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Review Article

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Mimicking Nature, Engineering Outcomes: Biomaterials in Stem Cell Therapy

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Abstract

The clinical translation of stem cell-based therapies remains limited by challenges in cell survival, engraftment, immune compatibility, and functional maturation. This review explores how biomaterials, both natural and synthetic, can be engineered to address these barriers and actively instruct cell fate. We examine the evolving role of biomaterials from passive carriers to dynamic microenvironments that mimic key features of the extracellular matrix, modulate mechanical forces, and provide spatially controlled biochemical signals. Special emphasis is given to scaffold composition, integrin-mediated adhesion, immune modulation, and growth factor delivery as determinants of in vivo success. The review also details how matrix stiffness, degradation profiles, and ligand presentation influence lineage commitment and maturation, especially for insulin-producing cells relevant to Type 1 diabetes. Furthermore, it highlights innovations in polymer design, such as PEGylation, self-assembling peptides, and 3D-printed scaffolds, which enhance vascularization, immune shielding, and host-tissue plasticity. Finally, we discuss functional biomarkers essential for assessing the safety, identity, and performance of transplanted cells. Together, these insights underscore the importance of combining stem cell biology with materials science to realize the full potential of regenerative medicine.

Keywords: Transplantation, iPSCs, Biomaterials, Polymers, Stem Cells

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Introduction

Stem cell therapy has emerged as a cornerstone of regenerative medicine, offering promising therapeutic avenues for a broad range of diseases. By harnessing the ability of stem cells to self-renew and differentiate into specialized cell types, stem cell transplantation aims to restore structure and function in damaged or diseased tissues. Human stem cells represent a heterogenous group of therapies based on source including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult mesenchymal stem/stromal cells (MSCs). Each has shown therapeutic potential in both autologous and allogeneic contexts [1,2].

Despite the promise of stem cell–based therapies, several critical limitations continue to hinder their clinical efficacy and widespread adoption. Immune rejection remains a major barrier, particularly in allogeneic transplantation settings. Even with immunosuppressive regimens, transplanted stem cells can elicit host immune responses that compromise graft survival and function [3,4]. Strategies such as the use of hypoimmunogenic stem cells or encapsulation technologies have shown potential, but immunogenicity remains a formidable hurdle. Additionally, uncontrolled differentiation poses a significant challenge, as transplanted cells may deviate from the intended lineage or form teratomas, especially when using pluripotent stem cells such as iPSCs and ESCs. These risks are exacerbated by incomplete or heterogeneous differentiation during *in vitro* preparation, underscoring the need for robust, lineage-specific pre-conditioning and monitoring protocols [5,6].

Moreover, inefficient tissue regeneration is frequently attributed to the absence of appropriate biophysical and mechanical cues in the post-transplantation microenvironment. *In vivo*, stem cell behavior is highly sensitive to extracellular matrix (ECM) stiffness, topography, and mechanical loading. Each aspect of the ECM is critical for guiding lineage-specific differentiation and functional integration [7,8]. Conventional transplantation methods often fail to recapitulate essential ECM cues, resulting in poor engraftment and suboptimal tissue repair. Recent advances in biomaterial scaffolds and dynamic culture systems aim to address this gap by providing controlled mechanical stimulation and mimicking the native biomechanical milieu, thereby enhancing regeneration outcomes [9,10]. To overcome the multifaceted challenges associated with stem cell transplantation biomaterial-based strategies have gained considerable traction [11]. Some biomaterials are specifically designed to mimic the structural and functional properties of ECM molecules, thereby promoting cellular adhesion, proliferation, and differentiation. For instance, collagen-based hydrogels replicate the fibrillar architecture of native ECM and provide biochemical cues for tissue regeneration [12]. Alginate modified with RGD peptides mimics integrin-binding motifs found in fibronectin, enhancing cell adhesion and signaling [13]. Similarly, self-assembling peptide scaffolds, such as those based on RAD16-I, emulate ECM nanostructure and support 3D tissue culture [14]. These biomimetic materials are essential in regenerative medicine, as they can be tuned to direct specific cell-matrix interactions.

In addition to this biomaterials play a crucial role in tissue engineering by offering a structural scaffold that mimics the native ECM, to deliver localized immunomodulatory cues and provides mechanical and biochemical signals that direct cell fate and function, thereby supporting cell proliferation and promoting tissue regeneration. As such, biomaterials not only serve as protective carriers of stem cells during therapeutic delivery but also enhance post-transplantation outcomes by promoting cell survival, facilitating tissue-specific migration, and supporting long-term integration into host tissue [15]. These functional outcomes result from bidirectional communication between the regenerating tissue and its surrounding microenvironment, driven by the principle of dynamic reciprocity [16]. The overarching goal of incorporating biomaterials into regenerative strategies is to optimize the therapeutic potential of stem cells and improve the predictability and durability of clinical outcomes [17,18].

The integration of dynamic, tissue-specific cues such as matrix stiffness, topography, and degradability has allowed for the creation of engineered microenvironments that more closely mimic native pancreatic niches. This shift has been instrumental in improving *in vitro* maturation of insulin-producing cells, moving from fetal-like phenotypes toward functionally competent beta-like cells capable of glucose-responsive insulin secretion [19]. Moreover, bioactive materials that present adhesive ligands or controlled-release growth factors have shown to accelerate lineage commitment and reduce heterogeneity within differentiating cultures [20]. These developments mark a transition from passive support to active instruction, positioning biomaterials as critical regulators in stem cell-derived therapy. As stem cell applications progress toward clinical translation, biomaterial design is no longer an afterthought but a core component in engineering cellular identity. This is reviewed in this manuscript.

Over the past decade, biomaterials research has significantly advanced our understanding of how the extracellular environment modulates stem cell fate, particularly in the context of pancreatic differentiation. Early studies primarily focused on inert scaffolds as structural support, yet it is now evident that the biochemical and biophysical properties of the matrix actively influence stem cell maturation and function [17,18].

Improving Transplanted Cell Engraftment

Ideal biomaterials for cell transplantation adhere to a stringent set of criteria to ensure biocompatibility, functional integration, and effective support for tissue regeneration. Such materials must be non-cytotoxic, non-immunogenic, and biodegradable into physiologically innocuous byproducts, thereby averting chronic inflammation and adverse immune reactions. Equally imperative is the biomaterial's capacity to recapitulate the native ECM of the target tissue not only in terms of its biochemical composition, but also its topographical and biomechanical landscape. To this end, the biophysical parameters of the material such as stiffness, viscoelastic-

ity, porosity, surface charge, roughness, hydrophilicity, and dimensionality must be tailored to match the niche-specific requirements of the cell type in question. For example, substrates mimicking the soft elasticity of neural tissue (~0.1–1 kPa) favor neuronal differentiation, whereas stiffer matrices (10–100 kPa) support osteogenic or myogenic commitment [17,21]. Similarly, hydrogels based on hyaluronic acid or gelatin-methacryloyl (GelMA) have been engineered with tunable stiffness and degradation rates, allowing for dynamic remodeling and facilitating integration with host tissue [22]. Hierarchical porosity is not a luxury but a necessity. Scaffold designs must ensure adequate micro- and macro-porosity to enable nutrient diffusion, waste removal, and neovascularization. In bone regeneration, for instance, calcium phosphate-based scaffolds and collagen-apatite composites have been developed to mimic trabecular architecture while supporting osteoblast adhesion and mineral deposition [23]. These structural attributes are critical not only for metabolic homeostasis but also for mechanical load distribution in weight-bearing tissues. However, the paradigm is shifting from passive structural support to active biological engagement. Modern biomaterials function as instructive platforms, providing spatially and temporally controlled biochemical cues that guide cellular fate. This includes the incorporation of integrin-binding motifs such as RGD (Arg-Gly-Asp) peptides, which facilitate cell anchorage and survival [24], as well as the localized release of growth factors such as VEGF, TGF-β, or BMP-2 to steer angiogenesis and lineage specification [25]. Of equal interest is the concept of degradation-mediated signaling, where breakdown products of biomaterials themselves act as bioactive messengers. For example, fragments of extracellular matrix-derived scaffolds can modulate macrophage polarization and enhance tissue remodeling in a pro-regenerative manner [26].

Building on these principles, recent advances have led to the creation of sophisticated, biomimetic three-dimensional (3D) scaffolds that more precisely control the cellular microenvironment. Examples include self-assembling peptide hydrogels that replicate nanofibrillar ECM networks and support organoid culture, or 3D-printed microarchitectures designed for tissue-specific integration [27]. These next-generation materials not only emulate the physical and biochemical features of native tissues but are also capable of dynamically regulating cellular processes post-transplantation. Through such innovations, the gap between synthetic constructs and biological function is gradually narrowing, offering renewed promise for cell-based therapies.

Engineering Polymer Scaffolds to Support Cellular Transplantation

The development of advanced polymer-based scaffolds within 3D microenvironments has become instrumental in enhancing the survival, integration, and function of transplanted cells. Rather than acting as passive carriers, these scaffolds now serve as dynamic microarchitectures that recreate key elements of the ECM to guide cellular behavior post-transplantation. Nowhere is this more evident than in pancreatic islet transplantation, where modulation of the local microenvironment significantly impacts graft viability, engraftment kinetics, and glucose-responsive insulin secretion.

In this context, solid biodegradable scaffolds have been successfully deployed as supportive matrices in alternative transplant sites, notably the omental pouch. One promising example is poly(D,L-lactide-co-ε-caprolactone) (PDLLCL), which has been engineered into porous, immunocompatible constructs to house islets within vascularizing subcutaneous or intraperitoneal niches, yielding improved long-term graft function [28]. The importance of polymer composition is underscored by comparative studies in which other materials-such as poly(ethylene oxide terephthalate)/polybutylene terephthalate (PEOT/PBT) and polysulfone were associated with reduced islet viability and impaired insulin release, emphasizing the delicate balance between structural support and biological compatibility [29].

Beyond Islets: Broader Applications of 3D Biomaterials

The same design principles have been translated to hepatocyte transplantation, where the omentum again emerges as a favorable engraftment site. In pioneering studies, poly(L-lactic acid) (PLA) and poly(DL-lactic-co-glycolic acid) (PLGA) were fashioned into highly porous sponges to support the transplantation of hepatocytes, culminating in the regeneration of functional hepatic tissue [30]. For central nervous system repair, particularly in retinal injuries, PLGA scaffolds have been further engineered to deliver matrix metalloproteinase-2 (MMP2) in concert with retinal progenitor cells, enhancing cellular integration, matrix remodeling, and retinal repopulation [31].

Immune Shielding: The Role of Polyethylene Glycol

A distinct yet complementary class of biomaterials centers on polyethylene glycol (PEG), one of the most widely applied polymers in transplantation science. PEG's value lies in its intrinsic non-fouling and stealth-like behavior. By forming a dense, hydrated shell around its polymer chains, PEG resists protein adsorption and subsequent opsonization, mitigating recognition by macrophages and dendritic cells [32]. This "immune quieting" effect has been leveraged to delay graft rejection and prolong cell survival in multiple settings, particularly in encapsulation-based transplantation approaches.

Biodegradable Polymers and Controlled Biochemical Signaling

The utility of biodegradable scaffolds extends beyond mere matrix support. These materials can be functionalized with enzymatic cross-linkers and biochemical moieties to orchestrate tissue ingrowth, angiogenesis, and cell migration. Moreover, the gradual breakdown of these matrices offers a precise temporal release of entrapped bioactive agents. Growth factors such as VEGF, BMP-2, or TGF-β can be incorporated through encapsulation or tethering to the scaffold surface. Upon degradation, they are released in a con-

trolled fashion, ensuring sustained bioavailability and promoting lineage-specific differentiation [25,33].

Integrin-Mediated Engagement and Scaffold Functionalization

At the core of effective cell-material interaction lies the ability of the scaffold to mimic integrin-binding domains found in native ECM proteins. Functionalization with RGD peptides enables the activation of integrin-mediated signaling cascades that regulate cell adhesion, spreading, and fate determination. For example, PEG-based hydrogels engineered with protease-sensitive linkers and RGD motifs have demonstrated improved fibroblast encapsulation and enhanced *in vivo* implantation outcomes [34]. Preclinical studies have further shown that pre-transplant exposure of islets to RGD-functionalized collagen matrices stimulates the formation of vinculin-positive focal adhesions, enhancing cellular anchorage and integration [35].

These principles are not limited to endocrine or hepatic systems. In the context of neural tissue engineering, RGD-modified scaffolds promote the infiltration of GFAP-positive glial cells and guide the outgrowth of neurofilament-positive axons along aligned polymeric matrices. In some cases, these axons penetrate deep into the scaffold, highlighting its potential for reconstructive strategies in the central nervous system [36].

Together, these advances underline the importance of material science in shaping the regenerative potential of transplanted cells. The interplay between scaffold composition, degradation kinetics, immune interaction, and biochemical signaling is critical to recapitulating the cellular microenvironment *in vivo*. Thoughtful engineering of such parameters paves the way for the next generation of precision cell therapies.

Natural vs. Synthetic Polymers

A wide range of natural and synthetic polymers have been explored as biomaterials due to their tunable physicochemical properties, biocompatibility, and ability to mimic key aspects of the ECM. Natural polymers are organic substances that occur naturally. The most prevalent natural polymers include polysaccharides like alginate, hyaluronic acid, and starch; proteins such as collagen, silk, and fibrin; as well as bacterial polyesters. The most frequently utilized natural biopolymers in biomedical applications include starch, xanthan, guar gum, carrageenan, alginate, pectin, cellulose, gelatin, agar, collagen, chitin, chitosan, keratin, silk, and elastin. Among these, collagen and elastin are typically insoluble in both aqueous and organic solvents, while silk and keratin exhibit high insolubility as well [37]. Various naturally derived ECM components (e.g., collagen, laminin, and fibronectin) are widely employed as cell delivery vehicles owing to their inherent cell-binding properties and their capacity to regulate the fate of transplanted cells over both acute and chronic timeframes [38]. Alginate, a naturally occurring polysaccharide, forms hydrogels in the presence of divalent cations. Structurally, alginate is a block copolymer composed of guluronic acid ("G") and mannuronic acid ("M") residues. The ratio of G to M units, as well as the arrangement of sequential G-blocks, M-blocks, or alternating blocks, critically influences the resulting hydrogel's physical properties [39]. Hyaluronic acid, a glycosaminoglycan prevalent in vertebrate connective tissues, can be engineered into hydrogels, sponges, and meshes. Chemical modifications, including crosslinking, enhance its mechanical strength and prolong *in vivo* residence time [39]. Cellulose derivatives are broadly classified into cellulose ethers and cellulose esters, each exhibiting distinct physicochemical and mechanical characteristics relevant to biomedical applications [40].

Synthetic polymers are a mainstay of medical device construction. Feasibility aspects of synthetic polymers related to mechanical properties and thermal stability, often render synthetic polymers superior to many naturally occurring polymers. The malleability facilitates the processing of synthetic fibers into a wide range of shapes. They are often cheaper than natural polymers, can be produced on a scale with uniformity, and have a long shelf time. Synthetic polymers can also contain a residue of initiators and other compounds/impurities that do not allow cell growth. Acrylic acid-based polymers, polyacrylamides, silicon, alkylene oxide-based homopolymers, and copolymers belong to synthetic polymers [40]. PLGA is often used for its mechanical properties and its tunable degradability which allows for controlling drug release [33].

However, natural polymers have significant utility both independently and in combination with synthetic polymers. Natural polymers are highly valued in biomedical applications due to their inherent biocompatibility and biodegradability. These properties make them useful both independently and in combination with synthetic polymers. Blending natural and synthetic polymers allows for the development of hybrid materials that integrate the biological advantages of natural polymers with the mechanical strength and tunability of synthetics [41]. Such polymer blends can serve as matrices for incorporating micro- and nanoparticles, leading to the creation of composite materials with enhanced mechanical performance, thermal stability, and biocompatibility compared to single component systems41. In addition, these polymeric blends can be reinforced with mineral phases that nucleate and grow within the matrix, enabling the formation of crystals with controlled size, shape, and distribution, which mimics the structure of native hard tissues [42]. For example, bio-composite films comprising non-crosslinked collagen (a natural polymer) and poly(ε-caprolactone) (PCL, a synthetic polymer) have been produced by impregnating lyophilized collagen mats with a PCL solution in dichloromethane. This method avoids the cytotoxicity typically associated with chemical crosslinking and yields composite scaffolds suitable for tissue engineering applications [43]. A broad range of materials, both naturally and synthetically derived, are currently employed in tissue engineering and regenerative medicine. Each material exhibits distinct physical, chemical, and biological characteristics, many of which can be tailored to optimize biocompatibility for specific applications (Figure 1). Biomaterials have been engineered into

various formats for cell transplantation, including injectable hydrogels, macroscopic scaffolds, microcarriers, and microspheres. Injectable systems such as Matrigel, collagen, fibrin, polysaccharides, hyaluronic acid, alginate, recombinant protein hydrogels, and self-assembling peptides are particularly advantageous as they enable localized delivery and minimally invasive application [38].

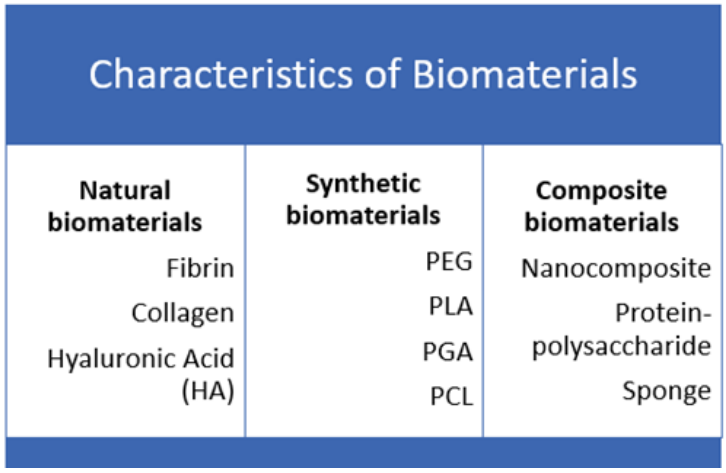

Figure 1: Characteristics of Biomaterials Used in Biomedical Applications. Biomaterials can be broadly classified into three categories: natural, synthetic, and composite. Natural biomaterials such as fibrin, collagen, and hyaluronic acid (HA) are derived from biological sources and offer inherent biocompatibility. Synthetic biomaterials-including polyethylene glycol (PEG), polylactic acid (PLA), polyglycolic acid (PGA), and polycaprolactone (PCL)-are engineered for controlled degradation and tunable mechanical properties. Composite biomaterials, such as nanocomposites, protein-polysaccharide matrices, and sponges, integrate features of both natural and synthetic materials to enhance structural and functional performance.

Using Biomaterials to overcome transplantation limitations

Biomechanical Forces

Biomaterials offer a promising strategy to address the challenges of implantation by enhancing cell survival, promoting tissue integration, and enabling localized immune modulation. Engineered biomaterials can serve as scaffolds for tissue regeneration, vehicles for therapeutic delivery, and protective matrices for transplanted cells or organs. As a result, biomaterials are playing an increasingly vital role in bridging the gap between transplantation demand and therapeutic efficacy. For example, during the transplantation process, cells are injected using a Newtonian fluid such as saline, which creates a shear and extensional force within the cell. When a needle with a smaller diameter than the syringe is used, it leads to a sharp increase in the extensional force at the syringe/needle interface. This force can rupture the cell membrane and trigger apoptosis which leads to cell death. Advances in injectable hydrogels, bioactive scaffolds, and immune-modulatory materials have demonstrated significant potential in improving graft function and longevity [44,45]. Injectable hydrogels, bioactive scaffolds, and hybrid materials have shown promise in providing localized immunomodulation, promoting vascularization, and mimicking native ECM properties [46]. However, conventional hydrogels often lack the mechanical strength required to withstand the dynamic environments of musculoskeletal or load-bearing tissues. To address this, hydrogels are increasingly being engineered with functional groups that enhance hydrophilicity and increase crosslinking density, thereby improving their mechanical resilience. One such example is the fibrin/hyaluronan (FB/HA) hydrogel, a modulated matrix capable of withstanding mechanical loading and previously demonstrated to support the repair of articular cartilage defects [47,48]. Another mechanically robust formulation includes a physical blend of hyaluronic acid and methylcellulose, which has been used to enhance the retention and distribution of renal stromal progenitor cells (RSPCs) following injection. Similarly, alginate-based hydrogels have been employed to support MSCs, ensuring their viability and functionality post-transplantation. In addition to hydrogels, rigid scaffold-forming polymers such as PLGA and chitosan offer structural reinforcement, protecting embedded cells from mechanical stress-induced apoptosis. Furthermore, biomaterial scaffolds, encompassing natural ECM-based constructs to synthetic or hybrid composites, can be precisely tuned in terms of degradation rate, porosity, and bioactivity. These materials are being used in diverse formats, including injectable hydrogels, macro-sized constructs, microcarriers, and microspheres, tailored for various cell transplantation strategies. Injectable biomaterials (e.g., Matrigel, collagen, fibrin, hyaluronic acid, alginate, recombinant protein hydrogels, and self-assembling peptides) offer minimally invasive delivery while maintaining site-specific localization and functional integration. Together, these advances illustrate the growing role of biomaterials in overcoming the traditional limitations of transplantation and advancing the field of regenerative medicine [38].

Lack of cell adhesion

Another common limitation in cell transplantation is the poor

retention, survival, and integration of transplanted cells at the target site, often due to limited cell adhesion within the host tissue microenvironment. Cell adhesion is a fundamental property of healthy cells that directly influences critical functions such as signal transduction, proliferation, migration, and survival. For transplanted stem cells to exert therapeutic effects, successful adhesion to the ECM is essential for their retention, engraftment, and subsequent migration to sites of injury. Loss of adhesion can lead to anoikis, a specific form of programmed cell death triggered when anchorage-dependent cells detach from the ECM. This phenomenon has been widely documented in MSCs, where poor adhesion to host tissues compromises therapeutic efficacy [48,49]. There are various strategies to enhance the ability of transplanted cell to adhere. These include treatment with cytokines, genetic modifications, hypoxic preconditioning, growth factors, and anti-apoptotic signaling.

Integrins, transmembrane receptors that mediate cell–cell and cell–ECM interactions, are key regulators of adhesion. These receptors transmit signals bidirectionally across the plasma membrane and play essential roles in mechanotransduction and cell survival. Integrin-linked kinase (ILK), a cytoplasmic adaptor protein that associates with the β_1 integrin subunit, is particularly important in mediating cell adhesion under hypoxic or ischemic conditions. In rat MSCs subjected to myocardial ischemia, ILK activation has been shown to enhance cell adhesion and survival through upregulation of the PI3K/Akt and ERK signaling pathways [49,50]. Moreover, the overexpression of tissue transglutaminase (tTG), which functions as a co-receptor with integrins for fibronectin, promotes focal adhesion complex formation. This, in turn, increases phosphorylation of key kinases such as focal adhesion kinase (FAK), Src, and PI3K, all of which contribute to enhanced cell adhesion and migration. These pathways also upregulate the Bcl-2/Bax ratio and suppress caspase-3 activity, thereby promoting cell survival under stress conditions. In addition, the mitogen-activated protein kinase (MAPK) cascade is another critical signaling pathway downstream of integrin activation that reinforces cytoskeletal organization and cell–ECM interactions [51,52]. Together, these molecular mechanisms underscore the importance of biomaterial-based strategies that promote integrin-mediated adhesion to improve stem cell engraftment and therapeutic outcomes.

Synthetic biomaterials can be modified with integrin-binding domains to mimic ECM mediated cell signaling events. Short bioactive peptides derived from ECM proteins have emerged as essential components in the design of biomaterials aimed at enhancing cell adhesion, survival, and functional integration after transplantation. Among these, the RGD sequence is the most well-characterized adhesion motif. RGD binds to at least eight different integrin heterodimers, facilitating cell attachment by recognizing ECM proteins such as fibronectin, vitronectin, and osteopontin [53] (Humphries *et al*., 2006). Incorporation of RGD motifs into synthetic or natural hydrogels has been shown to significantly improve the survival and retention of MSCs *in vitro*, as well as to promote bone regeneration following transplantation [50]. In addition to RGD, other ECM-derived peptides (e.g., IKVAV, YIGSR) originating from laminin and collagen-derived (i.e., GFOGER) have been widely utilized in the functionalization of biomaterials to direct specific cell–matrix interactions. Laminin-mimetic peptides have been employed in neural tissue engineering to support neuronal adhesion, differentiation, and survival, whereas the collagen-mimetic peptides have been used in musculoskeletal applications to enhance osteogenic differentiation and scaffold integration [54]. These peptide-modified scaffolds not only improve cellular adhesion but also modulate downstream signaling pathways involved in proliferation, migration, and survival, thereby increasing the overall therapeutic potential of stem cell-based interventions. While bioactive peptides such as RGD, IKVAV, and GFOGER play a pivotal role in enhancing cell adhesion and survival within biomaterial scaffolds, optimal integration and functional engraftment of transplanted cells often require additional biological cues. In this context, growth factors have emerged as critical modulators of the regenerative microenvironment.

Growth Factor Support

Growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), transforming growth factor-β_1 (TGF-β_1), prostaglandin E2 (PGE2), and bone morphogenetic protein-2 (BMP-2) have all been shown to significantly enhance the engraftment, survival, and functional integration of MSCs following transplantation [48,55]. Incorporating these growth factors into biomaterials, either through encapsulation, sustained release systems, or covalent tethering, can create a bioactive matrix that mimics key aspects of the native stem cell niche. This not only promotes cellular retention and survival but also guides cell fate decisions such as proliferation, migration, and lineage-specific differentiation. Thus, integrating growth factors into biomaterial design represents a promising strategy to overcome the limitations of poor cell engraftment and to enhance the therapeutic efficacy of cell-based therapies. This enhancement is mostly done by performing biological functions and immunomodulation [49].

Biomaterials play a multifaceted role in regenerative medicine, serving not only as passive carriers for cell delivery but also as bioactive matrices that support cell attachment, modulate the microenvironment, and enable controlled delivery of therapeutic molecules. In muscle cell transplantation, for example, successful regeneration requires a localized and sustained exposure to key mitogenic and pro-regenerative factors such as hepatocyte growth factor (HGF) and fibroblast growth factor-2 (FGF-2). Biomaterial-based delivery systems capable of co-releasing these factors in a spatiotemporally controlled manner significantly enhance the likelihood of effective tissue regeneration [56,57]. However, precise tuning of growth factor concentration and exposure duration is critical, as excessive or prolonged stimulation can have deleterious effects. For instance, chronic overexpression of transforming growth factor-alpha (TGF-α) in murine models has been associated with epithelial hyperplasia and tumorigenesis in organs such as the mammary gland and liver [39].

Optimizing the physicochemical properties of biomaterials (i.e., porosity, degradation rate, and molecular mobility) can modulate protein–protein interactions and growth factor release kinetics, thereby enhancing cell survival and engraftment. For example, composite scaffolds made of poly(L-lactic acid) (PLLA) have been engineered to co-deliver dopaminergic neurons and glial cell line-derived neurotrophic factor (GDNF) in a mouse model of Parkinson's disease, resulting in improved cell integration and neuroprotection [58]. Additionally, biomaterials can be combined with genetic modification strategies to further enhance therapeutic efficacy. One such approach involves the transfection of heat shock protein 20 (Hsp20), which activates the Akt signaling pathway and promotes the secretion of growth factors, ultimately enhancing the regenerative potential of transplanted cells [59,60]. These examples underscore the potential of rationally designed biomaterial systems to synergize mechanical support, biochemical signaling, and gene modulation for improved outcomes in cell-based therapies.

Limited Access to Host Vascularization

Therapeutic vascularization also remains a significant challenge in regenerative medicine. Revascularization and angiogenesis are central components of cell-based therapies to ensure the long-term survival of transplanted cells. Engineered bioartificial matrices harboring presenting protease-degradable sites, cell-adhesion motifs, and growth factors are beneficial to induce the vascularization *in vivo*. The endothelial cell functions are the main mediator of neovascular growth. Endothelial cell outgrowth is mediated by an array of angiogenic factors (e.g., VEGF and FGF) that operate in a highly coordinated manner and have been applied in an effort to improve the vascularization of engineered tissue. Growth factors are applied by incorporating them into the biomaterials, by either mixing them with the polymer particles of the scaffold or encapsulating them in microspheres, and by controlling their local release rate [61].

It has been shown that degradable constructs containing VEGF and RBP induce a significant number of vessels that grow into the site of the implant [62]. Hydrogels are widely used in cell transplantation due to their tunable degradation profiles and ability to support localized, controlled release of pro-angiogenic factors (e.g.,VEGF). When VEGF is encapsulated within hydrogel matrices, it can be released in response to cell-mediated enzymatic degradation, such as MMPs, which are upregulated during tissue remodeling. In one study, the incorporation of VEGF into an MMP-degradable synthetic hydrogel facilitated spatiotemporal release over approximately two weeks, significantly promoting the formation of mature and functional vasculature *in vivo* [59]. This degradative mechanism enables synchronized vascularization with host tissue regeneration. Similarly, basic FGF (bFGF) has been incorporated into biodegradable polymer systems for hepatocyte transplantation. These delivery platforms significantly enhanced angiogenesis and improved hepatocyte engraftment, likely due to bFGF's role in stimulating endothelial cell proliferation and migration [63].

Angiogenesis has also been enhanced in pancreatic islet transplantation using biodegradable constructs composed of chitosan or PLGA, either loaded with recombinant human VEGF (rhVEGF) or co-seeded with insulin-secreting pancreatic cell lines such as AR42J and INS-1. These constructs promoted local neovascularization, supporting graft survival and function (Kobayashi *et al*., 2006). Furthermore, pre-vascularization strategies using co-culture systems of dental pulp stem cells (DPSCs) and human adipose microvascular endothelial cells (HAMECs) have been shown to enhance microvascular formation within decellularized bone matrices, suggesting that pre-seeding scaffolds with angiogenic and supportive cell types can significantly improve vascular integration and tissue perfusion following implantation [64].

Controlling Transplanted Cell Differentiation

As previous discussed, growth factors are critical regulators of transplanted stem cell survival, proliferation, and lineage-specific differentiation. Immature stem cells have demonstrated greater resilience during dissociation and transplantation procedures compared to their more differentiated counterparts, likely due to their increased plasticity and resistance to environmental stressors [60]. Biomaterials are increasingly designed to deliver both mechanical and biochemical cues, thereby influencing stem cell fate decisions. One key mechanical factor is substrate stiffness, which modulates stem cell lineage commitment through mechanotransduction pathways. For instance, MSCs exhibit enhanced osteogenic differentiation on stiffer substrates, while softer matrices are more conducive to neurogenic and myogenic differentiation [21,65]. Recent studies have confirmed that tailoring hydrogel stiffness can enhance the expression of lineage-specific markers depending on the target tissue [66]. Biochemical cues such as cytokines and growth factors must also be precisely regulated to promote efficient differentiation. The spatiotemporal control of cytokine availability including residence time at the transplantation site, is a key determinant of therapeutic efficacy. For example, transforming growth factor-β_3 (TGF-β_3) and bone morphogenetic protein-2 (BMP2) are essential for bone formation and repair. Sustained release systems (e.g. PEG-based hydrogels), in which BMP2 is covalently immobilized using azide/alkyne click chemistry, have been shown to retain up to 47% of the growth factor post-injection and significantly enhance osteogenic differentiation of periodontal ligament stem cells *in vivo* [67]. In contrast, hydrogels that rapidly release BMP2 fail to maintain the biochemical signals required for prolonged differentiation, although short-term cell survival may remain unaffected.

Mechanical Stimulating Regeneration

The design of biomaterials with tunable structural and biomechanical properties is essential for recapitulating the native tissue environment and promoting functional cell integration. One of the most critical design parameters is material stiffness. Material stiffness influences a wide range of cellular behaviors, including proliferation, morphology, migration, and matrix permeability (Discher *et al*., 2005; Chaudhuri *et al*., 2020). Stiffness can be modulated through cross-linking density, polymer weight percent, and cross-linking chemistry. For example, increasing cross-linking density or polymer content reduces hydrogel diffusivity and nutrient

transport while increasing the elastic modulus. This elevation in stiffness can limit fibroblast proliferation and reduce the spreading of encapsulated cells [68].

The ECM not only provides mechanical support and spatial organization for cells but also transduces mechanical signals into biochemical responses, influencing gene expression independently of growth factor or integrin interactions [69]. Mechanical stimuli can modulate the release of encapsulated growth factors, ECM-mimetic molecules, or drugs from polymer matrices, enhancing local bioactivity. As pressure within the biomaterial increases, drug release can be mechanically regulated, and subsequent replenishment occurs during matrix relaxation via dissociation of bound components, allowing responsiveness to cyclic mechanical cues [70]. Collagen-based biomaterials exemplify the integration of structural and mechanical control in tissue engineering. When blended with methacrylated hyaluronic acid (MeHA), the strength, stress resistance, and stiffness can be finely tuned across several orders of magnitude, significantly improving cell viability (75–85%) during encapsulation of NIH-3T3 fibroblasts [71,72]. The mechanical environment also directs stem cell differentiation. For instance, neural progenitor cells differentiate into neurons on soft matrices (100–500 Pa), while glial differentiation is favored on stiffer matrices (1,000–10,000 Pa), highlighting how mimicking tissue-specific stiffness enhances lineage commitment (Engler *et al*., 2006). Similarly, collagen-coated polyacrylamide gels replicating the elasticity of native tissues have been used to direct mesenchymal progenitors toward osteogenic, chondrogenic, or neurogenic fates depending on substrate stiffness [73].

Additional innovations include the gelatin-graft-vinyl acetate (GeVAc) copolymer, a non-cytotoxic biomaterial used for vascular tissue engineering. GeVAc supports smooth muscle cell (SMC) proliferation and, under mechanical stimulation, promotes a contractile phenotype characterized by upregulation of α-smooth muscle actin (α-SMA), calponin, and SM22α, as well as increased ECM secretion [74]. Polyurethanes are also widely used due to their biocompatibility, tunable mechanical properties, and ease of fabrication into porous scaffolds, making them well-suited for soft tissue engineering applications [75]. Furthermore, bioinspired and stimuli-responsive materials that mimic the dynamic architecture of native tissues can reversibly alter their stiffness, shape, porosity, or density in response to external cues such as temperature, pH, or mechanical strain, providing advanced control over cell–material interactions [60].

Controlling the immune response

The host's response to the implanted biomaterial and specifically the tissue surrounding the implant drives the tissue-specific innate defenses and the following induction of adaptive immune responses. The feedback responses are mediated by the interplay between the biomaterial and the host immune system [76]. To avoid adverse events, immunomodulatory biomaterials are utilized to reduce neutrophil activation, optimize M1 to M2 macrophage polarization, Th1 to Th2 lymphocyte switch, and Treg induction. The optimal biomaterial physicochemical modifications can help tune the reaction of the host immune system to successfully implant the biomaterial, allow transplanted cells to integrate at the site of the implant and allow for tissue regeneration [76]. The biomaterial properties are designed to control encounters with immune signals from tissue, cell, molecular, to direct stimulation or regulation of immune function. To provide an immune-privileged environment for transplanted cells, encapsulated cells are protected in a polymeric membrane from the host immune system. Cells that have been encapsulated in both hollow fiber membranes and micro-spherical membranes, experience the passive diffusion of small nutrients, waste molecules, and therapeutic cell products. Larger immunoglobulins are excluded across the membrane due to the encapsulation barrier created [77].

Many biomaterials exhibit intrinsic immunogenic features that can trigger or modulate immune function. For example, arginine-rich polymers have been shown to activate the complement system, an innate immune pathway for the clearance of pathogens [78]. Incubation with PLA, poly-(g-glutamic acid) or poly-b-amino-ester-containing particles has been reported to promote dendritic cell maturation [79]. Physical characteristics of polymeric biomaterials, such as material chemistry, size and shape, surface texturing and charge, and hydrophobicity or hydrophilicity, play an important role in the way of immune cell activation of the inflammasome [28]. Budding microparticles activate the inflammasome complex and induce the secretion of IL-1 than smooth particles through activation of the NLRP3 inflammasome [80]. Biomaterial stiffness and charge alter interactions with immune cells to promote uptake. Hydrophobicity and charge can regulate inflammatory processing pathways [78]. Specific molecular mechanisms to mediate the recognition of polymers and related macromolecules by immune cells include specialized receptors with well-characterized physiological functions (e.g., integrin receptors, cell-cell recognition domains), as well as more generalized pattern recognition receptors (PRRs). Many PRRs on the cell surface (e.g., scavenger receptors, toll-like receptors (TLRs), etc.) identify pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) that are present in the biomaterial [81].

Strategies Influencing the Host Tissue Niche

Biomaterials are critical tools for modulating the host tissue niche to enhance the survival, integration, and function of transplanted cells. These strategies center around mimicking or remodeling the ECM, modulating immune responses, promoting angiogenesis, and controlling the local biochemical environment. Natural and synthetic biomaterials can be functionalized with ECM-derived peptides (e.g., RGD, IKVAV, GFOGER) to enhance cell adhesion and promote lineage-specific differentiation [82,83]. These biochemical modifications influence integrin signaling pathways and cytoskeletal dynamics, which are crucial for cell fate and survival in the host environment. Some biomaterials, such as hydrogels containing immunosuppressive cytokines or engineered to release anti-inflammatory agents (e.g., IL-10, TGF-β_1), can create a pro-regenerative

niche by modulating local immune responses. Recent studies have shown that incorporating IL-4 or immunomodulatory nanoparticles into biomaterials can polarize macrophages toward a tissue-repair (M2) phenotype, reducing graft rejection and fibrosis [74,84]. Delivery of pro-angiogenic factors (i.e., VEGF, FGF-2) via degradable scaffolds supports vascular ingrowth, which is essential for nutrient delivery and cell survival post-transplantation. Biomaterials engineered to degrade in response to matrix metalloproteinases enable controlled, cell-mediated release of these factors [85]. The stiffness, topography, and degradation kinetics of biomaterials also shape the host niche by influencing mechanotransduction pathways (e.g., YAP/TAZ). Tunable hydrogels that match tissue stiffness can promote appropriate cell-matrix interactions, improving engraftment and functionality [86]. Pre-seeding scaffolds with endothelial cells or using organoid-based systems can pre-vascularize the niche, accelerating host integration. Recent advances have demonstrated that scaffolds preloaded with adipose-derived stem cells and endothelial progenitors significantly enhance vascularization and tissue regeneration [87]. Together, these biomaterial-based strategies create a more permissive and supportive environment for cell transplantation, offering a platform to regulate spatiotemporal biological cues within the host tissue.

Inducing Plasticity in the Host Tissue

Just as biomaterials are engineered to modulate the extracellular environment and immune response, they can also be strategically designed to induce plasticity within the host tissue, reawakening developmental or regenerative programs that are otherwise dormant in adult tissues. Biomaterial-induced plasticity mirrors principles of reprogramming and niche modulation and is gaining traction as a means of enhancing tissue integration and repair. Biomaterials can influence host cell plasticity by altering chromatin accessibility through mechanotransduction and biochemical signaling. For example, tunable hydrogels that mimic the mechanical properties of developing tissue have been shown to activate YAP/TAZ and ERK signaling pathways, which promote a dedifferentiated, regenerative state in resident stromal or epithelial cells (Li *et al*., 2021; Lei *et al*., 2020). Scaffolds that release morphogens like Wnt, FGF, and BMP in a controlled, gradient-dependent manner can induce progenitor-like phenotypes in local cells. In spinal cord injury models, for instance, Wnt3a-loaded biomaterials have promoted neural progenitor activation and axonal sprouting (Pakulska *et al*., 2017). Biomaterials can be engineered to present chemoattractants (e.g., SDF-1α, HGF) or ECM mimetic ligands that recruit and activate endogenous progenitor cells. This strategy has been used in muscle and liver regeneration to mobilize satellite cells and hepatic progenitors, respectively (Murphy *et al*., 2020). Modulating the immune environment using cytokine-releasing biomaterials (e.g., IL-4, IL-10) encourages tissue-resident macrophages and dendritic cells to adopt pro-regenerative phenotypes, which in turn secrete factors that induce local cell plasticity and tissue remodeling (Shin *et al*., 2023; Sridharan *et al*., 2022).

Recent studies have demonstrated that biomaterial topography and stiffness can guide phenotype transitions in situ, via promoting fibroblast-to-myofibroblast or epithelial-to-mesenchymal transitions, depending on the outcome goal. This is particularly relevant in wound healing and fibrosis modulation [88]. These analogous strategies illustrate how biomaterials are not passive carriers but active agents that can reprogram the local tissue environment to favor regeneration through induced plasticity of host cells.

Functional Biomarkers and Clinical Translation of Stem Cell–Derived Insulin-Producing Cells in Type 1 Diabetes

As outlined in preceding section, the application of stem cell–derived insulin-producing cells offers transformative potential in the treatment of type 1 diabetes. While islet transplantation remains limited by donor scarcity and immunological complications, human pluripotent stem cells (hPSCs), including ESCs and iPSCs, offer a scalable and renewable source for generating replacement β-like cells. However, effective clinical translation demands rigorous assessment of cell identity, functionality, and safety. Biomarkers on molecular, functional, metabolic, and immunological level play a pivotal role in validating IPC differentiation both *in vitro* and *in vivo*.

Defining Functional Maturity: From Lineage Markers to Performance

Differentiation protocols have now advanced to the point where hPSCs can be directed through a stepwise sequence that mimics human pancreatic development, culminating in cells that express key β-cell markers and secrete insulin in response to glucose. Clinical trials by companies such as ViaCyte and Vertex Pharmaceuticals are exploring both encapsulated and directly implanted cell-based products, signaling a shift from preclinical proof-of-concept toward therapeutic reality. To ensure therapeutic success, IPCs must not only express appropriate markers but also display dynamic glucose responsiveness. Early markers such as PDX1, NKX6.1, and NEUROG3 indicate appropriate lineage commitment, while later expression of MAFA in combination with INS is strongly correlated with glucose-regulated insulin secretion. These transcription factors define the progression from pancreatic progenitor to functional β-like cell, but marker expression alone is insufficient.

The gold standard remains glucose-stimulated insulin secretion (GSIS), a functional assay that captures the ability of IPCs to respond physiologically to glucose fluctuations. Measuring both insulin and C-peptide release distinguishes de novo hormone production from exogenous contamination and reflects β-cell functionality more reliably. Immature IPCs often secrete insulin constitutively or lack phase-specific release, while mature IPCs exhibit biphasic insulin secretion in response to high glucose levels, a hallmark of physiological β-cells.

Epigenetic and Metabolic Readouts

Recent studies have highlighted that maturation is also accompanied by distinct epigenetic and metabolic changes. DNA methyl-

ation at the INS, PDX1, and MAFA loci shifts during differentiation, and aberrant methylation correlates with loss of function or instability. Functionally, mature IPCs shift from glycolytic metabolism to oxidative phosphorylation. This metabolic rewiring is essential for efficient ATP production and insulin granule exocytosis. Assessments such as Seahorse extracellular flux analysis or mitochondrial membrane potential profiling can serve as indirect biomarkers of cellular maturity and viability [19].

In Vivo Biomarkers: Graft Function and Survival

Once transplanted, the capacity of IPCs to reverse hyperglycemia in diabetic immunodeficient mice is considered the definitive test. Restoration of normoglycemia, along with human-specific C-peptide detection in the host serum, confirms both engraftment and endocrine function. Longitudinal bioluminescent imaging of luciferase-expressing cells enables non-invasive tracking of cell survival. Additionally, single-cell RNA sequencing of explanted grafts allows for high-resolution mapping of transcriptional fidelity, stability, and adaptation within the host microenvironment [89].

Safety and Immunological Profiling

Ensuring the absence of residual pluripotent cells marked by OCT4, SOX2, and NANOG is essential to mitigate the risk of teratoma formation. Furthermore, assessing immune-relevant markers such as HLA class I/II, PD-L1, and CD47 provides insight into graft immunogenicity and informs strategies for immune evasion or compatibility. Some protocols incorporate hypoimmunogenic hPSCs generated via CRISPR-Cas9–mediated gene editing to reduce alloreactivity and prolong graft survival.

The combination of lineage-specific markers, functional performance assays, metabolic profiling, and immune characterization enables a multidimensional assessment of IPC quality. While no single biomarker suffices, a composite readout integrating transcriptional, functional, and *in vivo* performance offers a robust framework for advancing stem cell–based therapies toward regulatory approval. The clinical promise of IPC therapy for T1D is no longer conceptual. Multiple trials have demonstrated safety and preliminary efficacy, and current research focuses on refining engraftment, minimizing immune rejection, and optimizing scalability. The use of biomaterials, both for encapsulation and niche engineering, further supports graft survival and maturation. Ultimately, the success of stem cell therapy for diabetes will rest on our ability to standardize and monitor cellular identity before, during, and after transplantation.

Conclusions and Future Perspectives

The integration of stem cell biology with biomaterials science is steadily reshaping the therapeutic landscape for Type 1 Diabetes. The ability to generate insulin-producing cells from human pluripotent stem cells, and to guide their maturation using tailored microenvironments, represents one of the most promising developments in regenerative medicine. Biomaterials, once seen merely as inert scaffolds, now serve as biologically active matrices that influence cell fate, protect grafts, and shape immunological responses. Together, these advances bring the concept of a functional cure for diabetes closer to reality.

The progress has been substantial, yet challenges remain. Differentiation protocols continue to yield heterogeneous populations, and many insulin-producing cells lack the full glucose responsiveness and resilience of native β-cells. The implantation of such cells into patients introduces further complexity, as survival, functional integration, and immunological acceptance must all be ensured. These difficulties underscore the importance of combining cellular engineering with smart biomaterial design to recreate not only the cells but also the niches in which they thrive.

One of the most critical contributions of biomaterials lies in their capacity to control the local microenvironment. Through spatial organization, matrix stiffness, biochemical gradients, and controlled degradation, they provide instructive signals that direct stem cell fate and function. Natural polymers such as alginate or fibrin have shown promise due to their biocompatibility and permeability, while synthetic matrices allow for precise modulation of material properties. Their role is particularly important in three-dimensional settings, where cell–matrix and cell–cell interactions mirror the complexity of native pancreatic tissue.

Equally important is the application of robust biomarkers for assessing cell identity, functional maturation, and *in vivo* performance. Advances in transcriptomic profiling, metabolic analysis, and imaging technologies now permit detailed and non-invasive tracking of cell fate, both *in vitro* and after transplantation. These tools are indispensable for product standardization, safety validation, and regulatory approval. A reliable biomarker framework not only improves reproducibility but also offers critical insight into therapeutic efficacy and long-term stability.

Looking forward, future research must address several interconnected goals. First, the development of dynamic biomaterials that evolve in parallel with the needs of differentiating or engrafting cells. These materials should not only support cell survival but also stimulate maturation, sensing, and insulin release. Second, strategies to evade or modulate the host immune response must be refined. While encapsulation technologies offer partial protection, emerging approaches such as immune-inert cell lines, local immune modulation, and genetic editing hold the potential for more durable solutions. Third, scalability must become a central concern. Producing clinically relevant numbers of high-quality insulin-producing cells under good manufacturing practice conditions remains a major bottleneck that must be overcome before widespread application is possible.

In parallel, the concept of patient-specific therapy through induced pluripotent stem cells or allogeneic off-the-shelf solutions must be evaluated not only for scientific feasibility but also for cost, logistics, and health system integration. In this regard, lessons can

be drawn from cell-based cancer immunotherapies and from transplantation medicine, where challenges in delivery, follow-up, and ethical oversight have been partially addressed.

Importantly, future efforts must remain patient centered. The aim is not merely to produce insulin *in vitro*, but to restore physiological glucose homeostasis *in vivo*, with minimal burden to the patient. The ideal therapy would provide stable, self-regulating insulin production, avoid the need for lifelong immunosuppression, and integrate seamlessly into the patient's life. Achieving this will require not only scientific innovation, but also thoughtful clinical trial design, cross-disciplinary collaboration, and sustained public engagement.

In conclusion, the field is at an inflection point. The scientific foundation is in place, and the biological tools are becoming more refined. Biomaterials now serve not just as delivery platforms, but as active participants in the engineering of functional β-cell systems. If the current pace of progress continues, it is conceivable that within the coming decade, stem cell–based therapy for diabetes will move from experimental to established treatment, offering durable and life-changing benefit to millions of patients worldwide.

References

1. Kirkeby A, Main H and Carpenter M (2025) Pluripotent stem-cell-derived therapies in clinical trial: A 2025 update. Cell Stem Cell 32(1): 10-37.
2. Rahimi Darehbagh R, Seyedoshohadaei SA, Ramezani R and Rezaei N (2024) Stem cell therapies for neurological disorders: current progress, challenges, and future perspectives. Eur J Med Res 29(1): 386.
3. Knoedler L, Dean J, Diatta F, Thompson N, Knoedler S, et al (2024) Immune modulation in transplant medicine: a comprehensive review of cell therapy applications and future directions. Front Immunol 15: 1372862.
4. Cha Z, Qiao Y, Lu Q, Wang Q, Lu X, et al (2024) Research progress and challenges of stem cell therapy for ischemic stroke. Front Cell Dev Biol 12: 1410732.
5. Vidman S, Ma YHE, Fullenkamp N and Plant GW (2025) Human induced pluripotent stem cell-derived therapies for regeneration after central nervous system injury. Neural Regen Res 20(11): 3063-3075.
6. Zeng N, Tang W, Wu Y, Fan H, Xie S, et al (2023) Harnessing stem cell and lineage reprogramming technology to treat cardiac fibrosis. Cell Regen Lond Engl 12(1): 39.
7. Muncie JM and Weaver VM (2018) The Physical and Biochemical Properties of the Extracellular Matrix Regulate Cell Fate. Curr Top Dev Biol 130: 1-37.
8. Xing H, Lee H, Luo L and Kyriakides TR (2020) Extracellular matrix-derived biomaterials in engineering cell function. Biotechnol Adv 42: 107421.
9. Bessy T, Itkin T and Passaro D (2021) Bioengineering the Bone Marrow Vascular Niche. Front Cell Dev Biol 9: 645496.
10. Zhao T, Zhang ZN, Rong Z and Xu Y (2011) Immunogenicity of induced pluripotent stem cells. Nature 474(7350): 212-215.
11. Sindhi K, Pingili RB, Beldar V, Bhattacharya S, Rahaman J, et al (2025) The role of biomaterials-based scaffolds in advancing skin tissue construct. J Tissue Viability 34(2): 100858.
12. Wang Y, Wang Z and Dong Y (2023) Collagen-Based Biomaterials for Tissue Engineering. ACS Biomater Sci Eng 9(3): 1132-1150.
13. Rowley JA, Madlambayan G and Mooney DJ (1999) Alginate hydrogels as synthetic extracellular matrix materials. Biomaterials 20(1): 45-53.
14. Holmes TC, de Lacalle S, Su X, Liu G, Rich A, et al (2000) Extensive neurite outgrowth and active synapse formation on self-assembling peptide scaffolds. Proc Natl Acad Sci U S A 97(12): 6728-6733.
15. Kharbikar BN, Mohindra P and Desai TA (2022) Biomaterials to enhance stem cell transplantation. Cell Stem Cell 29(5): 692-721.
16. Eichinger JF, Haeusel LJ, Paukner D, Aydin RC, Humphrey JD, et al (2021) Mechanical homeostasis in tissue equivalents: a review. Biomech Model Mechanobiol 20(3): 833-850.
17. Discher DE, Janmey P and Wang YL (2005) Tissue cells feel and respond to the stiffness of their substrate. Science 310(5751): 1139-1143.
18. Gjorevski N and Lutolf MP (2017) Synthesis and characterization of well-defined hydrogel matrices and their application to intestinal stem cell and organoid culture. Nat Protoc 12(11): 2263-2274.
19. Nair GG, Liu JS, Russ HA, Tran S, Saxton MS, et al (2019) Recapitulating endocrine cell clustering in culture promotes maturation of human stem-cell-derived β cells. Nat Cell Biol 21(2): 263-274.
20. Guan W and Zhang L (2025) Applications and prospects of biomaterials in diabetes management. Front Bioeng Biotechnol 13: 1547343.
21. Engler AJ, Sen S, Sweeney HL and Discher DE (2006) Matrix elasticity directs stem cell lineage specification. Cell 126(4): 677-689.
22. Nichol JW, Koshy ST, Bae H, Hwang CM, Yamanlar S, et al (2010) Cell-laden microengineered gelatin methacrylate hydrogels. Biomaterials 31(21): 5536-5544.
23. Zhou H and Lee J (2011) Nanoscale hydroxyapatite particles for bone tissue engineering. Acta Biomater 7(7): 2769-2781.
24. Hersel U, Dahmen C and Kessler H (2003) RGD modified polymers: biomaterials for stimulated cell adhesion and beyond. Biomaterials 24(24): 4385-4415.
25. Chen FM, Zhang M and Wu ZF (2010) Toward delivery of multiple growth factors in tissue engineering. Biomaterials 31(24): 6279-6308.
26. Brown BN and Badylak SF (2014) Extracellular matrix as an inductive scaffold for functional tissue reconstruction. Transl Res J Lab Clin Med 163(4): 268-285.
27. Zhang YS, Yue K, Aleman J, Moghaddam KM, Bakht SM, et al (2017) 3D Bioprinting for Tissue and Organ Fabrication. Ann Biomed Eng 45(1): 148-163.
28. Weber LM, Lopez CG and Anseth KS (2009) Effects of PEG hydrogel crosslinking density on protein diffusion and encapsulated islet survival and function. J Biomed Mater Res A 90(3): 720-729.
29. de Vos P, Lazarjani HA, Poncelet D and Faas MM (2014) Polymers in cell encapsulation from an enveloped cell perspective. Adv Drug Deliv Rev 67-68: 15-34.
30. Ouyang EC, Wu CH, Walton C, Promrat K and Wu GY (2001) Transplantation of human hepatocytes into tolerized genetically immunocompetent rats. World J Gastroenterol 7(3): 324-330.
31. Wu KY, Dhaliwal JK, Sasitharan A and Kalevar A (2024) Cell Therapy for Retinal Degenerative Diseases: Progress and Prospects. Pharmaceutics 16(10): 1299.
32. Knop K, Hoogenboom R, Fischer D and Schubert US (2010) Poly(ethylene glycol) in drug delivery: pros and cons as well as potential alternatives. Angew Chem Int Ed Engl 49(36): 6288-6308.
33. Patel ZS, Young S, Tabata Y, Jansen JA, Wong MEK, et al (2008) Dual delivery of an angiogenic and an osteogenic growth factor for bone regeneration in a critical size defect model. Bone 43(5): 931-940.

34. Lutolf MP, Lauer-Fields JL, Schmoekel HG, Metters AT, Weber FE, et al (2003) Synthetic matrix metalloproteinase-sensitive hydrogels for the conduction of tissue regeneration: engineering cell-invasion characteristics. Proc Natl Acad Sci U S A 100(9): 5413-5418.

35. Villa C, Manzoli V, Abreu MM, Verheyen CA, Seskin M, et al (2017) Effects of Composition of Alginate-Polyethylene Glycol Microcapsules and Transplant Site on Encapsulated Islet Graft Outcomes in Mice. Transplantation 101(5): 1025-1035.

36. Yang F, Murugan R, Wang S and Ramakrishna S (2005) Electrospinning of nano/micro scale poly(L-lactic acid) aligned fibers and their potential in neural tissue engineering. Biomaterials 26(15): 2603-2610.

37. Reddy MSB, Ponnamma D, Choudhary R and Sadasivuni KK (2021) A Comparative Review of Natural and Synthetic Biopolymer Composite Scaffolds. Polymers 13(7): 1105.

38. Shafiq M, Jung Y and Kim SH (2016) Insight on stem cell preconditioning and instructive biomaterials to enhance cell adhesion, retention, and engraftment for tissue repair. Biomaterials 90: 85-115.

39. Smith GH, Sharp R, Kordon EC, Jhappan C and Merlino G (1995) Transforming growth factor-alpha promotes mammary tumorigenesis through selective survival and growth of secretory epithelial cells. Am J Pathol 147(4): 1081-1096.

40. Alves TF, Morsink MAEM, Batain F, Chaud MV, Almedia T, et al (2020) Applications of Natural, Semi-Synthetic, and Synthetic Polymers in Cosmetic Formulations. Cosmetics 7(4).

41. Sionkowska A (2011) Current research on the blends of natural and synthetic polymers as new biomaterials: Review. Progress Polym Sci 36(9): 1254-1276.

42. Donnaloja F, Jacchetti E, Soncini M and Raimondi MT (2020) Natural and Synthetic Polymers for Bone Scaffolds Optimization. Polymers 12(4): 905.

43. Coombes AGA, Verderio E, Shaw B, Li X, Griffin M, et al (2002) Biocomposites of non-crosslinked natural and synthetic polymers. Biomaterials 23(10): 2113-2118.

44. Park JE and Kim DH (2025) Advanced Immunomodulatory Biomaterials for Therapeutic Applications. Adv Healthc Mater 14(5): e2304496.

45. Zhong JX, Raghavan P and Desai TA (2023) Harnessing Biomaterials for Immunomodulatory-Driven Tissue Engineering. Regen Eng Transl Med 9(2): 224-239.

46. Zhang Z (2017) Injectable biomaterials for stem cell delivery and tissue regeneration. Expert Opin Biol Ther 17(1): 49-62.

47. Zhao T, Wei Z, Zhu W, Weng X et al (2022) Recent Developments and Current Applications of Hydrogels in Osteoarthritis. Bioeng Basel Switz 9(4): 132.

48. Wang G, Zhang X, Bu X, An Y, Bi H, et al (2022) The Application of Cartilage Tissue Engineering with Cell-Laden Hydrogel in Plastic Surgery: A Systematic Review. Tissue Eng Regen Med 19(1): 1-9.

49. Lee S, Choi E, Cha MJ and Hwang KC (2015) Cell adhesion and long-term survival of transplanted mesenchymal stem cells: a prerequisite for cell therapy. Oxid Med Cell Longev 2015: 632902.

50. Xu F, Dawson C, Lamb M, Mueller E, Stefanek E, et al (2022) Hydrogels for Tissue Engineering: Addressing Key Design Needs Toward Clinical Translation. Front Bioeng Biotechnol 10: 849831.

51. Cargnello M and Roux PP (2011) Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. Microbiol Mol Biol Rev MMBR 75(1): 50-83.

52. Katoh K (2025) Integrin and Its Associated Proteins as a Mediator for Mechano-Signal Transduction. Biomolecules 15(2): 166.

53. Niland S and Eble JA (2012) Integrin-mediated cell-matrix interaction in physiological and pathological blood vessel formation. J Oncol 2012: 125278.

54. Borelli AN, Schultze CL, Young MW, Kirkpatrick BE and Anseth KS (2025) Ligand presentation controls collective MSC response to matrix stress relaxation in hybrid PEG-HA hydrogels. Bioact Mater 44: 152-163.

55. Tu C, Mezynski R and Wu JC (2020) Improving the engraftment and integration of cell transplantation for cardiac regeneration. Cardiovasc Res 116(3): 473-475.

56. Tam RY, Fuehrmann T, Mitrousis N and Shoichet MS (2014) Regenerative therapies for central nervous system diseases: a biomaterials approach. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol 39(1): 169-188.

57. Wang X, Zhao T, Huang W, Wang T, Qian J, et al (2009) Hsp20-engineered mesenchymal stem cells are resistant to oxidative stress via enhanced activation of Akt and increased secretion of growth factors. Stem Cells Dayt Ohio 27(12): 3021-3031.

58. Marques CR, Fuzeta M de A, Dos Santos Cunha RM, Silva D, (2023) et al (2023) Neurodifferentiation and Neuroprotection Potential of Mesenchymal Stromal Cell-Derived Secretome Produced in Different Dynamic Systems. Biomedicines 11(5): 1240.

59. Li Y, Hoffman MD and Benoit DSW (2021) Matrix metalloproteinase (MMP)-degradable tissue engineered periosteum coordinates allograft healing via early stage recruitment and support of host neurovasculature. Biomaterials 268: 120535.

60. Liu M, Zeng X, Ma C, Yi H, Ali Z, et al (2017) Injectable hydrogels for cartilage and bone tissue engineering. Bone Res 5: 17014.

61. Johnson EO, Troupis T and Soucacos PN (2011) Tissue-engineered vascularized bone grafts: basic science and clinical relevance to trauma and reconstructive microsurgery. Microsurgery 31(3): 176-182.

62. Luo W, Zhang H, Wan R, Cai Y, Liu Y, et al (2024) Biomaterials-Based Technologies in Skeletal Muscle Tissue Engineering. Adv Healthc Mater 13(18): e2304196.

63. Sakiyama-Elbert SE and Hubbell JA (2000) Development of fibrin derivatives for controlled release of heparin-binding growth factors. J Control Release Off J Control Release Soc 65(3): 389-402.

64. Dikici S, Claeyssens F and MacNeil S (2020) Pre-Seeding of Simple Electrospun Scaffolds with a Combination of Endothelial Cells and Fibroblasts Strongly Promotes Angiogenesis. Tissue Eng Regen Med 17(4): 445-458.

65. Zhou JQ, Wan HY, Wang ZX and Jiang N (2023) Stimulating factors for regulation of osteogenic and chondrogenic differentiation of mesenchymal stem cells. World J Stem Cells 15(5): 369-384.

66. Darieva Z, Zarrineh P, Phillips N, et al (2025) Ubiquitous MEIS transcription factors actuate lineage-specific transcription to establish cell fate. EMBO J 44(8): 2232-2262.

67. Park J, Park S, Kim JE, Jang KJ, Seonwoo H, et al (2021) Enhanced Osteogenic Differentiation of Periodontal Ligament Stem Cells Using a Graphene Oxide-Coated Poly(ε-caprolactone) Scaffold. Polymers 13(5): 797.

68. Han Y, Shao Z, Zhang Y, Zhao H, Sun Z, et al (2024) 3D matrix stiffness modulation unveils cardiac fibroblast phenotypic switching. Sci Rep 14(1): 17015.

69. Provenzano PP and Keely PJ (2011) Mechanical signaling through the cytoskeleton regulates cell proliferation by coordinated focal adhesion and Rho GTPase signaling. J Cell Sci 124(8): 1195-1205.

70. Mooney DJ and Vandenburgh H (2008) Cell delivery mechanisms for tissue repair. Cell Stem Cell 2(3): 205-213.

71. Li N, Oberley TD, Oberley LW and Zhong W (1998) Inhibition of cell growth in NIH/3T3 fibroblasts by overexpression of manganese superoxide dismutase: mechanistic studies. J Cell Physiol 175(3): 359-369.

72. Yue K, Trujillo-de Santiago G, Alvarez MM, Tamayol A, et al (2015) Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels. Biomaterials 73: 254-271.

73. Wei Q, Wang S, Han F, Wang H, Zhang Z, et al (2021) Cellular modulation by the mechanical cues from biomaterials for tissue engineering. Biomater Transl 2(4): 323-342.

74. Yang H, Cheng H, Dai R, Shang L, Zhang X, et al (2023) Macrophage polarization in tissue fibrosis. PeerJ 11: e16092.

75. Krishani M, Shin WY, Suhaimi H and Sambudi NS (2023) Development of Scaffolds from Bio-Based Natural Materials for Tissue Regeneration Applications: A Review. Gels Basel Switz 9(2): 100.

76. Mariani E, Lisignoli G, Borzì RM and Pulsatelli L (2019) Biomaterials: Foreign Bodies or Tuners for the Immune Response? Int J Mol Sci 20(3): 636.

77. Guo B and Ma PX (2018) Conducting Polymers for Tissue Engineering. Biomacromolecules 19(6): 1764-1782.

78. Tsai SJ, Black SK and Jewell CM (2020) Leveraging the modularity of biomaterial carriers to tune immune responses. Adv Funct Mater 30(48): 2004119.

79. De Koker S, Lambrecht BN, Willart MA, Kooyk YV, Grooten J, et al (2011) Designing polymeric particles for antigen delivery. Chem Soc Rev 40(1): 320-339.

80. Vaine CA, Patel MK, Zhu J, Lee E, Finberg RW, et al (2013) Tuning innate immune activation by surface texturing of polymer microparticles: the role of shape in inflammasome activation. J Immunol Baltim Md 190(7): 3525-3532.

81. Soni SS and Rodell CB (2021) Polymeric materials for immune engineering: Molecular interaction to biomaterial design. Acta Biomater 133: 139-152.

82. Gu C, Feng J, Waqas A, Deng Y, Zhang Y, et al (2021) Technological Advances of 3D Scaffold-Based Stem Cell/Exosome Therapy in Tissues and Organs. Front Cell Dev Biol 9: 709204.

83. Bellis SL (2011) Advantages of RGD peptides for directing cell association with biomaterials. Biomaterials 32(18): 4205-4210.

84. Wynn TA and Vannella KM (2016) Macrophages in Tissue Repair, Regeneration, and Fibrosis. Immunity 44(3): 450-462.

85. Zhao P, Sun T, Lyu C, Liang K and Du Y (2023) Cell mediated ECM-degradation as an emerging tool for anti-fibrotic strategy. Cell Regen Lond Engl 12(1): 29.

86. Li L, Chen X, Wang WE and Zeng C (2016) How to Improve the Survival of Transplanted Mesenchymal Stem Cell in Ischemic Heart? Stem Cells Int 2016: 9682757.

87. Oliveri MB, Mautalen C, Mega M and Rossi E (1994) Congenital erythropoietic porphyria: skeletal manifestations and effect of pamidronate treatment. Bone 15(1): 101-104.

88. Di Gregorio J, Robuffo I, Spalletta S, Giambuzzi G, Iuliis VD, et al (2020) The Epithelial-to-Mesenchymal Transition as a Possible Therapeutic Target in Fibrotic Disorders. Front Cell Dev Biol 8: 607483.

89. Velazco-Cruz L, Song J, Maxwell KG, Goedegebuure MM, Augsornworawat P et al (2019) Acquisition of Dynamic Function in Human Stem Cell-Derived β Cells. Stem Cell Rep 12(2): 351-365.