrication and their properties.

Material Category	Material	Advantages	Disadvantages	Applications	Ref.
Natural Polymers	Collagen	Excellent biocompatibility, cell adhesion, and biodegradability.	Batch-to-batch variability, limited mechanical strength, potential immunogenicity.	Skin, bone, cartilage, and vascular tissue engineering.	[21-25]
	Gelatin	Similar to collagen, but often more processable and readily available.	Lower mechanical strength than collagen, potential immunogenicity.	Wound healing, drug delivery, cell encapsulation.	[26-28]
	Hyaluronic Acid (HA)	Excellent biocompatibility, inherent bioactivity (CD44 receptor binding), regulates inflammation.	Rapid degradation and limited mechanical strength.	Cartilage, skin, and wound healing applications.	[28]
	Alginate	Easy gelation, biocompatible, relatively inexpensive.	Limited cell adhesion, rapid degradation in vivo.	Cell encapsulation, drug delivery, wound dressings.	[29, 30]
	Chitosan	Antimicrobial properties promote wound healing.	Variable purity, limited mechanical strength.	Wound healing, bone regeneration, drug delivery.	[31]
	Silk Fibroin	High mechanical strength, biocompatibility, slow degradation.	It can be challenging to process, potential for immunogenicity.	Bone, cartilage, and tendon/ligament regeneration.	[32, 33]
Synthetic Polymers	Poly(lactic-co-glycolic acid) (PLGA)	Biodegradable, biocompatible, tunable degradation rate.	Acidic degradation products, lack cell adhesion sites.	Drug delivery, bone regeneration, suture material.	[18, 34]
	Polycaprolactone (PCL)	Biodegradable, slow degradation rate, good mechanical properties.	Hydrophobic, slow degradation, lack of cell adhesion sites.	Bone regeneration, vascular grafts, long-term implants.	[16, 35]
	Poly(lactic acid) (PLA)	Biodegradable, biocompatible, good mechanical properties.	Brittle, slow degradation, acidic degradation products.	Bone screws, suture material, drug delivery.	[17, 35, 36]
Bioceramics	Hydroxyapatite (HAp)	Osteoconductive, biocompatible, promotes bone ingrowth.	Brittle, low tensile strength.	Bone regeneration, dental implants, drug delivery.	[37, 38]
	Tricalcium Phosphate (TCP)	Osteoconductive, biocompatible, bioresorbable.	With lower mechanical strength than HAp, the degradation rate can be difficult to control.	Bone regeneration, drug delivery.	[39, 40]
	Bioactive Glasses (BG)	Osteoconductive and bioactive promote angiogenesis.	Brittle can be challenging to process.	Bone regeneration, wound healing.	[41, 42]
Biodegradable Metals	Magnesium (Mg) and its alloys	Biodegradable, good mechanical properties, promotes bone formation.	Rapid degradation and hydrogen gas evolution can cause local alkalization.	Bone fixation screws, cardiovascular stents.	[43-45]
	Zinc (Zn) and its alloys	Biodegradable, essential trace element, antibacterial properties.	Limited mechanical strength can be brittle.	Small bone implants, wound healing.	[44, 45]
	Iron (Fe) and its alloys	Biodegradable, good mechanical strength.	Slower degradation than Mg, the potential for iron overload.	Cardiovascular stents, bone fixation devices.	[46, 47]

Composite Materials	Hydroxyapatite (HAp) / Polymer Composite	Combines osteoconductivity of HAp with tunable degradation and mechanical properties of the polymer.	It can be challenging to achieve uniform distribution of HAp, which has the potential for delamination.	Bone and dental regeneration.	[21, 26, 37, 48, 49]
	Collagen and polymer Composite	Enhanced biocompatibility promotes cell adhesion. Antimicrobial properties (chitosan), tunable mechanical properties (synthetic polymers)	Chitosan variability, limited mechanical strength, potential immunogenicity, degradation control challenges.	Wound healing, bone/ cartilage regeneration, nerve conduits.	[50-52]
	Decellularized ECM / Synthetic Polymer Composite	Provides natural ECM signals with enhanced mechanical properties and processability from synthetic components	Decellularization can change native architecture, and it can be challenging to maintain ECM bioactivity during the processing.	Vascular grafts, soft tissue, and nerve repair	[53-55]

b. Bioceramics

Bioceramics like Hydroxyapatite (HAp) and tricalcium phosphate (TCP) are widely used in dental and bone tissue engineering due to their biocompatibility, osteoconductivity, and ability to promote bone regeneration [21, 26]. While offering advantages like non-toxicity and inherent bioactivity, they are brittle and have low elasticity, promoting their use in composites for weight-bearing applications [26].

c. Metal implants

Traditional metal implants, made of stainless steel [56] and titanium alloys [57], are characterized by their strength, corrosion resistance, and cost-effectiveness [58], but their non-biodegradable nature has inspired the development of biodegradable porous metal implants, such as magnesium [43], iron [46] and zinc [44] based implants, which offer controlled corrosion properties. While these biodegradable metals offer biocompatibility and bone-like mechanical properties, they face challenges, including slow degradation and MRI incompatibility [59].

d. Composite Materials

Combining various materials in scaffold design can provide tunable properties to simulate target tissue properties. Introducing synthetic polymers, such as PLGA or PCL, often enhances the mechanical strength, degradation control, and processability of scaffolds derived from naturally sourced materials like collagen, chitosan, or alginate. However, the inherent biocompatibility of natural polymers can be compromised. Synthetic polymers may elicit an inflammatory response or generate acidic degradation products that negatively affect cell viability and tissue regeneration. Ultimately, designing successful synthetic-natural polymer blends necessitates a delicate balance to optimize mechanical properties while minimizing adverse biological responses and promoting effective tissue integration. Collagen-PLGA composites offer enhanced cell adhesion and controlled degradation [59]. Incorporating bioactive ceramics like hydroxyapatite into polymer matrices enhances osteoconductivity for bone regeneration [38]. Silk fibroin-based composites are also gaining attention due to their excellent mechanical properties and biocompatibility in cartilage regeneration [32].

It is worth noting that standardized testing and validation for demonstrating scaffold biocompatibility is essential for the successful translation of scaffold-based therapies. Available in vitro and in vivo techniques to evaluate the scaffold's biocompatibility include cell viability assays, cytokine release assays and histological analysis [60].

2. Scaffold degradation

The scaffold degradation process (including both biodegradation and biosorption) is a critical design parameter to achieve optimal outcomes in regenerative scaffolds. Ideally, a scaffold should degrade at a rate proportional to new tissue formation to ensure that the mechanical support provided by the scaffold gradually diminishes as the newly formed tissue gains its own structural integrity. Disproportionality in these rates can lead to a variety of complications where premature degradation causes scaffold collapse, while slow degradation hinders tissue remodeling.

Several factors influence the degradation rate of a scaffold, including the material composition, crosslinking density, porosity, and the presence of enzymes [36]. Synthetic polymers like

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.1.1282

polycaprolactone (PCL) and poly(lactic acid) (PLA) are widely used due to their controllable degradation profiles [35]. Also, it has been reported that incorporating bioceramic materials such as hydroxyapatite (HA) into polymer scaffolds in high concentrations can often lead to slower scaffold degradation rates [37].

In some cases, scaffold degradation products can promote tissue regeneration. The release of Zn^{2+} ions from degrading zinc alloys can promote osteogenesis and angiogenesis [45]. Recent studies have explored developing "smart" scaffolds that respond to microenvironmental stimuli and degrade in a controlled manner [61].

Scaffold degradation mediated by enzymes is a key contributing factor to the success of regenerative scaffolds. Collagenases, specifically matrix metalloproteinases (MMP) secreted by fibroblasts and immune cells, metabolize collagen in scaffolds such as collagen-based sponges or decellularized ECM, thereby affecting the rate of tissue integration and vascularization [62]. In addition, Esterases hydrolyze ester bonds prevalent in synthetic biodegradable polymers like poly(lactic acid) (PLA) and poly(ε-caprolactone) (PCL) [63].

Recent studies have shown that a variety of techniques can be used to monitor in vivo degradation, such as histological evaluation, imaging modalities, and biochemical assays [64]. Further research into the mechanisms of in-vivo scaffold degradation and the effects of degradation products on the host response will pave the way for the development of more effective and biocompatible regenerative therapies.

3. Mechanical Properties

In designing scaffolds, understanding how mechanical properties influence cell behavior and tissue regeneration is critical due to the mechanosensitive nature of cells. Scaffold's mechanical characteristics, such as stiffness (Young's modulus), tensile strength, elasticity, viscoelasticity, and compressive strength, may govern cell fate, ECM production, and, ultimately, the functional integrity of engineered tissues [24]. Consequently, studies to balance these mechanical attributes are essential to effectively mimic the native tissue microenvironment in engineered scaffolds. A summary of scaffold mechanical properties in relation to engineered tissue is presented in Table 2.

Scaffold stiffness plays a crucial role in directing cell behavior and tissue regeneration. Cells, being mechanosensitive, will migrate towards regions of optimal stiffness for their specific phenotype. Mesenchymal stem cells (MSCs), for instance, exhibit differential differentiation based on substrate stiffness, with softer substrates promoting neurogenic lineages and stiffer substrates favoring osteogenic differentiation. This mechanotransduction mechanism highlights the need to carefully consider the target tissue's inherent stiffness during scaffold design [65].

Furthermore, the presence of stiffness gradients within a scaffold is a feature that directs regeneration events toward mimicking the mechanical properties of native tissues. Native tissues, such as bone or cartilage, rarely exhibit uniform stiffness; instead, they display gradual transitions in mechanical properties across different regions and interfaces, providing cells with positional information and guiding their migration and differentiation.

Table 2: A summary of scaffold mechanical properties in relation to engineered tissue.

Tissue	Key Mechanical Property	Desired Range	Typical Scaffold Materials	Ref.
Bone	Compressive Strength	2-200 MPa (Cancellous) 100-200 MPa (Cortical)	Hydroxyapatite (HAp), Tricalcium Phosphate (TCP), PLGA/HAp Composites, PCL, Metals (Ti, Mg)	[66]
	Elastic Modulus	0.02-20 GPa (Cancellous) 10-30 GPa (Cortical)	HAp, TCP, PLGA/HAp Composites, PCL	
	Viscoelasticity	energy absorption during impact.	HAp/Polymer Composites, Collagen-mineral composites	
Cartilage	Compressive Modulus	0.1-10 MPa	Collagen, Hyaluronic Acid (HA), Agarose, Alginate, PCL/Collagen Composites	[67]
	Tensile Strength	1-10 MPa	Collagen, Silk Fibroin, HA	
	Viscoelasticity	load distribution and shock absorption.	HA, Agarose, Alginate, crosslinked Collagen hydrogels with specific crosslinking.	

Tendon/ Ligament	Tensile Strength	50-100 MPa	Collagen, Silk Fibroin, Electrospun Polymers (PCL, PLA), Collagen/Polymer Composites	[68]
	Elastic Modulus	100-1000 MPa	Collagen, Silk Fibroin, Electrospun Polymers (PCL, PLA)	
	Viscoelasticity	energy dissipation under dynamic loading.	Aligned Collagen fibers, PCL, and composite materials.	
Skeletal Muscle	Elastic Modulus	1-100 kPa	Hydrogels (Fibrin, GelMA, PEG), Electrospun Polymers	[68]
	Tensile Strength	0.1-1 MPa	Hydrogels (Fibrin, GelMA, PEG)	
	Viscoelasticity	muscle's ability to withstand contractions.	Fibrin, GelMA, composites with tunable degradation.	
Vascular Tissue	Tensile Strength	1-3 MPa (Artery)	Elastin, Collagen, PCL, Decellularized Vessels, Elastin-like Polypeptides (ELPs)	[69]
	Elastic Modulus	0.1-10 MPa (Artery)	Elastin, Collagen, PCL, Decellularized Vessels, ELPs	
	Viscoelasticity	damping pulsatile blood flow and preventing aneurysms.	Elastin-rich materials, dynamically crosslinked polymers.	
Neural Tissue	Elastic Modulus	0.1-10 kPa	Hydrogels (Agarose, Hyaluronic Acid, PEG), Self-Assembling Peptides	[70]
	Compressive Modulus	Similar to Elastic Modulus	Hydrogels (Agarose, Hyaluronic Acid, PEG), Self-Assembling Peptides	
	Viscoelasticity	Plays a role in neuronal signaling and axonal guidance.	Self-assembling peptides, very soft hydrogels	

Processes. In this context, scaffolds engineered with stiffness gradients create a more biomimetic environment that can trigger different intracellular signaling pathways through varying mechanical forces promoting controlled tissue regeneration [71].

Tensile strength, the capacity of a scaffold to resist breaking under tension, is also a fundamental determinant of scaffold performance. A scaffold with low tensile strength will prematurely fail under physiological loads, compromising its structural integrity and impeding tissue regeneration. A scaffold's tensile strength requirements vary considerably depending on the target tissue, reflecting the diverse mechanical demands of different organs [72]. For highly tensile tissues like tendons and ligaments, scaffold tensile strength is paramount to withstand physiological loads during movement [73]. In vascular tissue engineering, scaffolds must maintain structural integrity while preventing aneurysmal dilation or rupture of engineered blood vessels under pulsatile blood pressure [74]. In bone regeneration, higher tensile strength correlates with slower degradation, which is important where the scaffold needs to provide long-term support for bone ingrowth and mineralization [75]. For skin regeneration, adequate tensile strength in dermal scaffolds provides a stable platform for fibroblast infiltration, growth, and production of ECM, preventing wound contraction and promoting a natural skin architecture [76].

Elasticity, defined as a material's ability to return to its original shape after deformation, directly impacts the performance of scaffolds in tissue engineering applications. For highly elastic tissues such as arteries and lung alveoli, the scaffold must exhibit sufficient elasticity to withstand repetitive cycles of expansion and contraction without permanent deformation, ensuring long-term structural integrity and functionality [75]. Furthermore, scaffold elasticity directly influences cellular mechanotransduction. Cells adhere to the scaffold via integrins, forming focal adhesions that link the scaffold matrix to the intracellular cytoskeleton. The scaffold's elastic behavior then creates a biomimetic microenvironment that influences intracellular signaling pathways that regulate cell proliferation and differentiation [77] to promote successful tissue regeneration.

Viscoelasticity, which describes a material's time-dependent response to applied stress, affects scaffold performance by influencing and modulating cell-matrix interactions within the scaffold [78]. Viscoelastic scaffolds exhibit energy dissipation, with a portion of the energy being dissipated as heat due to internal friction. The significance of viscoelasticity stems from its ability to more closely mimic the mechanical behavior of many native tissues, particularly those subjected to complex, dynamic loading [79]. Cartilage, a highly viscoelastic tissue, exhibits a time-dependent response to compressive forces, allowing it to efficiently

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.1.1282

dissipate energy during joint loading. Scaffolds that mimic this viscoelastic behavior can better protect chondrocytes from excessive mechanical stress, promoting matrix synthesis and preventing tissue degradation [79].

At the cellular level, the viscoelastic properties of a scaffold can directly modulate the dynamics of cell-matrix interactions. Cells respond not only to the magnitude of the applied force but also to the rate at which the force is applied, a feature that is inherently encoded in viscoelastic materials [80]. For example, studies have shown that viscoelastic substrates can promote enhanced integrin clustering and focal adhesion formation, leading to increased cell adhesion and spreading [81], and can provide dynamic mechanical guides that promote stem cell differentiation along specific lineages, such as osteogenesis or chondrogenesis [30].

Compressive strength, defined as a material's ability to withstand axial compressive loads before failure, is a critical mechanical property in scaffold design. A scaffold with insufficient compressive strength will deform or collapse under physiological loading conditions, compromising its structural integrity and hindering tissue regeneration. Bone scaffolds, for example, must possess adequate compressive strength to support weight-bearing and promote bone ingrowth [82]. Similarly, cartilage scaffolds must withstand compressive forces within joints, maintaining joint space and facilitating shock absorption [31]. In addition, compressive strength also influences cellular behavior within the scaffold. For instance, compressive forces can enhance chondrocyte differentiation and promote the synthesis of cartilage-specific extracellular matrix components [83]. Therefore, matching the compressive strength of the scaffold to the target tissue's mechanical demands is crucial for successful integration and long-term functionality.

4. Surface Properties

The design of regenerative scaffolds depends not only on bulk properties but on scaffold surface characteristics as well, where the scaffold-cell interactions govern the overall success of the regeneration process. Key factors that influence cell fate on scaffolds include surface topography (particularly roughness and surface pits/grooves) and surface chemistry (particularly wettability and functional groups). A summary of scaffold surface properties in relation to cell adhesion and differentiation is presented in Table 3.

Studies have demonstrated the significant influence of scaffold topography on cell behavior [71]. Implants with nano grooves/pits exhibit enhanced bone ingrowth compared to smooth surfaces. Furthermore, the size and distribution of surface features can influence cell adhesion, with certain configurations promoting enhanced osteoblast attachment. Surface roughness also differentially affects cell types, with osteoblast proliferation increasing with roughness while fibroblast proliferation decreases [84].

Scaffold surface chemistry also plays a crucial role in cell adhesion. Generally, an increase in scaffold hydrophilicity promotes osteoblast adhesion, while fibroblast adhesion peaks at intermediate wettability. Conversely, hydrophobic surfaces may hinder cell adhesion and can even promote microbial biofilm formation. In addition, hydrophilic surfaces also facilitate protein adsorption and cell spreading, fostering a more favorable environment for cell growth. An excellent review by Idaszek J. et al. discusses the effect of surface properties on scaffold performance [85].

Furthermore, scaffold surface modification can improve biocompatibility and enhance regenerative outcomes. By strategically modifying the scaffold surface, researchers can create a microenvironment that provides control over cell adhesion, spreading, migration, differentiation, and the production of extracellular matrix. Surface modification strategies can be generally classified into physical, chemical, and biological modifications [86].

Table 3: A summary of scaffold surface properties in relation to cell adhesion and differentiation.

Surface Property	Impact on Cell Attachment	Impact on Cell Differentiation	Modification Techniques	Ref.
Surface Roughness (Ra, Sq)	Increased roughness generally enhances cell adhesion by providing more surface area for cell attachment and promoting integrin clustering. Nanoroughness can be particularly effective.	It can direct cell fate. Certain lineages (e.g., osteogenic) are often enhanced on rougher surfaces.	Sandblasting, acid etching, plasma etching, micro/nanofabrication, self-assembling nanostructures.	[87, 88]
Surface Topography (Grooves, Pits, Nanopatterns)	Aligned features (e.g., grooves, nanofibers) provide contact guidance cues, directing cell alignment and elongation.	Can influence cell lineage commitment and function. Aligned features can promote differentiation along specific lineages (e.g., tenogenic, myogenic).	Micro/nanofabrication (e.g., lithography, etching), electrospinning, microcontact printing.	[39, 84]
Wettability (Hydrophilicity/Hydrophobicity)	Hydrophilic surfaces generally promote protein adsorption, which is crucial for initial cell attachment.	It can influence the lineage commitment of stem cells. Some lineages (e.g., fibroblast) prefer moderately hydrophilic surfaces.	Plasma treatment, surface grafting of hydrophilic polymers (e.g., PEG), self-assembled monolayers (SAMs) with hydrophilic terminal groups.	[89, 90]
Surface Charge (Positive/Negative)	Influences protein adsorption (charge-charge interactions). Positive charges can enhance cell attachment in some cases.	It can affect signaling pathways involved in cell differentiation.	Plasma treatment, surface grafting of charged polymers (e.g., poly(acrylic acid)), chemical modification with charged functional groups.	[91]
Growth Factor Immobilization	Enhances cell recruitment and differentiation by providing localized growth factor signaling.	Directly promotes differentiation by activating specific growth factor receptors and downstream signaling pathways.	Physical adsorption, covalent grafting, encapsulation within micro/nanoparticles.	[92, 93]

Physical methods, such as plasma treatment, surface roughening, and micro/nanofabrication, alter the scaffold's topography and roughness to influence cell adhesion and alignment. It was found [94] that increasing the roughness of a titanium implant surface can promote osteoblast adhesion and the subsequent growth of bone tissue while creating aligned microgrooves on a polymer scaffold can guide cell orientation and the deposition of extracellular matrix in anisotropic tissues like muscle or nerve [95].

Chemical methods involve introducing or modifying functional groups on the scaffold surface. This affects properties like wettability, which can improve protein adsorption and cell adhesion. In addition, a surface charge can influence the recruitment of specific proteins or cells. Techniques like chemical self-assembled monolayers and surface grafting can be used to create surfaces with specific chemical functionalities [86].

Finally, biological methods involve immobilizing bioactive molecules such as cell adhesion peptides directly onto the scaffold surface [87]. This technique allows control over cell signaling to promote very specific cellular responses. The optimal surface modification strategy will depend on the specific needs of the tissue that is being engineered and the precise cellular behaviors that need to be encouraged.

B. Scaffold Architecture:

While material selection and bioactivity are crucial for proper scaffold design, it is the architecture of the scaffold that exerts a dominant influence on its clinical success. Scaffold architecture features like porosity and fiber alignment will be discussed.

1. Porosity

Porosity exerts a dominant influence on the scaffold microenvironment and, consequently, its performance. The pore's size and interconnectivity control nutrient and waste transport through the scaffold and cell infiltration.

a. Pore size

The importance of pore size in facilitating cell migration, nutrient diffusion, and vascularization

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.1.1282

within the scaffold for successful tissue regeneration is well recognized. Macropores create pathways for cells to migrate into the interior of the scaffold, access nutrients, and get rid of metabolic waste products. It is noteworthy that the optimal pore size can vary depending on the specific tissue being engineered. For bone tissue, studies suggest that a combination of smaller pores (50-100 μm) to promote initial cell attachment and larger pores (200-400 μm) to enhance nutrient diffusion and angiogenesis is most effective. For other tissues, such as skin, smaller pores (1-12 μm) have demonstrated the greatest support for cell attachment [96, 97].

b. Interconnectivity

Similar to pore size, the interconnectivity of scaffold pores is also crucial. While pore size dictates cellular accessibility, interconnected pores establish continuous pathways for mass transport throughout the scaffold 3D structure, enhancing diffusion and transport of essential nutrients to cells deep within and facilitating the efficient removal of metabolic waste products, preventing accumulations that can inhibit cellular function, leading to apoptosis or necrosis, and compromise extracellular matrix (ECM) synthesis. In this context, pores interconnectivity is essential for maintaining cellular viability and promoting proliferation [98].

In large, complex scaffolds with increased diffusion distances, pore interconnectivity becomes more significant in preventing nutrient depletion and waste accumulation in the scaffold core by providing efficient mass transport pathways across the scaffold volume. This transport system helps keeping a proper microenvironment across the scaffold, promotes uniform cellular distribution, robust tissue formation, and long-term functional integration [99]. However, scaffold porosity can compromise its mechanical properties. This creates a necessity to balance scaffold requirements for the design of effective scaffolds.

2. Fiber Alignment

Many native tissues, including nerves, muscles, tendons, and blood vessels, exhibit highly organized microstructures in which cells and ECM components are aligned in a specific direction (anisotropic). This precise alignment is vital for imparting the required functional mechanical characteristics, facilitating cell communication, and, ultimately, ensuring proper tissue function. In this context, fiber alignment within regenerative scaffolds (mimicking the anisotropic architectures of native tissues) exerts a significant influence on cellular organization and function. Scaffolds with controlled fiber alignment guide cell interactions within the scaffold by providing topographical signals that influence extracellular matrix (ECM) deposition, induce cell directional orientation, promote cell-cell communication along the longitudinal axis, and mirror the native tissue structure [100].

The effects of fiber alignment are particularly relevant in musculoskeletal system regeneration. In tendon and ligament engineering, it was reported [101] that aligned electrospun nanofibers were able to guide stem cell differentiation toward the tenocyte lineage, fostering the development of longitudinal organization of collagen fibrils with enhanced mechanical properties and the upregulation of tenogenic markers in seeded cells. Furthermore, in neural tissue engineering, aligned nanofibers were found to create guidance templates for axonal extension, promoting directional nerve regeneration [102].

C. Bioactivity

Regenerative scaffolds provide an artificial ECM for cells to adhere, proliferate, and differentiate. The ability of cells to interact effectively with the microenvironment within the regenerative scaffold (bioactivity) directs the formation of new tissue. Consequently, increasing scaffold bioactivity can help achieve scaffold functional success. Various strategies are adopted to increase scaffold bioactivity, including the incorporation of cell adhesion motifs, growth factors, immunomodulators, and the addition of encapsulated phytoconstituents. A summary of scaffold bioactivity strategies is presented in Table 4.

Table 4: A summary of the scaffold bioactivity strategies.

Bioactivity Strategy	Mechanism of Action	Examples	Benefits	Limitations	Representative Tissues Studied	Ref.
Incorporation of Cell Adhesion Motifs	Promotes cell attachment and spreading by providing specific binding sites for integrins	-RGD (Arginine-Glycine-Aspartic acid) peptides -YIGSR (Tyrosine-Isoleucine-Glycine-Serine-Arginine) peptides	Enhances cell adhesion, migration, and ECM production; improves cell-scaffold integration; enables selective cell binding through specific motif choice.	It may not be sufficient for all cell types or tissue types, requiring combinations of motifs; it can be costly to synthesize peptides; motif presentation and accessibility can be challenging; and susceptibility to enzymatic degradation.	Bone, Cartilage, Skin, Neural Tissue	[103-105]
Growth Factor Delivery (Controlled Release)	It provides tissue-specific localized and sustained stimulation of cell proliferation, differentiation, and angiogenesis.	- BMP-2 (Bone Morphogenetic Protein-2) - VEGF (Vascular Endothelial Growth Factor) - TGF-β (Transforming Growth Factor-β) - NGF (Nerve Growth Factor)	Promotes targeted cell responses, enhances tissue formation, accelerates healing; allows for precise control over GF dose and release kinetics.	Requires careful optimization of release kinetics and dose to avoid supra-physiological levels; potential for off-target effects if GF diffuses away from the intended site; GFs can be unstable and prone to degradation.	Bone, Cartilage, Vascular Tissue, Neural Tissue, Wound Healing	[106-109]
Immunomodulation	Twists macrophage polarization from pro-inflammatory (M1) to pro-regenerative (M2); reduces inflammation and promotes tissue repair.	- Incorporation of M2-polarizing cytokines: (IL-4, IL-10) - Use immunomodulary biomaterials (Decellularized ECM, hyaluronic acid, and chitosan).	Enhanced tissue regeneration; reduced fibrosis and scar formation; improved cell survival; modulated host-graft response.	Potential for off-target effects; requires careful control of cytokine dosage and release kinetics; dECM can be immunogenic if not properly processed; long-term effects on immune system not fully understood.	Bone, Cartilage, Wound Healing, Spinal Cord Injury, Vascular Grafts	[110-112]
Incorporation of Phytoconstituents	Modulate cell behavior through reduced oxidative stress and promote wound healing through natural bioactive compounds.	- flavonoids and essential oils (antioxidant, anti-inflammatory) - Aloe vera (wound healing)	Enhanced cell proliferation, differentiation, and migration; reduced inflammation and oxidative stress; improved angiogenesis and ECM deposition; can have antimicrobial properties.	Bioavailability limitations; potential for cytotoxicity at high concentrations; stability issues; batch-to-batch variability; some have limited aqueous solubility.	Skin, Wound Healing, Bone Regeneration, Nerve Regeneration	[113-115]

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.1.1282

1. Cell Adhesion Motifs

Cell adhesion motifs are short peptide sequences derived from ECM proteins, that mimic the natural signals that cells utilize to attach to and interact with their surroundings, thereby, influencing cell morphology, migration, gene expression, and ultimately, tissue organization.

Integrins, a family of transmembrane receptors, are the primary mediators of cell adhesion to the ECM. Integrins recognize and bind to specific amino acid sequences within ECM proteins, triggering intracellular signaling pathways that regulate cell behavior. As such, incorporating integrin-binding motifs such as arginine-glycine-aspartic acid (RGD) sequence (found in a variety of ECM proteins, including fibronectin, vitronectin, and laminin) can effectively promote cell adhesion, spreading, and migration on a wide range of scaffold biomaterials. This sequence is one of the most widely studied cell-adhesive motifs and is recognized by several different integrins. RGD functionalization has also proven valuable in stimulating the differentiation of mesenchymal stem cells [33].

The method of presenting cell adhesion motifs is also an important consideration. Simply incorporating adhesion ligands into the scaffold bulk may not be sufficient to promote cell adhesion, as they may be buried within the material core and inaccessible to cells. Surface modification methods like plasma treatment, chemical grafting, and layer-by-layer assembly can be used to ensure proper surface presentation [116]. Continued research into novel ECM-derived motifs, delivery strategies, and the synergistic effects of multiple bioactive signals will pave the way for the development of even more effective and clinically relevant regenerative therapies.

2. Growth Factor Delivery

Growth factors (GFs) are naturally occurring signaling proteins that play an essential role in almost all aspects of scaffold biological performance, regulating cell proliferation, differentiation, migration, and ECM synthesis. Although integrating growth factors within scaffolds can be challenging due to the inherent problems of bioavailability, short half-life, and potential side effects, their delivery from biomaterial scaffolds is swiftly becoming a vital research topic for promoting tissue regeneration. The choice of growth factor and its delivery strategy are highly tissue-specific. Scaffolds serve as vehicles for delivering GFs to the site of tissue regeneration. The controlled release of GFs from scaffolds is crucial, as the timing and dose can profoundly affect cell response, including cell recruitment, tissue-specific differentiation, and tissue development [117].

Delivery of GFs ranges from simple GF incorporation within the scaffold matrix to sophisticated micro- or nano-encapsulation that provides sophisticated control over the GFs release within scaffolds, enhancing their regenerative potential [118]. Microparticles and nanoparticles can encapsulate GFs within a variety of materials, including polymers, lipids, and inorganic materials, protecting the GFs from degradation and enabling sustained release profiles. These systems are integrated into the scaffold structure, allowing for localized GF delivery [119]. PLGA microspheres loaded with bone morphogenetic protein-2 (BMP-2) were found to be successful in bone regeneration, providing a controlled release of BMP-2 that promotes osteoblast differentiation and bone formation [106]. Transforming growth factor-β (TGF-β) has been incorporated into hydrogels for cartilage regeneration, promoting chondrogenesis and cartilage matrix synthesis [120]. In addition, the liposomal hydrogel was found to deliver vascular endothelial growth factor (VEGF) in a sustained manner in order to enhance the osteogenesis of MG-63 cells [121]. Overall, growth factors have become important means of promoting certain cellular behaviors by directing cells toward desired outcomes.

3. Immunomodulatory signals.

The host's immune response to the implanted scaffold and/or its degradation products represents one of the primary concerns for developing a successful regenerative scaffold [22]. Scaffolds can trigger immune responses, directing macrophage polarization towards either pro-inflammatory M1 or pro-regenerative M2 phenotypes. This property is a key factor that governs the overall healing outcomes. M1 macrophages release pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, promoting chronic inflammation and scaffold failure, while M2 macrophages secrete anti-inflammatory cytokines such as IL-10 and TGF-β that promote tissue repair, angiogenesis, ECM remodeling, and resolution of inflammation, making them highly desirable in regenerative settings. Consequently, the modulation of macrophage polarization towards the M2 phenotype is an increasingly desirable strategy in scaffold design.

Several approaches are being explored to achieve this immunomodulation. Certain biomaterial hydrogels, such as hyaluronic acid and chitosan, possess inherent immunomodulatory properties, capable of steering the immune response toward a pro-regenerative state [122]. The use of decellularized ECM (dECM) holds significant promise, as it inherently contains tissue-specific growth factors and ECM proteins that can influence macrophage behavior [123].

4. Phytoconstituents

Incorporating phytoconstituents such as flavonoids and polyphenolic compounds in wound healing scaffolds significantly enhances their regenerative potential. They act as antioxidants, reduce inflammation, and promote a wound healing microenvironment. They offer distinct advantages of biocompatibility and complex mechanisms of action. Optimized phytoconstituents loading, release kinetics, and loaded scaffold degradation profiles are all responsible for attained therapeutic efficacy [124, 125].

In addition, encapsulating essential oils (EOs) within scaffolds also represents a promising strategy for enhancing their performance in a multifaceted approach. First, many EOs exert antimicrobial activity (disrupt bacterial cell membranes and inhibit biofilm formation), creating a cleaner environment that promotes cell survival and proliferation within the scaffold, reducing the risk of scaffold-associated infections, a significant barrier to successful tissue integration. In addition, many EOs possess anti-inflammatory properties, reducing the expression of pro-inflammatory cytokines and promoting an immunomodulatory shift towards a pro-regenerative immune response and preventing chronic inflammation, which can hinder tissue repair and lead to fibrosis. Also, certain EOs promote the release of vascular endothelial growth factor (VEGF), stimulating angiogenesis essential for nutrient supply and waste removal within the scaffold [126].

Encapsulation of EOs from scaffolds not only protects EOs from degradation but also allows for sustained and localized delivery, maximizing their therapeutic effect while minimizing potential cytotoxicity associated with high concentrations. Various encapsulation methods, including microencapsulation, nanoencapsulation, and complexation with cyclodextrins, are employed to create EO-loaded delivery systems suitable for incorporation into a variety of scaffold materials [127]. This multifaceted modulation of the scaffold microenvironment by EOs helps increase their bioactivity for successful tissue regeneration and functional integration.

4. Fabrication Techniques

The proper selection of a suitable fabrication technique directly influences the scaffold's porosity, mechanical properties, and drug delivery capabilities, all of which are vital to the proper direction of cell behavior and tissue regeneration. In this context, the ideal fabrication method must be carefully considered with respect to the specific requirements of the target tissue and the desired scaffold characteristics, in addition to the scalability and cost-effectiveness of the technique for eventual clinical translation [128]. A summary of common scaffold Fabrication Techniques is presented in Table 5.

Traditional fabrication methods are simpler and more accessible and still present potential value. Solvent casting and particulate leaching are foundational for creating porous scaffolds with controlled pore size, are useful in bone regeneration, and provide a basic template for osteoblast attachment. Gas foaming, known for avoiding organic solvents, is suitable for enhancing biocompatibility in scaffolds designed for soft tissue applications. Freeze-drying, or lyophilization, creates highly porous structures, mimicking the architecture of ECM and serving as a versatile starting point for deposition and cell infiltration in bone and skin regeneration. Each technique, though established, continues to be refined and adapted for novel applications [128, 129]. Advanced fabrication technologies, on the other hand, provide broader outcomes and versatility. Electrospinning creates nanofiber scaffolds with control over fiber alignment, which is essential for directional cell organization in anisotropic tissues like tendons, ligaments, and nerves. 3D printing, encompassing techniques like fused deposition modeling, stereolithography, and bioprinting, enables the creation of complex, customized scaffolds tailored to the patient's anatomy.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.1.1282

Table 5: Summary of common scaffold Fabrication Techniques.

Fabrication technique	Process description	Advantages	Limitations	Examples	Ref.
Solvent casting/particulate leaching	The polymer solution is cast into a mold with porogen (salt, sugar); the solvent evaporates, and the porogen leaches out.	Simple, cost-effective, controlled pore size and porosity.	Poor pore interconnectivity hinders nutrient transport in larger constructs, as well as difficult, complex geometries and potential solvent contamination.	PLGA scaffolds for non-load-bearing bone regeneration.	[129-131]
Gas foaming	Polymer saturated with gas (CO_2) under pressure; pressure release creates pores.	Avoids organic solvents, potentially improving biocompatibility.	Difficult to control pore size and interconnectivity; often, closed-pore structures restrict cell infiltration and nutrient diffusion.	PCL scaffolds for soft tissue regeneration.	[129, 132]
Freeze-drying (lyophilization)	The polymer solution was frozen, and the solvent was sublimated under a vacuum.	Simple, versatile; high porosity promotes cell infiltration.	Limited control pore size and interconnectivity; anisotropic pore structures restrict cell migration and ECM deposition.	Collagen scaffolds and skin regeneration.	[129, 133, 134]
Temperature-induced phase separation (TIPS)	Polymer solution undergoes liquid-liquid or solid-liquid phase separation upon cooling, followed by solvent extraction.	Good control over pore size and morphology; highly interconnected porous structures can be achieved, which promotes cell infiltration and nutrient transport.	It can be challenging to remove all solvents; mechanical properties can be limited.	PCL, PLGA, and collagen scaffolds for various tissue engineering applications.	[129, 135, 136]
Electrospinning	The polymer solution is ejected through a spinneret under high voltage, forming nanofibers.	High surface area promotes cell adhesion, and controlled fiber alignment guides cell orientation.	Limited control of pore size and porosity hinders cell infiltration and transport.	PU scaffolds for vascular grafts.	[129, 137]
3D printing (additive manufacturing)	Digital design builds scaffolds layer by layer (FDM, SLS, SLA, bioprinting).	Precise control geometry, pore size/interconnectivity, promotes optimal cell infiltration, nutrient transport & material composition; customized scaffolds provides control over mechanical properties.	Time-consuming, expensive, specialized equipment, material limitations.	PCL bone scaffolds, hydrogel cartilage scaffolds.	[129, 137, 138]
Decellularization	Cells removed from native tissues/organs, leaving ECM scaffold.	Retains natural ECM architecture, composition, and biomechanical properties, which provide a natural microenvironment.	Difficult complete decellularization, potential immune response, limited control geometry and properties.	wound healing, heart valves for valve replacement.	[123, 139, 140]

Combining different scaffold fabrication techniques is quickly gaining interest in overcoming the limitations of individual methods and creating scaffolds with tailored properties for complex applications. Examples of commonly combined fabrication techniques are listed in Table 6. By synergistically integrating multiple approaches, researchers can achieve greater control over scaffold architecture, mechanical properties, and bioactivity. These hybrid approaches leverage the strengths of each technique, resulting in scaffolds that better mimic the complex microenvironment of native tissues and promote enhanced tissue regeneration.

As the field advances, further research is needed to develop novel fabrication techniques, optimize existing techniques, and translate these promising technologies into clinical applications.

5. Conclusion

Successful scaffold design for regenerative medicine requires a meticulous balance of material properties, geometry, bioactivity, and selected fabrication technique. To optimize material properties, continued research into biocompatible materials is crucial for minimizing adverse host responses, while controlled degradation mechanisms are necessary to ensure scaffold breakdown aligns with new tissue formation. Matching scaffold mechanical properties to native tissue properties is vital for creating biomimetic environments that promote appropriate cell responses. Regarding geometry, advanced fabrication methods are critical for achieving precise control over architecture, porosity, and pore interconnectivity, facilitating optimal cell infiltration and nutrient transport. Simultaneously, ongoing investigations into microfabrication techniques allow for the creation of surface features that enhance cell adhesion and direct cell behavior. Ultimately, optimizing scaffold bioactivity depends on research into novel ECM-derived motifs for cell signaling, innovative delivery strategies for growth factors and therapeutic agents, and a deeper understanding of the synergistic effects of multiple bioactive signals. A careful selection and implementation of suitable fabrication techniques are critical for improving tissue regeneration outcomes and successful clinical translation.

Table 6: Examples of Combined Scaffold Fabrication Techniques.

Combination of Techniques	Key Benefits Achieved	Target Tissue	Ref.
3D Printing + Electrospinning	Precise macropore architecture (3D printing) combined with aligned nanofiber guidance (electrospinning) for enhanced osteoblast differentiation and bone ingrowth.	Bone	[137, 141, 142]
Freeze-Drying + Gas Foaming	High porosity from freeze-drying, combined with interconnected pores, is achieved through gas foaming.	Bone	[143, 144]
Electrospinning + Solvent Casting/ Particulate Leaching	Aligned nanofibers for chondrocyte alignment, combined with macroporous structure for nutrient transport.	Cartilage	[145]
Electrospinning + Decellularization	Aligned nanofibers for chondrocyte alignment and decellularized ECM for enhanced biocompatibility and cell-specific cues	Cartilage	[146]
3D Printing + Decellularization	3D printed support structure providing mechanical strength, combined with decellularized ECM for enhanced biocompatibility and cell-specific signals.	Vascular Graft	[147, 148]
Electrospinning + Bioprinting	The electrospun layer provides dermal support, combined with a printed epidermal layer for enhanced skin regeneration.	Skin	[149, 150]

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.1.1282

References

1. Aiman AR, Vigneswari S, Amran NA, Murugaiyah V, Amirul AA, Ramakrishna S. Advancing Regenerative Medicine Through the Development of Scaffold, Cell Biology, Biomaterials and Strategies of Smart Material. Regen Eng Transl Med. 2022;8(2).

2. Bradshaw KJ, Leipzig ND. Applications of Regenerative Tissue-Engineered Scaffolds for Treatment of Spinal Cord Injury. Tissue Eng Part A. 2025 Feb 1;31(3–4):108–25.

3. Lian L, Xie M, Luo Z, Zhang Z, Maharjan S, Mu X, et al. Rapid Volumetric Bioprinting of Decellularized Extracellular Matrix Bioinks. Advanced Materials. 2024 Aug 20;36(34).

4. Ramesh P, Moskwa N, Hanchon Z, Koplas A, Nelson DA, Mills KL, et al. Engineering cryoelectrospun elastin-alginate scaffolds to serve as stromal extracellular matrices. Biofabrication. 2022;14(3).

5. Asadi N, Del Bakhshayesh AR, Davaran S, Akbarzadeh A. Common biocompatible polymeric materials for tissue engineering and regenerative medicine. Mater Chem Phys. 2020;242.

6. Callaghan NI, Rempe CN, Froom ZSCS, Medd KT, Davenport Huyer L. Cell dynamics and metabolism of the foreign body response: characterizing host-biomaterial interactions for next-generation medical implant biocompatibility. Mater Adv. 2024;5(17):6719–38.

7. Koons GL, Diba M, Mikos AG. Materials design for bone-tissue engineering. Vol. 5, Nature Reviews Materials. 2020.

8. Modrák M, Trebuňová M, Balogová AF, Hudák R, Živčák J. Biodegradable Materials for Tissue Engineering: Development, Classification and Current Applications. Vol. 14, Journal of Functional Biomaterials. 2023.

9. Reddy MSB, Ponnamma D, Choudhary R, Sadasivuni KK. A comparative review of natural and synthetic biopolymer composite scaffolds. Vol. 13, Polymers. 2021.

10. Biswas MC, Jony B, Nandy PK, Chowdhury RA, Halder S, Kumar D, et al. Recent Advancement of Biopolymers and Their Potential Biomedical Applications. Vol. 30, Journal of Polymers and the Environment. 2022.

11. Puertas-Bartolomé M, Mora-Boza A, García-Fernández L. Emerging biofabrication techniques: A review on natural polymers for biomedical applications. Vol. 13, Polymers. 2021.

12. Yoon DM, Fisher JP. Natural and Synthetic Polymeric Scaffolds. In: Biomedical Materials. 2021. p. 257–83.

13. Ebhodaghe SO. Natural Polymeric Scaffolds for Tissue Engineering Applications. Vol. 32, Journal of Biomaterials Science, Polymer Edition. 2021.

14. Echeverria Molina MI, Malollari KG, Komvopoulos K. Design Challenges in Polymeric Scaffolds for Tissue Engineering. Vol. 9, Frontiers in Bioengineering and Biotechnology. 2021.

15. Terzopoulou Z, Zamboulis A, Koumentakou I, Michailidou G, Noordam MJ, Bikiaris DN. Biocompatible Synthetic Polymers for Tissue Engineering Purposes. Biomacromolecules. 2022;23(5).

16. Liu D, Nie W, Li D, Wang W, Zheng L, Zhang J, et al. 3D printed PCL/SrHA scaffold for enhanced bone regeneration. Chemical Engineering Journal. 2019;362.

17. Diomede F, Gugliandolo A, Cardelli P, Merciaro I, Ettorre V, Traini T, et al. Three-dimensional printed PLA scaffold and human gingival stem cell-derived extracellular vesicles: A new tool for bone defect repair. Stem Cell Res Ther. 2018;9(1).

18. Chew SA, Arriaga MA, Hinojosa VA. Effects of surface area to volume ratio of PLGA scaffolds with different architectures on scaffold degradation characteristics and drug release kinetics. J Biomed Mater Res A. 2016;104(5).

19. Bhaskar B, Owen R, Bahmaee H, Wally Z, Sreenivasa Rao P, Reilly GC. Composite porous scaffold of PEG/PLA support improved bone matrix deposition in vitro compared to PLA-only scaffolds. J Biomed Mater Res A. 2018;106(5).

20. Chen F, Liu X, Ge X, Wang Y, Zhao Z, Zhang X, et al. Porous polydroxyalkanoates (PHA) scaffolds with antibacterial property for oral soft tissue regeneration. Chemical Engineering Journal. 2023;451.

21. Arahira T, Todo M. Development of novel collagen scaffolds with different bioceramic particles for bone tissue engineering. Composites Communications. 2019;16.

22. Dobaj Štiglic A, Lackner F, Nagaraj C, Beaumont M, Bračič M, Duarte I, et al. 3D-Printed Collagen-Nanocellulose Hybrid Bioscaffolds with Tailored Properties for Tissue Engineering Applications. ACS Appl Bio Mater. 2023;6(12).

23. Fan C, Li X, Xiao Z, Zhao Y, Liang H, Wang B, et al. A modified collagen scaffold facilitates endogenous neurogenesis for acute spinal cord injury repair. Acta Biomater. 2017;51.

24. Gurumurthy B, Janorkar A V. Improvements in mechanical properties of collagen-based scaffolds for tissue engineering. Vol. 17, Current Opinion in Biomedical Engineering. 2021.

25. Mobaraki M, Bizari D, Soltani M, Khshmohabat H, Raahemifar K, Amirdehi MA. The effects of curcumin nanoparticles incorporated into collagen-alginate scaffold on wound healing of skin tissue in trauma patients. Polymers (Basel). 2021;13(24).

26. Abbas Z, Dapporto M, Tampieri A, Sprio S. Toughening of bioceramic composites for bone regeneration. Vol. 5, Journal of Composites Science. 2021.

27. Choi DJ, Park SJ, Gu BK, Kim YJ, Chung S, Kim CH. Effect of the pore size in a 3D bioprinted gelatin scaffold on fibroblast proliferation. Journal of Industrial and Engineering Chemistry. 2018;67.

28. Pfeifer CG, Berner A, Koch M, Krutsch W, Kujat R, Angele P, et al. Higher ratios of hyaluronic acid enhance chondrogenic differentiation of human MSCs in a hyaluronic acid-gelatin composite scaffold. Materials. 2016;9(5).

29. Grulova I, Slovinska L, Blaško J, Devaux S, Wisztorski M, Salzet M, et al. Delivery of Alginate Scaffold Releasing Two Trophic Factors for Spinal Cord Injury Repair. Sci Rep. 2015;5.

30. Wang L, Liu Y, Zhang Y, Sun Q, Wang X, Li Q, et al. Dual-crosslinkable alginate hydrogel with dynamic viscoelasticity for chondrogenic and osteogenic differentiation of mesenchymal stem cells. Int J Biol Macromol. 2025;142346.

31. Shen Y, Xu Y, Yi B, Wang X, Tang H, Chen C, et al. Engineering a highly biomimetic chitosan-based cartilage scaffold by using short fibers and a cartilage-decellularized matrix. Biomacromolecules. 2021;22(5).

32. Ribeiro VP, da Silva Morais A, Maia FR, Canadas RF, Costa JB, Oliveira AL, et al. Combinatory approach for developing silk fibroin scaffolds for cartilage regeneration. Acta Biomater. 2018;72.

33. Wei J, Sun XQ, Hou BX. Evaluation of Silk Fibroin-RGD-Stem Cell Factor Scaffold Effect on Adhesion, Migration, and Proliferation of Stem Cells of Apical Papilla. Stem Cells Int. 2021;2021.

34. Mohammadalizadeh Z, Bahremandi-Toloue E, Karbasi S. Recent advances in modification strategies of pre- and post-electrospinning of nanofiber scaffolds in tissue engineering. Vol. 172, Reactive and Functional Polymers. 2022.

35. Hlushchenko V, Oleshko T, Berladir K, Oleshko O, Rybarczyk J, Boiko V. Study of the Features of in Vitro Degradation of PCL, PLA, and Polymer 3D Scaffolds in Static and Dynamic Conditions. In 2024. p. 308–23.

36. Li C, Guo C, Fitzpatrick V, Ibrahim A, Zwierstra MJ, Hanna P, et al. Design of biodegradable, implantable devices towards clinical translation. Vol. 5, Nature Reviews Materials. 2020.

37. Dias GJ, Mahoney P, Hung NA, Sharma LA, Kalita P, Smith RA, et al. Osteoconduction in keratin–hydroxyapatite composite bone-graft substitutes. J Biomed Mater Res B Appl Biomater. 2017;105(7).

38. Rahman MM, Shahruzzaman M, Islam MS, Khan MN, Haque P. Preparation and properties of biodegradable polymer/nano-hydroxyapatite bioceramic scaffold for spongy bone regeneration. Journal of Polymer Engineering. 2019;39(2).

39. Vu AA, Burke DA, Bandyopadhyay A, Bose S. Effects of surface area and topography on 3D printed tricalcium phosphate scaffolds for bone grafting applications. Addit Manuf. 2021;39.

40. Lu H, Zhou Y, Ma Y, Xiao L, Ji W, Zhang Y, et al. Current Application of Beta-Tricalcium Phosphate in Bone Repair and Its Mechanism to Regulate Osteogenesis.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.1.1282

Vol. 8, Frontiers in Materials. 2021.

41. Palivela BC, Bandari SD, Mamilla RS. Extrusion-based 3D printing of bioactive glass scaffolds-process parameters and mechanical properties: A review. Vol. 27, Bioprinting. 2022.

42. Jain S, Gujjala R, Abdul Azeem P, Ojha S, Samudrala RK. A review on mechanical and In-vitro studies of polymer reinforced bioactive glass-scaffolds and their fabrication techniques. Vol. 48, Ceramics International. 2022.

43. Hendea RE, Raducanu D, Claver A, García JA, Cojocaru VD, Nocivin A, et al. Biodegradable Magnesium Alloys for Personalised Temporary Implants. J Funct Biomater. 2023;14(8).

44. Qin Y, Liu A, Guo H, Shen Y, Wen P, Lin H, et al. Additive manufacturing of Zn-Mg alloy porous scaffolds with enhanced osseointegration: In vitro and in vivo studies. Acta Biomater. 2022;145.

45. Wang Z, Wang W, Zhang X, Cao F, Zhang T, Bhakta Pokharel D, et al. Modulation of Osteogenesis and Angiogenesis Activities Based on Ionic Release from Zn–Mg Alloys. Materials. 2022;15(20).

46. Salama M, Vaz MF, Colaço R, Santos C, Carmezim M. Biodegradable Iron and Porous Iron: Mechanical Properties, Degradation Behaviour, Manufacturing Routes and Biomedical Applications. J Funct Biomater. 2022;13(2).

47. Gąsior G, Szczepański J, Radtke A. Biodegradable iron-based materials—what was done and what more can be done? Vol. 14, Materials. 2021.

48. Wang W, Zhang B, Li M, Li J, Zhang C, Han Y, et al. 3D printing of PLA/n-HA composite scaffolds with customized mechanical properties and biological functions for bone tissue engineering. Compos B Eng. 2021;224.

49. Bernardo MP, da Silva BCR, Hamouda AEI, de Toledo MAS, Schalla C, Rütten S, et al. PLA/Hydroxyapatite scaffolds exhibit in vitro immunological inertness and promote robust osteogenic differentiation of human mesenchymal stem cells without osteogenic stimuli. Sci Rep. 2022;12(1).

50. Suo H, Zhang J, Xu M, Wang L. Low-temperature 3D printing of collagen and chitosan composite for tissue engineering. Materials Science and Engineering C. 2021;123.

51. Dewey MJ, Milner DJ, Weisgerber D, Flanagan CL, Rubessa M, Lotti S, et al. Repair of critical-size porcine craniofacial bone defects using a collagen-polycaprolactone composite biomaterial. Biofabrication. 2022;14(1).

52. Entekhabi E, Haghbin Nazarpak M, Shafieian M, Mohammadi H, Firouzi M, Hassannejad Z. Fabrication and in vitro evaluation of 3D composite scaffold based on collagen/hyaluronic acid sponge and electrospun polycaprolactone nanofibers for peripheral nerve regeneration. J Biomed Mater Res A. 2021;109(3).

53. Xu P, Kankala RK, Wang S, Chen A. Decellularized extracellular matrix-based composite scaffolds for tissue engineering and regenerative medicine. Vol. 11, Regenerative Biomaterials. 2024.

54. Li S, Deng R, Zou X, Rong Q, Shou J, Rao Z, et al. Development and fabrication of co-axially electrospun biomimetic periosteum with a decellularized periosteal ECM shell/PCL core structure to promote the repair of critical-sized bone defects. Compos B Eng. 2022;234.

55. Mao X, Li T, Cheng J, Tao M, Li Z, Ma Y, et al. Nerve ECM and PLA-PCL based electrospun bilayer nerve conduit for nerve regeneration. Front Bioeng Biotechnol. 2023;11.

56. Nouri A, Wen C. Stainless steels in orthopedics. In: Structural Biomaterials. Elsevier; 2021. p. 67–101.

57. Chen Q, Thouas GA. Metallic implant biomaterials. Materials Science and Engineering: R: Reports. 2015 Jan;87:1–57.

58. Sridhar TM, Vinodhini SP, Kamachi Mudali U, Venkatachalapathy B, Ravichandran K. Load-bearing metallic implants: electrochemical characterisation of corrosion phenomena. Materials Technology. 2016;31(12).

59. Bandyopadhyay A, Mitra I, Avila JD, Upadhyayula M, Bose S. Porous metal implants: processing, properties, and

challenges. Vol. 5, International Journal of Extreme Manufacturing. 2023.

60. Hsieh DJ, Srinivasan P, Yen KC, Yeh YC, Chen YJ, Wang HC, et al. Protocols for the preparation and characterization of decellularized tissue and organ scaffolds for tissue engineering. Biotechniques. 2020;70(2).

61. Montoya C, Du Y, Gianforcaro AL, Orrego S, Yang M, Lelkes PI. On the road to smart biomaterials for bone research: definitions, concepts, advances, and outlook. Vol. 9, Bone Research. 2021.

62. Helling AL, Tsekoura EK, Biggs M, Bayon Y, Pandit A, Zeugolis DI. In Vitro Enzymatic Degradation of Tissue Grafts and Collagen Biomaterials by Matrix Metalloproteinases: Improving the Collagenase Assay. ACS Biomater Sci Eng. 2017;3(9).

63. Mukundan S, Sant V, Goenka S, Franks J, Rohan LC, Sant S. Nanofibrous composite scaffolds of poly(ester amides) with tunable physicochemical and degradation properties. Eur Polym J. 2015;68.

64. Lin W, Zhang H, Zhang W, Qi H, Zhang G, Qian J, et al. In vivo degradation and endothelialization of an iron bioresorbable scaffold. Bioact Mater. 2021;6(4).

65. Yi B, Xu Q, Liu W. An overview of substrate stiffness guided cellular response and its applications in tissue regeneration. Vol. 15, Bioactive Materials. 2022.

66. Lin CY, Kang JH. Mechanical properties of compact bone defined by the stress-strain curve measured using uniaxial tensile test: A concise review and practical guide. Vol. 14, Materials. 2021.

67. Wang W, Shi Y, Lin G, Tang B, Li X, Zhang J, et al. Advances in Mechanical Properties of Hydrogels for Cartilage Tissue Defect Repair. Vol. 23, Macromolecular Bioscience. 2023.

68. Bramson MTK, Van Houten SK, Corr DT. Mechanobiology in Tendon, Ligament, and Skeletal Muscle Tissue Engineering. J Biomech Eng. 2021;143(7).

69. Leal BBJ, Wakabayashi N, Oyama K, Kamiya H, Braghirolli DI, Pranke P. Vascular Tissue Engineering: Polymers and Methodologies for Small Caliber Vascular Grafts. Front Cardiovasc Med. 2021;7.

70. Amini S, Salehi H, Setayeshmehr M, Ghorbani M. Natural and synthetic polymeric scaffolds used in peripheral nerve tissue engineering: Advantages and disadvantages. Vol. 32, Polymers for Advanced Technologies. 2021.

71. Liu E, Zhu D, Gonzalez DIaz E, Tong X, Yang F. Gradient Hydrogels for Optimizing Niche Cues to Enhance Cell-Based Cartilage Regeneration. Tissue Eng Part A. 2021;27(13–14).

72. Esmaeili J, Jalise SZ, Pisani S, Rochefort GY, Ghobadinezhad F, Mirzaei Z, et al. Development and characterization of Polycaprolactone/chitosan-based scaffolds for tissue engineering of various organs: A review. Int J Biol Macromol. 2024 Jun;272:132941.

73. Mao Z, Fan B, Wang X, Huang X, Guan J, Sun Z, et al. A Systematic Review of Tissue Engineering Scaffold in Tendon Bone Healing in vivo. Vol. 9, Frontiers in Bioengineering and Biotechnology. 2021.

74. Omid H, Abdollahi S, Bonakdar S, Haghighipour N, Shokrgozar MA, Mohammadi J. Biomimetic vascular tissue engineering by decellularized scaffold and concurrent cyclic tensile and shear stresses. J Mater Sci Mater Med. 2023;34(3).

75. Javid-Naderi MJ, Behravan J, Karimi-Hajishohreh N, Toosi S. Synthetic polymers as bone engineering scaffold. Vol. 34, Polymers for Advanced Technologies. 2023.

76. Hosseini M, Shafiee A. Engineering Bioactive Scaffolds for Skin Regeneration. Vol. 17, Small. 2021.

77. Saraswathibhatla A, Indana D, Chaudhuri O. Cell–extracellular matrix mechanotransduction in 3D. Vol. 24, Nature Reviews Molecular Cell Biology. 2023.

78. Wu DT, Jeffreys N, Diba M, Mooney DJ. Viscoelastic Biomaterials for Tissue Regeneration. Vol. 28, Tissue Engineering - Part C: Methods. 2022.

79. Baghersad S, Sathish Kumar A, Kipper MJ, Popat K, Wang Z. Recent Advances in Tissue-Engineered Cardiac Scaffolds—The Progress and Gap in Mimicking Native Myocardium Mechanical Behaviors. Vol. 14,

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.1.1282

Journal of Functional Biomaterials. 2023.

80. Zhang Y, Wang Z, Sun Q, Li Q, Li S, Li X. Dynamic Hydrogels with Viscoelasticity and Tunable Stiffness for the Regulation of Cell Behavior and Fate. Vol. 16, Materials. 2023.

81. Li L, Wang S, Chen Y, Dong S, Zhang C, Liao L, et al. Hydrogels mimicking the viscoelasticity of extracellular matrix for regenerative medicine: Design, application, and molecular mechanism. Chemical Engineering Journal. 2024 Oct;498:155206.

82. Collins MN, Ren G, Young K, Pina S, Reis RL, Oliveira JM. Scaffold Fabrication Technologies and Structure/Function Properties in Bone Tissue Engineering. Vol. 31, Advanced Functional Materials. 2021.

83. Uzieliene I, Bironaite D, Bernotas P, Sobolev A, Bernotiene E. Mechanotransducive biomimetic systems for chondrogenic differentiation in vitro. Vol. 22, International Journal of Molecular Sciences. 2021.

84. Xiao L, Sun Y, Liao L, Su X. Response of mesenchymal stem cells to surface topography of scaffolds and the underlying mechanisms. Vol. 11, Journal of Materials Chemistry B. 2023.

85. Idaszek J, Kijeńska E, Łojkowski M, Swieszkowski W. How important are scaffolds and their surface properties in regenerative medicine. Appl Surf Sci. 2016;388.

86. Qian Y, Lin H, Yan Z, Shi J, Fan C. Functional nanomaterials in peripheral nerve regeneration: Scaffold design, chemical principles and microenvironmental remodeling. Vol. 51, Materials Today. 2021.

87. Ghorbani F, Ghalandari B, Sahranavard M, Zamanian A, Collins MN. Tuning the biomimetic behavior of hybrid scaffolds for bone tissue engineering through surface modifications and drug immobilization. Materials Science and Engineering C. 2021;130.

88. Calore AR, Srinivas V, Groenendijk L, Serafim A, Stancu IC, Wilbers A, et al. Manufacturing of scaffolds with interconnected internal open porosity and surface roughness. Acta Biomater. 2023;156.

89. Młotek M, Gadomska-gajadhur A, Sobczak A, Kruk A, Perron M, Krawczyk K. Modification of pla scaffold surface for medical applications. Applied Sciences (Switzerland). 2021;11(4).

90. Raja IS, Lee SH, Kang MS, Hyon SH, Selvaraj AR, Prabakar K, et al. The predominant factor influencing cellular behavior on electrospun nanofibrous scaffolds: Wettability or surface morphology? Mater Des. 2022;216.

91. Shin CS, Cabrera FJ, Lee R, Kim J, Ammassam Veettil R, Zaheer M, et al. 3D-Bioprinted Inflammation Modulating Polymer Scaffolds for Soft Tissue Repair. Advanced Materials. 2021;33(4).

92. Bavaro T, Tengattini S, Rezwan R, Chiesa E, Temporini C, Dorati R, et al. Design of epidermal growth factor immobilization on 3D biocompatible scaffolds to promote tissue repair and regeneration. Sci Rep. 2021;11(1).

93. Shen H, Hu X. Growth factor loading on aliphatic polyester scaffolds. Vol. 11, RSC Advances. 2021.

94. Teimouri R, Abnous K, Taghdisi SM, Ramezani M, Alibolandi M. Surface modifications of scaffolds for bone regeneration. Journal of Materials Research and Technology. 2023;24.

95. Gao H, Xiao J, Wei Y, Wang H, Wan H, Liu S. Regulation of Myogenic Differentiation by Topologically Microgrooved Surfaces for Skeletal Muscle Tissue Engineering. ACS Omega. 2021;6(32).

96. Xia P, Luo Y. Vascularization in tissue engineering: The architecture cues of pores in scaffolds. Vol. 110, Journal of Biomedical Materials Research - Part B Applied Biomaterials. 2022.

97. Swanson WB, Omi M, Zhang Z, Nam HK, Jung Y, Wang G, et al. Macropore design of tissue engineering scaffolds regulates mesenchymal stem cell differentiation fate. Biomaterials. 2021;272.

98. Mukasheva F, Adilova L, Dyussenbinov A, Yernaimanova B, Abilev M, Akilbekova D. Optimizing scaffold pore size for tissue engineering: insights across various tissue types. Front Bioeng Biotechnol. 2024 Nov 12;12.

99. Fattahpour H, Sanaei P. Effects of nutrient concentration and scaffold elasticity on the tissue growth in a tissue engineering scaffold channel. Physics of Fluids. 2023 Nov 1;35(11).

100. Xing J, Liu N, Xu N, Chen W, Xing D. Engineering Complex Anisotropic Scaffolds beyond Simply Uniaxial Alignment for Tissue Engineering. Vol. 32, Advanced Functional Materials. 2022.

101. Yang Q, Li J, Su W, Yu L, Li T, Wang Y, et al. Electrospun aligned poly(ε-caprolactone) nanofiber yarns guiding 3D organization of tendon stem/progenitor cells in tenogenic differentiation and tendon repair. Front Bioeng Biotechnol. 2022;10.

102. Hu Y, Zhang H, Wei H, Cheng H, Cai J, Chen X, et al. Scaffolds with anisotropic structure for neural tissue engineering. Engineered Regeneration. 2022 Jun;3(2):154–62.

103. Li J, Zhang Y, Zhou X, Wang S, Hao R, Han J, et al. Enzymatically functionalized RGD-gelatin scaffolds that recruit host mesenchymal stem cells in vivo and promote bone regeneration. J Colloid Interface Sci. 2022;612.

104. Jha A, Moore E. YIGSR, A Laminin-Derived Peptide, Dictates a Concentration-Dependent Impact on Macrophage Phenotype Response. Cell Mol Bioeng. 2024 Oct 26;17(5):423–40.

105. Gao H, Liu Y, Guan W, Sun S, Zheng T, Wu L, et al. Surface topologized ovalbumin scaffolds containing YIGSR peptides for modulating Schwann cell behavior. Int J Biol Macromol. 2023;253.

106. Li W, Li S, Zhang J, Zhong H, Liang J, Huang S, et al. Fabrication and evaluation of bone morphogenetic protein-2 microspheres coated black phosphorus nanosheets@ polylactic-glycolic acid copolymers scaffold: A multifunctional antibacterial photothermal scaffold for bone regeneration. Int J Biol Macromol. 2022;210.

107. Pajooh AMD, Tavakoli M, Al-Musawi MH, Karimi A, Salehi E, Nasiri-Harchegani S, et al. Biomimetic VEGF-loaded bilayer scaffold fabricated by 3D printing and electrospinning techniques for skin regeneration. Mater Des. 2024;238.

108. Wang T, Dogru S, Dai Z, Kim SY, Vickers NA, Albro MB. Physiologic Doses of TGF-b Improve the Composition of Engineered Articular Cartilage. bioRxiv. 2023;

109. Xu H, Yu Y, Zhang L, Zheng F, Yin Y, Gao Y, et al. Sustainable release of nerve growth factor for peripheral nerve regeneration using nerve conduits laden with Bioconjugated hyaluronic acid-chitosan hydrogel. Compos B Eng. 2022;230.

110. Tian G, Jiang S, Li J, Wei F, Li X, Ding Y, et al. Cell-free decellularized cartilage extracellular matrix scaffolds combined with interleukin 4 promote osteochondral repair through immunomodulatory macrophages: In vitro and in vivo preclinical study. Acta Biomater. 2021;127.

111. Caldwell AS, Rao V V., Golden AC, Bell DJ, Grim JC, Anseth KS. Mesenchymal stem cell-inspired microgel scaffolds to control macrophage polarization. Bioeng Transl Med. 2021;6(2).

112. Wu Y, Chen X, Song P, Li R, Zhou Y, Wang Q, et al. Functional Oxidized Hyaluronic Acid Cross-Linked Decellularized Heart Valves for Improved Immunomodulation, Anti-Calcification, and Recellularization. Adv Healthc Mater. 2024 Jun 15;13(16).

113. Unalan I, Fuggerer T, Slavik B, Buettner A, Boccaccini AR. Antibacterial and antioxidant activity of cinnamon essential oil-laden 45S5 bioactive glass/soy protein composite scaffolds for the treatment of bone infections and oxidative stress. Materials Science and Engineering C. 2021;128.

114. Astaneh ME, Noori F, Fereydouni N. Curcumin-loaded scaffolds in bone regeneration. Heliyon. 2024 Jun;10(11):e32566.

115. Darzi S, Paul K, Leitan S, Werkmeister JA, Mukherjee S. Immunobiology and application of aloe vera-based scaffolds in tissue engineering. Vol. 22, International Journal of Molecular Sciences. 2021.

116. Yang Q, Peng J, Xiao H, Xu X, Qian Z. Polysaccharide hydrogels: Functionalization, construction and served as scaffold for tissue engineering. Vol. 278, Carbohydrate Polymers. 2022.

117. Oliveira ÉR, Nie L, Podstawczyk D, Allahbakhsh A, Ratnayake J, Brasil DL, et al. Advances in growth factor delivery for bone

tissue engineering. Vol. 22, International Journal of Molecular Sciences. 2021.

118. Chen T, Jiang Y, Huang JP, Wang J, Wang ZK, Ding PH. Essential elements for spatiotemporal delivery of growth factors within bio-scaffolds: A comprehensive strategy for enhanced tissue regeneration. Vol. 368, Journal of Controlled Release. 2024.

119. Shan BH, Wu FG. Hydrogel-Based Growth Factor Delivery Platforms: Strategies and Recent Advances. Vol. 36, Advanced Materials. 2024.

120. Ye W, Yang Z, Cao F, Li H, Zhao T, Zhang H, et al. Articular cartilage reconstruction with TGF-β1-simulating self-assembling peptide hydrogel-based composite scaffold. Acta Biomater. 2022;146.

121. Tsai MH, Megat Abdul Wahab R, Zainal Ariffin SH, Azmi F, Yazid F. Enhanced Osteogenesis Potential of MG-63 Cells through Sustained Delivery of VEGF via Liposomal Hydrogel. Gels. 2023;9(7).

122. Lynch RI, Lavelle EC. Immuno-modulatory biomaterials as anti-inflammatory therapeutics. Vol. 197, Biochemical Pharmacology. 2022.

123. Luo P, Huang R, Wu Y, Liu X, Shan Z, Gong L, et al. Tailoring the multiscale mechanics of tunable decellularized extracellular matrix (dECM) for wound healing through immunomodulation. Bioact Mater. 2023;28.

124. Ajith G, Tamilarasi GP, Sabarees G, Gouthaman S, Manikandan K, Velmurugan V, et al. Recent Developments in Electrospun Nanofibers as Delivery of Phytoconstituents for Wound Healing. Drugs and Drug Candidates. 2023;2(1).

125. Kamal NH, Heikal LA, Ali MM, Aly RG, Abdallah OY. Development and evaluation of local regenerative biomimetic bone-extracellular matrix scaffold loaded with nano-formulated quercetin for orthopedic fractures. Biomaterials Advances. 2023;145.

126. Unalan I, Boccaccini AR. Essential oils in biomedical applications: Recent progress and future opportunities. Vol. 17, Current Opinion in Biomedical Engineering. 2021.

127. Yadav N, Mudgal D, Anand R, Jindal S, Mishra V. Recent development in nanoencapsulation and delivery of natural bioactives through chitosan scaffolds for various biological applications. Vol. 220, International Journal of Biological Macromolecules. 2022.

128. Hutmacher DW, Tandon B, Dalton PD. Scaffold design and fabrication. In: Tissue Engineering. Elsevier; 2023. p. 355–85.

129. Koyyada A, Orsu P. Recent Advancements and Associated Challenges of Scaffold Fabrication Techniques in Tissue Engineering Applications. Vol. 7, Regenerative Engineering and Translational Medicine. 2021.

130. Borbolla-Jiménez F V., Peña-Corona SI, Farah SJ, Jiménez-Valdés MT, Pineda-Pérez E, Romero-Montero A, et al. Films for Wound Healing Fabricated Using a Solvent Casting Technique. Vol. 15, Pharmaceutics. 2023.

131. Gupta S, Javaid S, Dey M, Matzke C, Eades E, Ji Y. Exploration of solvent casting for designing engineered microstructures for biomedical and functional applications. Journal of the American Ceramic Society. 2022;105(3).

132. Fanovich MA, Di Maio E, Salerno A. Current Trend and New Opportunities for Multifunctional Bio-Scaffold Fabrication via High-Pressure Foaming. Vol. 14, Journal of Functional Biomaterials. 2023.

133. Katrilaka C, Karipidou N, Petrou N, Manglaris C, Katrilakas G, Tzavellas AN, et al. Freeze-Drying Process for the Fabrication of Collagen-Based Sponges as Medical Devices in Biomedical Engineering. Vol. 16, Materials. 2023.

134. Angraini N, Syarifuddin S, Rauf N, Tahir D. Advancements in Bone Tissue Engineering: A Comprehensive Review of Biomaterial Scaffolds and Freeze-Drying Techniques From Perspective Global and Future Research. Artif Organs. 2025 Feb 24;

135. Zeinali R, Del Valle LJ, Torras J, Puiggalí J. Recent progress on biodegradable tissue engineering scaffolds prepared by thermally-induced phase separation (Tips). Vol. 22, International Journal of Molecular Sciences. 2021.

136. Friuli M, Nitti P, Madaghiele M, Demitri C. A possible method to avoid skin effect

in polymeric scaffold produced through thermally induced phase separation. Results in Engineering. 2021;12.

137. Wang Z, Wang Y, Yan J, Zhang K, Lin F, Xiang L, et al. Pharmaceutical electrospinning and 3D printing scaffold design for bone regeneration. Vol. 174, Advanced Drug Delivery Reviews. 2021.

138. Prem Ananth K, Jayram ND. A comprehensive review of 3D printing techniques for biomaterial-based scaffold fabrication in bone tissue engineering. Vol. 13, Annals of 3D Printed Medicine. 2024.

139. Bakhtiar H, Ashoori A, Rajabi S, Pezeshki-Modaress M, Ayati A, Mousavi MR, et al. Human amniotic membrane extracellular matrix scaffold for dental pulp regeneration in vitro and in vivo. Int Endod J. 2022;55(4).

140. Puthiya Veettil J, Sasikumar Lolitha D, Payanam Ramachandra U. Combinatorial Decellularization as a Better Approach to Porcine Liver Extracellular Matrix Scaffold Fabrication With Preserved Bioactivity: A Comparative Evaluation. Xenotransplantation. 2025 Jan 17;32(1).

141. Yang DL, Faraz F, Wang JX, Radacsi N. Combination of 3D Printing and Electrospinning Techniques for Biofabrication. Vol. 7, Advanced Materials Technologies. 2022.

142. Qi Y, Lv H, Huang Q, Pan G. The Synergetic Effect of 3D Printing and Electrospinning Techniques in the Fabrication of Bone Scaffolds. Vol. 52, Annals of Biomedical Engineering. 2024.

143. Hashimoto K, Oikawa H, Shibata H. Characterization of Porous β-Type Tricalcium Phosphate Ceramics Formed via Physical Foaming with Freeze-Drying. Int J Mol Sci. 2024 May 14;25(10):5363.

144. Qamash M, Imani SM, Omidi M, Glancy C, Tayebi L. Investigation of the Effect of Preparation Parameters on the Structural and Mechanical Properties of Gelatin/Elastin/Sodium Hyaluronate Scaffolds Fabricated by the Combined Foaming and Freeze-Drying Techniques. Journal of Composites Science. 2024 Oct 4;8(10):408.

145. Rosalia M, Giacomini M, Tottoli EM, Dorati R, Bruni G, Genta I, et al. Investigation on Electrospun and Solvent-Casted PCL-PLGA Blends Scaffolds Embedded with Induced Pluripotent Stem Cells for Tissue Engineering. Pharmaceutics. 2023;15(12).

146. Mohammadi N, Alikhasi Amnieh Y, Ghasemi S, Karbasi S, Vaezifar S. Evaluation of the effects of decellularized extracellular matrix nanoparticles incorporation on the polyhydroxybutyrate/nano chitosan electrospun scaffold for cartilage tissue engineering. Int J Biol Macromol. 2024 Jul;273:133217.

147. Matejka R, Kanokova D, Supova M, Matejkova J, Chlupac J. Vascular Grafts Derived from Decellularized Tissues Modified with 3D Bioprinting. In 2024. p. 406–13.

148. Isik M, Karakaya E, Arslan TS, Atila D, Erdogan YK, Arslan YE, et al. 3D Printing of Extracellular Matrix-Based Multicomponent, All-Natural, Highly Elastic, and Functional Materials toward Vascular Tissue Engineering. Adv Healthc Mater. 2023;12(20).

149. Song Y, Hu Q, Liu S, Wang Y, Zhang H, Chen J, et al. Electrospinning/3D printing drug-loaded antibacterial polycaprolactone nanofiber/sodium alginate-gelatin hydrogel bilayer scaffold for skin wound repair. Int J Biol Macromol. 2024;275.

150. Hosseini SA, Planz V, Stelzer EHK, Windbergs M, Pampaloni F. A hybrid bioprinting-electrospinning platform integrating nanofibers and mesenchymal cell spheroids for customizable wound healing dressings. 2024.