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Citation: Facklam, Amanda L. et al. "Biomaterials for Personalized Cell Therapy." Advanced Materials 32, 13 (September 2019): 1902005. © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

As Published: http://dx.doi.org/10.1002/adma.201902005

Publisher: Wiley

Persistent URL: https://hdl.handle.net/1721.1/132610

Version: Original manuscript: author's manuscript prior to formal peer review

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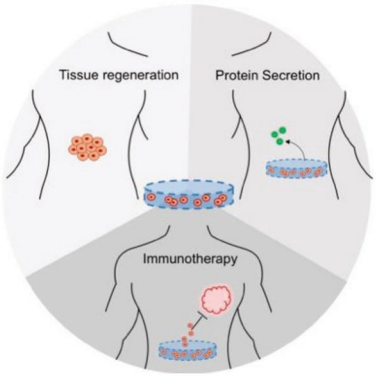
Massachusetts Institute of Technology

REVIEWS

Personalized Cell Therapy

A. L. Facklam, L. R. Volpatti,
D. G. Anderson* 1902005

Biomaterials for Personalized Cell Therapy



Biomaterials enable personalized cell therapies with applications in tissue regeneration, therapeutic protein delivery, and immunotherapy. Cell therapies provide localized, dynamic treatment through their innate ability to sense and respond to their microenvironment and orchestrate complex biological processes. Toward translation of personalized cell therapies, biomaterials are under development to support cell viability and functionality and instruct cell behavior including differentiation from induced pluripotent stem cells.

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Biomaterials for Personalized Cell Therapy

Amanda L. Facklam, Lisa R. Volpatti, and Daniel G. Anderson*

Cell therapy has already had an important impact on healthcare and provided new treatments for previously intractable diseases. Notable examples include mesenchymal stem cells for tissue regeneration, islet transplantation for diabetes treatment, and T cell delivery for cancer immunotherapy. Biomaterials have the potential to extend the therapeutic impact of cell therapies by serving as carriers that provide 3D organization and support cell viability and function. With the growing emphasis on personalized medicine, cell therapies hold great potential for their ability to sense and respond to the biology of an individual patient. These therapies can be further personalized through the use of patient-specific cells or with precision biomaterials to guide cellular activity in response to the needs of each patient. Here, the role of biomaterials for applications in tissue regeneration, therapeutic protein delivery, and cancer immunotherapy is reviewed, with a focus on progress in engineering material properties and functionalities for personalized cell therapies.

1. Introduction

Cell therapies are diverse in nature and have the potential to provide treatment for many diseases.[1] Some cells possess the ability to differentiate into several different cell types in response to environmental cues. Others have evolved to release certain factors in response to changes in their environment. Due to the inherent ability to dynamically sense and respond to changing physiological conditions, cell therapy has broad potential impact. A major challenge in translating cell therapies to approved cell products, however, is maintaining the viability and efficacy of transplanted cells.[2] Biomaterials may enhance the retention, viability, and function of these therapeutic cells by acting as delivery vehicles, barriers from the host immune system, and instructive templates. Therefore, many cell therapies include a biomaterial carrier designed to support and direct cell behavior during and after transplantation. For example, recent clinical trials for cell therapies containing biomaterials include the delivery of autologous chondrocytes with collagen for cartilage repair and alginate-encapsulated islet cell delivery for diabetes treatment.[3]

Personalized medicine aims to treat patients on an individual basis according to their specific characteristics and disease state. In the context of this review, we define personalized cell therapies as those in which the therapeutic cells and/or biomaterial carrier are individualized to patient needs.[4] Within this definition, personalized cells include both patient-derived cells as well as protein-secreting cells which respond dynamically to each patient's therapeutic needs. Personalized or precision biomaterials, such as 3D-printed scaffolds[5] and immunomodulatory materials,[6] are designed to specifically interact with the physiological environment post-transplantation.

While other reviews have highlighted the use of biomaterials for cell delivery,[7] here we focus on strategies for personalized therapies. We discuss recent advances in personalized biomaterials-based cell therapies for tissue regeneration,[8] therapeutic protein delivery,[7a] and immunotherapy[9] (**Figure 1**). For tissue regeneration, we focus on engineering material mechanical properties, topography, and composition to deliver and direct personalized cells in addition to designing personalized cell scaffolds. For protein delivery, we discuss the importance of material dimensions and pore size in the design of cell carriers and opportunities to improve oxygen availability and modulate the host immune system with the design of precision biomaterials. Finally, we discuss delivering patient-specific immune cells with materials engineered for immune system activation and cell trafficking.

2. Biomaterials in Cell Therapies for Tissue Regeneration

Stem cells are promising tools for tissue regeneration due to their self-renewing and proliferative capacities as well as their ability to differentiate into a number of different lineages.[8a,10] Although there is debate surrounding their name and function,[11] mesenchymal stem cells (MSCs) are generally understood to have the potential to differentiate into multiple cell types including osteoblasts, chondrocytes, and adipocytes.[12] MSCs have the additional therapeutic benefit of being able to secrete soluble factors such as growth factors and anti-inflammatory compounds that may aid in angiogenesis and tissue repair.[12,13] Pluripotent stem cells (PSCs), such as embryonic stem cells (ESCs), have the capability to differentiate into essentially any cell type. However, the clinical translation of ESC therapies has been limited by ethical considerations as well as their potential immunogenicity and tumorigenicity.[14] The discovery of induced pluripotent stem cells (iPSCs)[15]

A. L. Facklam, L. R. Volpatti, Prof. D. G. Anderson
Koch Institute for Integrative Cancer Research
500 Main Street, 76-653F, Cambridge, MA 02139, USA
E-mail: dgander@mit.edu
The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adma.201902005.

DOI: 10.1002/adma.201902005

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enables the possibility of using a patient's own somatic cells for personalized tissue regeneration (**Figure 2**). While iPSCs were initially induced in 2D culture by the introduction of the four so-called Yamanaka factors,[15a] materials science approaches have since shown that cues from the 3D microenvironment can promote iPSC generation.[16]

The reprogramming of autologous cells into iPSCs circumvents ethical concerns associated with human embryos and reduces the potential of an immune response. However, the isolation and expansion of a clinically relevant number of stem cells remains a barrier to the translation of personalized therapies.[2b,17] Additionally, the direct injection of PSCs is associated with teratoma formation. To reduce tumorigenicity, PSCs can be differentiated in vitro with undifferentiated cells removed prior to transplantation or delivered within an instructive matrix to promote complete differentiation in vivo (Figure 2).[18] Since the diseased or damaged tissue is not conducive to cell growth and proliferation, an artificial matrix also provides the stem cells with structural support and environmental cues to promote differentiation.[19] Future strategies for personalized cell therapies include the direct differentiation of a patient's cells without the need to reprogram and the downstream manipulation of cells to impart them with additional functionalities (Figure 2). Biomaterials thus play a key role in the efficacy of these personalized therapies by creating a stem cell niche that enables differentiation, transplantation, and survival of patient-specific therapeutic cells.

2.1. Material Strategies for Autologous Stem Cell Differentiation

The decision of adult stem cells to maintain their stemness or commit to a certain lineage in vivo relies on instructive signals from the soluble factors and the biophysical and biochemical properties of the extracellular matrix (ECM) that comprise the stem cell niche. The in vitro differentiation of stem cells by soluble factors is relatively well established. As such, iPSCs have been successfully differentiated into cardiomyocytes,[20] chrondrocytes,[21] osteoblasts,[22] neural cells,[23] retinal cells,[24] lung epithelial cells,[25] pancreatic β cells,[26] and hepatocyte-like cells,[27] among others, for applications in personalized regenerative medicine. Initial methods used feeder cells—a layer of mouse embryonic fibroblasts—or a cell-derived ECM mixture such as Matrigel to support the culture of undifferentiated PSCs. To reduce batch-to-batch variability and remove xenogenic components, recent research has focused on developing synthetic alternatives to Matrigel[28] and a fully defined culture system[29] for the expansion and differentiation of stem cells. In the investigation of stem cell behavior in response to culture on various substrates, the mechanical and molecular properties of materials have been shown to influence lineage commitment.[30] For example, MSCs have been shown to specify lineage according to substrate elasticity with more rigid matrices promoting osteogenesis.[31] Understanding the individual and combined effects of matrix mechanical and material properties will enable better control of stem cell fate and may improve the safety of personalized stem cell-based therapies by reducing their tumorigenicity and potential for teratoma formation in vivo (**Figure 3**).

Amanda L. Facklam is currently a Ph.D. candidate in biological engineering at the Massachusetts Institute of Technology. In the laboratories of Daniel G. Anderson and Robert Langer, her research focuses on biomaterial strategies to evade the foreign body response to implantable materials, particularly in the context of materials for islet transplantation. She received her B.S. in biomedical engineering from Johns Hopkins University where she researched stem-cell-derived vascular cells for tissue engineering.

Lisa R. Volpatti is currently a Ph.D. candidate in the laboratory of Daniel G. Anderson in the Department of Chemical Engineering at the Massachusetts Institute of Technology where her research focuses on the development of stimuli-responsive biomaterials for applications in drug delivery. She received her M.Phil. from the University of Cambridge Department of Chemistry as a Whitaker International Fellow where she worked with Tuomas P. J. Knowles on self-assembled protein microgels.

Daniel G. Anderson is an associate professor at the Massachusetts Institute of Technology in Chemical Engineering and the Institute of Medical Engineering and Science. He is also a member of the Koch Institute for Integrative Cancer Research. He received his Ph.D. in molecular genetics from the University of California at Davis before coming to MIT to work on developing biomaterial libraries for applications in drug delivery, cell therapy, and medical devices.

2.1.1. Effects of Material Mechanical Properties on Personalized Stem Cell Differentiation

In addition to sensing and responding to their physical environment, stem cells have been reported to remember past mechanical cues.[32] For example, increased culture time on stiff

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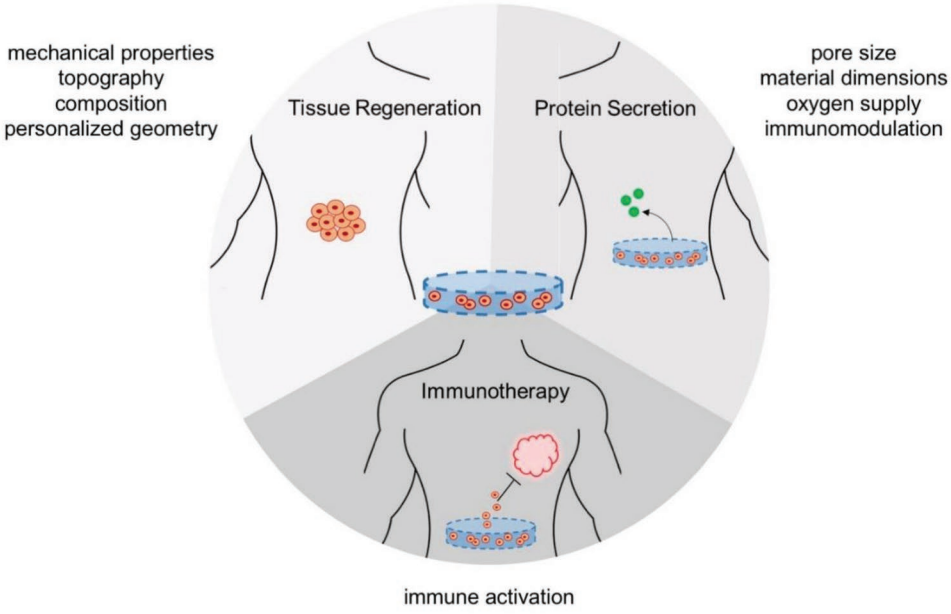

Figure 1. Schematic of applications for biomaterial-based cell therapies, including tissue regeneration, therapeutic protein secretion, and immunotherapy for cancer treatment, as well as material design considerations for each application.

polystyrene prior to culture on soft polyethylene glycol (PEG) was reported to promote osteogenic differentiation of MSCs.[32] This mechanical memory may have important implications in understanding how the in vitro culture and expansion of stem cells affect their phenotype and lineage commitment. Stiffening hydrogels—materials which stiffen with time—can probe the cellular response of stem cells to dynamic mechanical properties. MSC differentiation was shown to depend on stiffening induction time of hyaluronic acid (HA)-based hydrogels with earlier stiffening times favoring osteogenesis and later times favoring adipogenesis.[33]

Stress-stiffening hydrogels—materials that stiffen with increasing applied stress beyond a critical stress value—have also been shown to influence stem cell differentiation. Adhered stem cells can induce this stress-stiffening behavior through their applied traction forces and respond by altering their shape and ultimately commitment.[34] For example, MSCs cultured in polyisocyanopeptide-based hydrogels with low critical stress predominantly exhibited adipogenesis while osteogenesis was observed with increasing values of critical stress.[34] In contrast to stress stiffening, stress relaxation is defined by a reduction in the stress response to an applied strain over time. Therefore, matrices that exhibit partial stress relaxation, such as collagen and fibrin, initially resist applied strain with a certain stiffness which decreases with time.[35] MSCs cultured in alginate hydrogels with faster relaxation times were shown to exhibit enhanced spreading, proliferation, and osteogenic commitment.[35] These results suggest that a range of biomaterial mechanical properties, in addition to the elastic modulus, may affect stem cell culture and differentiation. Moreover, these material properties are important considerations in the design of precision biomaterials to enable the expansion, differentiation, and delivery of stem cell-based therapies for personalized medicine.

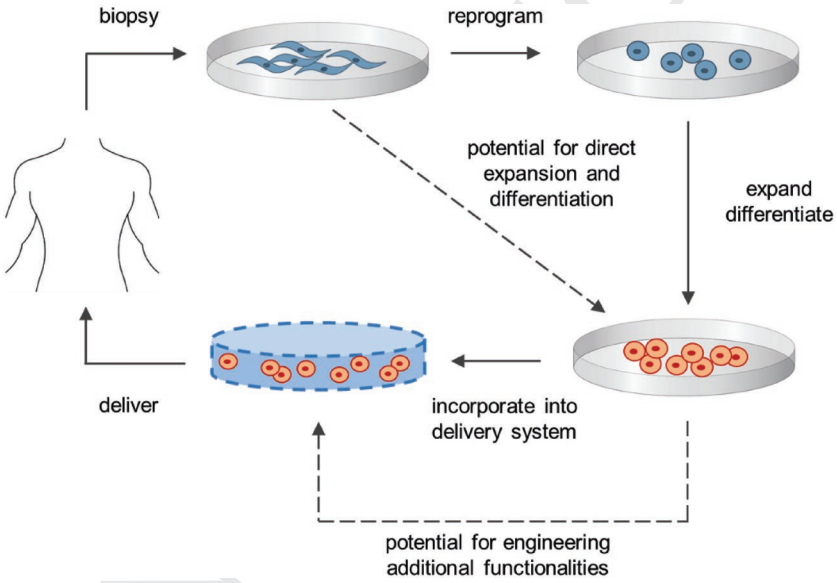

Figure 2. In personalized regenerative medicine, a patient's cells can be biopsied, reprogramed into iPSCs, expanded and differentiated with soluble factors and/or physical and chemical cues from the microenvironment, incorporated into a custom biomaterial-based delivery system, and delivered to the site of diseased or damaged tissue. The dotted lines represent personalized cell therapy options that may be delivered in a future clinical setting, including the direct differentiation and expansion of a patient's biopsied cells without the need to reprogram as well as the potential for genetically engineering the cells to impart additional functionalities.

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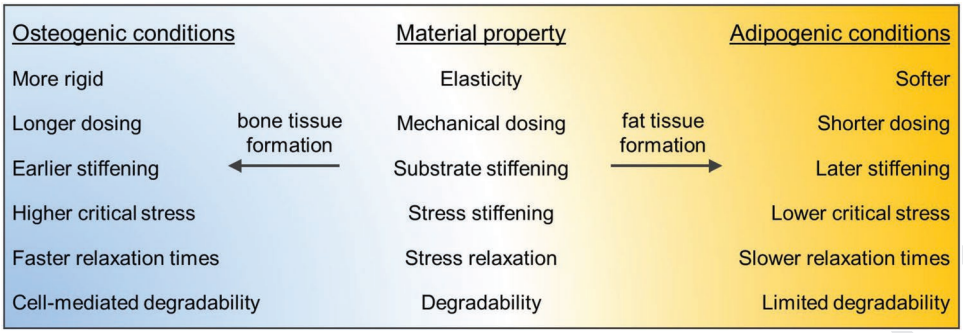

Figure 3. In addition to soluble factors, physical and chemical cues from the stem cell niche can influence lineage commitment. More rigid substrates and increased contact time with stiffer environments is reported to promote osteogenesis while softer substrates and increased contact time with soft matrices is reported to promote adipogenesis.

The mechanism by which matrix stiffness influences stem cell fate has also been of recent interest[30c,36] with yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ),[37] myosin II,[31] and nuclear lamin A,[38] among others, playing roles in mechanosensing and mechanotransduction. To provide insights into this mechanism, poly(vinyl alcohol) (PVA) stiffness gradient hydrogels have been used to study stem cell differentiation across multiple stiffness values, with results that corroborate those from homogenous hydrogels.[39] By varying the gradient of stiffness of polyacrylamide hydrogels, Hadden et al. were able to study adipose-derived stem cell mechanotransduction without the confounding effects of cell migration and reported dose-dependent responses of YAP to intermediate hydrogel stiffness.[40] Studies of MSC behavior and differentiation in micropatterned PEG gels with 2D spatially varied elasticity also reported that higher concentrations of stiff regions resulted in higher YAP activation in a dose-dependent manner.[35] However, changing from a regular to random pattern resulted in lower levels of YAP activation, suggesting that small variations in the local environment are also important in determining transcriptional events and cellular morphologies.[35] While these results have led to increased mechanistic understanding, further materials science approaches should be employed to take into account the 3D intricacies of native ECM. These studies would thus aid in the development of next-generation precision biomaterials that better recapitulate the 3D physiological stem cell niche for the expansion, differentiation, and delivery of personalized therapeutic cells.

2.1.2. Effects of Material Topography and Composition on Autologous Stem Cell Differentiation

In addition to matrix mechanical properties, the topography and composition of substrates have been suggested to play a role in the regulation of stem cell commitment.[41] Several strategies have been used to decouple interacting effects, including substrate stiffness, porosity, and integrin adhesion. To investigate the role of matrix porosity, polyacrylamide gels of constant stiffness were formed with varying porosities by altering the ratio of acrylamide monomer and bis-acrylamide crosslinker.[42] Substrate stiffness was the primary determinant of stem cell fate for both adipose stromal cells and MSCs, and neither hydrogel deformations resulting from stem cell traction forces nor stem cell differentiation was significantly impacted by altering the porosity alone.[42] Void-forming alginate hydrogels were similarly developed to decouple elasticity and pore formation and showed that substrate elasticity governed osteogenesis of MSCs while matrix chemistry controlled cell deployment.[43] To study the effects of matrix degradation, HA hydrogels were modified with matrix metalloproteinase (MMP)-sensitive peptides to permit cell-mediated degradation.[44] A subset of hydrogels were subsequently covalently crosslinked through the photopolymerization of methacrylates to reduce their degradability. The cell-degradable hydrogels promoted MSC spreading, high tractions, and osteogenesis while the photopolymerized hydrogels promoted adipogenesis.[44] Thus, while the porosity of the substrate and its ability to form pores had little effect on stem cell fate in these studies, cell-mediated matrix degradability has been reported to promote osteogenic commitment.

The presence of functional binding motifs including RGD (the adhesive domain of fibronectin in ECM) and HAVDI (an adhesive sequence of the transmembrane protein N-cadherin) is also thought to influence stem cell fate. To test this hypothesis, nanoarrays of PEG hydrogels conjugated with RGD peptides decoupled of the effects of stiffness and surface chemistry.[45] The spacing of the adhesive peptides in this study was found to affect both the spreading area and differentiation of cultured MSCs independent of hydrogel stiffness.[45] In addition to cell–ECM interactions, the influence of cell–cell adhesion was analyzed with HA hydrogels conjugated with HAVDI.[46] The presence of HAVDI altered the ability of MSCs to mechanically sense the stiffening ECM and may thus be used to modify the cellular response to matrix stiffness in the design of synthetic biomaterials for personalized cell therapies.[46] A study of cell–cell contact in combination with substrate stiffness reported variable effects of these two factors in the different stages of osteogenesis.[47] For example, while nuclear localization of transcription factors depended only on substrate stiffness, both cell–cell contact and stiff substrates were required for enhanced expression of alkaline phosphatase, an early protein marker for osteogenesis in MSCs.[47] Therefore, in addition to substrate mechanical properties, the spacing of adhesive peptides and cell density may be confounding factors that should be taken into consideration in the expansion and differentiation of therapeutic stem cells.

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With the multitude of factors influencing stem cell commitment, it can be challenging to individually vary parameters to find the optimal biomaterial matrix for the differentiation of patient-derived stem cells. To greatly reduce the total number of experimental runs while maintaining the ability to determine significant trends within the design space, the statistical design of experiment (DOE) technique of fractional factorial design can be used to select a subset of experiments that provide the most possible information for biomaterial optimization.[48] In the context of patient-derived stem cell culture, DOE methods have already been used to determine the optimal concentration of three ECM-derived peptide adhesive domains (RGD, YIGSR, and IKVAV) on a HA hydrogel to promote the culture of iPSC-derived neural progenitor cells.[49] The multifactorial design used in this study was able to ascertain the individual and combined effects of each of these peptides to determine the optimal concentration for cell survival.[49] To translate this system in vivo, the concentration of codelivered growth factors was similarly optimized to improve cell survival and differentiation upon transplantation in a mouse model of stroke.[50] Other matrices have been engineered to promote the differentiation of iPSCs into osteoblasts,[51] neural cells,[52] and hepatocytes.[53] However, in order to make significant progress toward the translation of personalized therapies, DOE should be used to ensure optimal conditions for the differentiation and therapeutic efficacy of patient-derived stem cells.

2.2. Personalized Cell Delivery Platforms for Tissue Regeneration

A key determinant of efficacy for many cell therapies is survival during and after transplantation. Biomaterials have the potential to protect stem cells from mechanical forces exerted during injection and provide them with a supportive matrix for anchorage-dependence within the diseased or damaged tissue. Moreover, these matrices provide structural support that enhances cellular retention and therapeutic action at the local site of administration. Biomaterial-based cell delivery systems can be derived from naturally occurring materials such as alginate,[54] HA,[55] gelatin,[56] and collagen[57] or based on synthetic materials such as PEG,[58] poly(lactic-*co*-glycolic acid) (PLGA),[59] poly(N-isopropylacrylamide) (PNIPAM),[60] and polycaprolactone (PCL).[61] While naturally occurring materials often have biological advantages, synthetic materials are more easily tailored to specific applications by modulating their biofunctionality, mechanical properties, and degradation rates. In addition to cells, these materials can be used to codeliver therapeutic agents such as growth factors or immunomodulatory molecules to aid in cellular engraftment.[62] While many delivery platforms exist, this review highlights recent advances in promising cell delivery strategies in the context of personalized therapies, including injectable hydrogels, 3D-printed scaffolds, and hydrogel patches (**Table 1**).

Table 1. Materials and methods of cell delivery with applications in personalized tissue regeneration.

Delivery method	Application	Material	Cell types
Injectable hydrogel	Spinal cord injury	HA/methylcellulose	iPSC-derived oligodendrocytes[69]
	Cartilage repair	Gelatin	Primary chondrocytes[63]
		Gelatin	Bone marrow MSCs[64]
		HA/alginate	hMSCs[65]
		HA/collagen	Primary chondrocytes[79b]
		Four-arm star PEG	Primary chondrocytes[71]
		PEG/PCL	Primary chondrocytes and bone marrow stem cells[77a]
		Polypeptides	Bone marrow MSCs[66]
	Bone regeneration	PEG/PCL	Human turbinate MSCs,[76e] human periodontal ligament stem cells[79a]
		PNIPAM/gelatin	MSCs[76a,d]
		Silk fibroin	hMSCs[72]
	Myocardial infarction	PEG	hiPSC-derived cardiomyocytes[70]
		PNIPAM/collagen	Bone marrow MSCs[76c]
	Ischemia	Chitosan	Human adipose-derived stem/stromal cells[76b]
Cardiac patch	Myocardial infarction	Alginate	hMSCs[90]
		Collagen	hMSCs[90]
		ECM-derived thermoresponsive hydrogel	hiPSC-derived cardiomyocytes and hiPSC-derived endothelial cells[5]
		Fibrin/Matrigel	hiPSC-derived cardiomyocytes[91b]
		Fibrin	hiPSC-derived cardiomyocytes[91d]
	Left ventricular wall defect	Fibrin	hiPSC-derived cardiomyocytes and hiPSC-derived endothelial cells[91c]
3D-printed scaffold	Cartilage repair	Fibrin/gelatin/HA	Primary chondrocytes[86]
		Gelatin/PEG	MSCs[81a,b]
	Perfusable tissue	Fibrin/gelatin	hMSCs[84]

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2.2.1. Injectable Hydrogels for Autologous Cell Delivery

Injection of cells is generally preferred over surgical intervention due to its lower invasiveness. However, the process of directly injecting stem cells through a needle can cause mechanical disruption that reduces cell viability.[67] Biomaterial-based delivery systems can protect stem cells during injection and also provide an artificial stem cell niche that enhances the survival, proliferation, and retention of cells at the injection site.[10]

Shear-thinning and self-healing hydrogels are able to protect stem cells during injection by altering the fluid flow profile through the syringe and reducing the forces exerted on the cells.[68] Therefore, shear-thinning hydrogels containing personalized cells have been the focus of several recent preclinical studies for the repair of several tissue types including spinal cord,[69] heart,[70] cartilage,[71] and bone.[72] Nevertheless, the relatively weak mechanical properties of most shear-thinning hydrogels represent a major drawback since their kinetics of erosion are often faster than the kinetics of ECM regeneration. It has been hypothesized that the rate of scaffold degradation should correspond to the rate of tissue formation for a given application to optimize therapeutic efficacy of biomaterial-based cell delivery systems.[73] Thus, recent efforts have focused on enhancing the structural integrity of shear-thinning hydrogels to improve their retention in vivo.[74]

To obtain hydrogels that exhibit higher structural stability, precursors can be injected that induce crosslinking in vivo. In situ-forming hydrogels have the advantage of conforming to different shape defects and integrate well with the host tissue, thus enabling patient- and defect-specific therapies.[75] Crosslinking can be triggered by an intrinsic stimulus such as temperature[76] or extrinsic stimulus such as UV light to initialize photopolymerization.[77] However, thermal gelation is difficult to precisely control and photopolymerization is limited by light penetration and potential cytotoxicity.[78] Precursor solutions that react with the appropriate kinetics can also be injected as in situ-forming hydrogel cell carriers without the need for an additional trigger.[79] In order to be effective, the reaction kinetics of these systems must be controlled; rapid kinetics may result in gelation inside the syringe while delayed kinetics may result in cell death and migration from the administration site. Moreover, depending on the mechanical properties of the precursor solution, cells delivered in in situ-forming hydrogels may still be subjected to high shear and extensional forces during the injection process.

Combining the beneficial properties of both shear-thinning and in situ-forming hydrogels using two-step gelation is one strategy for improving the retention and efficacy of injected stem cells. For example, a dock-and-lock system based on peptide-modified HA and polypeptide precursors uses photoinitiation to stabilize the hydrogels with secondary crosslinks.[74a] Physically and chemically crosslinked hydrogels can have moduli as high as ten times those from hydrogels crosslinked with physical interactions alone.[74a] Correspondingly, gel erosion can be extended over a period of months and cultured MSCs exhibit enhanced viability compared to those cultured in hydrogels based on physical crosslinks alone.[74a] Similarly, hydrogels based on PNIPAM and PEG that undergo two physical crosslinking processes—the first ex vivo and the second in situ—reduce the rate of material degradation and significantly enhance retention of adipose-derived stem cells in vivo compared to singly crosslinked hydrogels.[74b] More biocompatible hydrogels based on elastin-like proteins (ELP) and HA have also been engineered to undergo a two-stage crosslinking process.[74c] Gelation initially occurs through dynamic covalent bonds to form a shear-thinning, self-healing material that protects MSCs during injection. The second stage occurs as the ELP undergoes a thermal phase transition that stabilizes the hydrogel and decreases the degradation rate by an order of magnitude.[74c]

These examples illustrate the potential of a two-stage crosslinking approach for injectable cell delivery that can be tailored to the needs of individual defects and specific diseases. A proposed approach to tailor hydrogels to an individual patient includes taking a biopsy of the patient's tissue, isolating and analyzing the autologous cells, inputting quantifiable cellular activity data into a predictive model, and identifying the optimal hydrogel design for the given target.[4c] Advanced computational models employing machine learning techniques are required to make this proposed solution a reality but their accuracy may be limited by the practical quality and size of the cellular activity data in the training sets. Moreover, depending on the tissue type, taking a biopsy of the patient's diseased tissue may be an invasive process. Increasingly complex models that can predict the activity of diseased tissue given a sample of the patient's healthy tissue may be required to reduce the invasiveness of this therapy. We envision that a similar strategy can be used to optimize a personalized cocktail of growth factors, cytokines, and anti-inflammatory molecules to be delivered alongside the cells to enhance tissue integration and therapeutic outcomes.[80]

2.2.2. 3D-Printed Scaffolds for Custom-Designed Cell Delivery

3D printing has emerged as a strategy for the additive manufacturing of cell-laden biomaterials to produce tissue constructs that can be customized to the anatomy of each patient for personalized regenerative medicine.[81] In addition to the material properties required for conventional tissue scaffolds, such as biocompatibility, biodegradability, and mechanical strength, "bioinks" for 3D bioprinters must be amenable to printer deposition. Similar to injectable hydrogels, bioinks should protect cells from mechanical disruption as they flow through the printer nozzle. Depending on the size of the construct, the incorporation of perfusable vasculature may be required to support transport of nutrients to maintain cell viability and graft functionality. Methods of creating vascularized networks include printing sacrificial carbohydrate glass that can be removed to form endothelialized perfusable channels,[82] coprinting several materials and cell types through four independently controlled printheads,[83] and controlling the tissue microenvironment through custom 3D perfusion chips (**Figure 4**).[84]

Acellular custom 3D-printed medical devices have already been personalized for use in patients, for example, in the treatment of tracheobronchomalacia.[85] Many researchers share the

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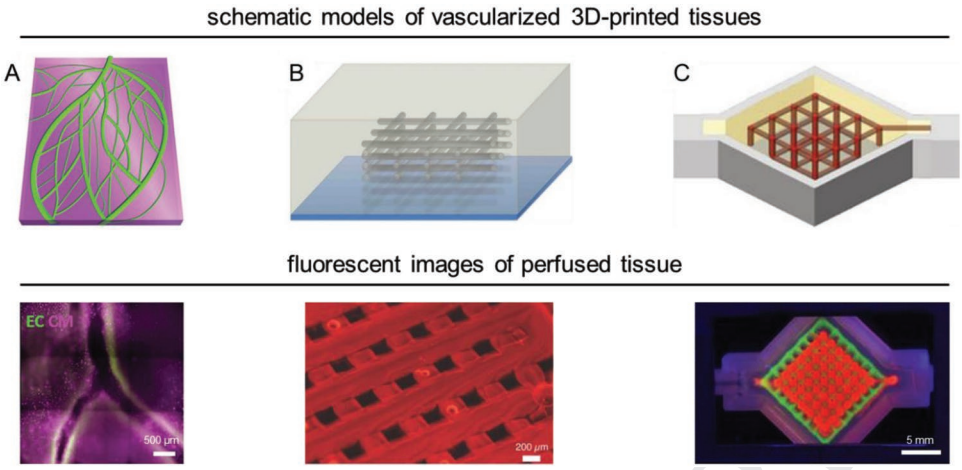

Figure 4. A) Schematic models and fluorescent images of perfused vascular 3D-printed tissues from fully personalized cardiac patches fabricated from ECM-derived hydrogels and CT images to match a patient's biology and anatomy. Adapted with permission.[5] Copyright 2019, Wiley-VCH. B) Coprinting several materials and cell types. Adapted with permission.[83] Copyright 2014, Wiley-VCH. C) Custom fabricated 3D perfusion chips.[84]

vision that this process can extend to 3D printing of autologous cellularized scaffolds for personalized tissue regeneration in the near future. Toward this vision, an integrated tissue-organ printer (ITOP) was reported to produce cellular human-scale tissue constructs with structural stability and vascularization.[86] Proof-of-concept of this bioprinter was demonstrated by fabricating mandible bone, calvarial bone, ear cartilage, and skeletal muscle from a computer model of an anatomical defect.[86] Further improvements in the resolution of clinical imaging and bioprinting techniques may enable this vision to become a reality. Additionally, advances in printed bioinks that can adapt to their environment over time may facilitate the translation of personalized scaffolds for tissue repair.[87]

2.2.3. Cardiac Patches for Personalized Myocardial Repair

Due to the prevalence and severity of cardiovascular diseases,[88] a large body of research has focused on the application of personalized cell therapies to myocardial repair. In the context of myocardial infarction (MI), directly injected iPSC-derived cardiomyocytes have been shown to regenerate nonhuman primate hearts,[89] indicative of the potential of personalized cell therapies in the treatment of cardiac disease. However, the observance of ventricular arrhythmias suggests the need for further research to fully assess their incidence and risk. To enhance the regenerative capacity of iPSC-derived cardiomyocytes, engineered biomaterial patches can provide robust mechanical, contractile, and electrical properties to functionally support the cells after transplantation into an infarct region. Cellular patches may thus offer advantages that outweigh the ease of administration of injectable cell delivery formulations for cardiac regeneration. A comparison of biomaterials for MSC delivery in MI showed that epicardial patches exhibit a fluorescence signal representative of cell viability ≈50-fold higher than the saline control, whereas injectable hydrogels exhibit only an ≈10-fold increase.[90] These data suggest that cells delivered in a biomaterial patch may be advantageous for applications in cardiac tissue engineering.

The integral function of fibrin in the natural wound healing process has led to its extensive use as a matrix for cardiac patches.[91] For example, cardiac patches from human iPSC-derived cardiomyocytes and iPSC-derived endothelial cells in a fibrin matrix improved left ventricular function in a guinea pig model with electrical coupling to the host tissue observed in a subset of animals.[91c] Furthermore, human iPSC-derived cardiomyocytes delivered in fibrin patches releasing insulin-like growth factor-1 (IGF-1) did not cause arrhythmias in a porcine model of MI.[91d] Thus, iPSC-derived tissues in fibrin matrices have the potential to be individualized to each patient and may even electrically integrate with the patient's intact heart tissue to reduce arrhythmogenic risks.[91c]

Noor et al. recently reported the generation of fully personalized, perfusable cardiac patches that match the patient's immunology, biochemistry, and anatomy (Figure 4a).[5] After a biopsy of an omental tissue is taken from the patient, cells are reprogrammed to iPSCs and differentiated into cardiomyocytes and endothelial cells. The decellularized ECM is then processed into a printable patient-specific, thermoresponsive hydrogel. The cardiomyocytes and endothelial cells are separately mixed with the personalized hydrogel to form bioinks for cardiac and vascular tissues, respectively. Finally, a personal cardiac patch is printed using a computer-aided design of the patient's left ventricle based on anatomical data from computerized tomography (CT) images of the patient's heart and mathematical modeling of blood vessel architecture (Figure 4).[5] Although advances in both imaging and 3D printing technology are needed to precisely recapitulate the complete vascular network with small diameter vessels, this report marks an important progression in the development of personalized tissue engineered therapies.

3. Biomaterials in Cell Therapies for Therapeutic Protein Secretion

Cell-based therapies offer an alternative to traditional therapeutic soluble protein delivery. Delivering cells capable of secreting the therapeutic of interest enables long-term and

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patient-specific treatment.[7a,92] Therapeutic cells that dynamically respond to environmental cues have the potential to offer personalized treatment for a wide variety of diseases including diabetes,[93] neurodegenerative disorders,[94] and cancer.[95]

3.1. Applications for Cell-Based Protein Delivery

Type 1 diabetes is one of the most studied applications for cell-based therapies due to limitations of current insulin treatments and the great therapeutic potential of transplanted insulin-producing cells.[96] Numerous patients have already received donor islet transplants and achieved insulin independence but are reliant on immunosuppressive drugs to prevent islet rejection.[96] Patient-derived stem cells may be differentiated into β-cells as an alternative to donor islets; however, more extensive study is required to ensure their safety and efficacy.[97] Since type 1 diabetes is an autoimmune disorder, even patient-derived cells may require protection from the host immune system.[98] To avoid the systemic toxicity of immunosuppression, encapsulation materials are under development to provide a barrier between donor cells and the host. Current efforts are focused on improving cell viability and functionality by enhancing oxygen supply,[99] improving permeation control,[100] and modulating the host immune system.[6b,93a,101] While many aspects of encapsulation have been studied in the context of diabetes, the progress in this field can be applied to several other therapeutic applications.

Cell-based treatment of neurodegenerative diseases is of great interest in part due to the challenge of delivering drugs across the blood–brain barrier. With cell delivery, therapeutic proteins can be continuously directed to the site of interest post-implantation. Encapsulation in biomaterials can prevent these cells from being rejected and help maintain their viability over time.[7a,94a] Cell encapsulation approaches have shown promise in Alzheimer's disease,[102] Parkinson's disease,[103] Huntington's disease,[104] and amyotrophic lateral sclerosis (ALS).[105]

Cells can also be used for the delivery of therapeutics for cancer treatment.[106] Cell-based delivery approaches for cancer include anti-angiogenesis therapy,[107] immunotherapy,[108] and suicide gene therapy.[95b] Stem cells have been studied in particular for their natural ability to migrate to and inhibit tumors.[95c] To further promote anticancer activity, stem cells have been engineered to secrete interleukins and interferons to stimulate anticancer immune activity or proteins that promote tumor cell apoptosis.[109] Similar to neurodegenerative disorders, cell therapies implanted in the brain for brain tumor therapy could also be particularly beneficial for continuous protein secretion without the need to cross the blood–brain barrier.[95a]

Genetic engineering has the potential to introduce new functionality into cells which can be leveraged for therapeutic strategies.[100a] For example, transcriptional regulators allow cells to respond to molecular signals in their environment for inducible therapeutic secretion.[110] One potential application is in the treatment of metabolic disorders, where synthetic gene circuits can be introduced into cells prior to transplantation to maintain metabolite levels in the recipient.[111] The field is progressing toward complex network design to more closely match the dynamics of natural cell regulatory behavior. With elements like genetic oscillators, cells can be designed to sense and respond to their microenvironment in a dynamic and precise fashion.[111,112] Therefore, synthetic biology may be a particularly useful tool for designing cells which can respond to a patient's specific therapeutic needs.[113]

3.2. Biomaterial Approaches for Cell-Based Therapeutic Delivery

In order to successfully deliver cells for long-term therapeutic delivery, biomaterial carriers can be used to enhance cell viability and functionality. Strategies include microencapsulation of cells in small capsules, conformal coating of materials to cell surfaces, and macroencapsulation of cells in one larger material or device (**Figure 5**). A key consideration for these therapies is

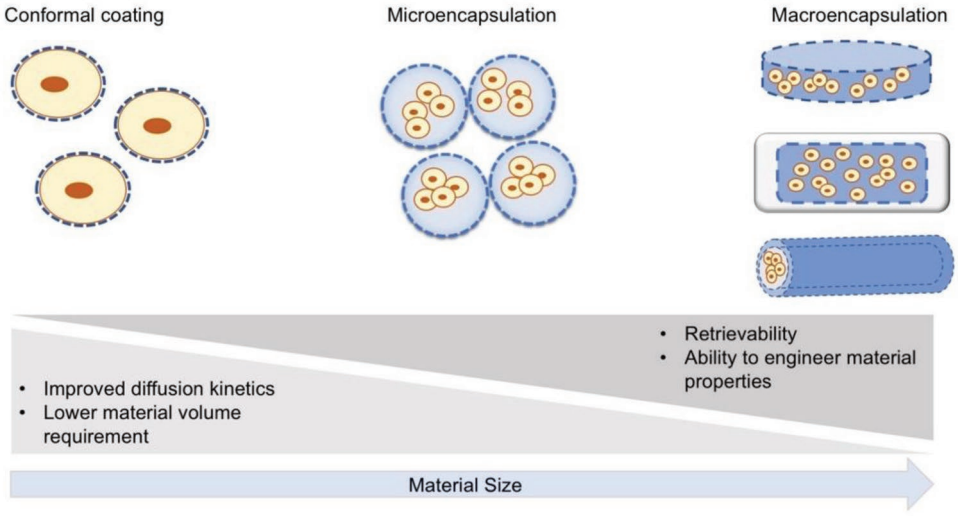

Figure 5. Biomaterial strategies vary for the delivery of cells secreting therapeutic proteins in terms of material choice and size. Strategies include (1) conformal coating of thin materials at the surface of each cell, (2) microencapsulation of cells within semipermeable capsules, and (3) macroencapsulation of cells within one larger structure including polymer scaffolds, hollow fibers, and membrane devices.

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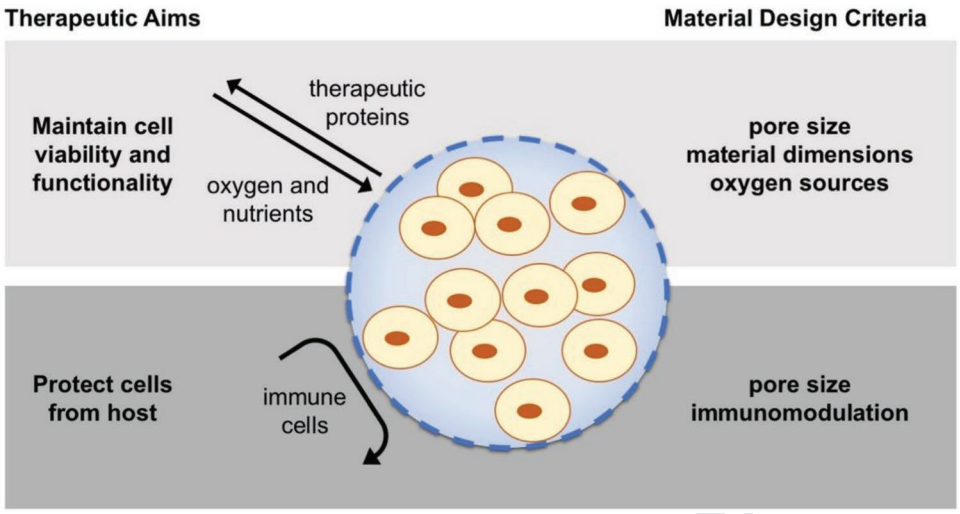

Figure 6. Biomaterial carriers for cell-based therapy aim to maintain cell viability and functionality while protecting cells from the host immune system. Critical design criteria include pore size, material dimensions, and oxygen sources to maintain cells and pore size and immunomodulation for immunoprotection.

the protection of cells from the host environment and immune system while maintaining access to nutrients and oxygen (**Figure 6**). Protection from the host is particularly important for cells which are not genetically matched to the recipient as they can be rejected by the immune system.[114] Some strategies for differentiating iPSCs toward patient-specific therapeutic cells are under development but these cells may still require protection from the immune system.[97,115] To protect and support cells, important material design criteria include pore size, material dimensions, and oxygen sources.[116] Additionally, precision biomaterials can be designed to incorporate bioactive components to improve cell functionality,[117] promote host vascularization for increased oxygen supply,[118,172] and modulate the host immune system.[6b]

3.2.1. Microencapsulation

Microencapsulation is a common strategy for isolating therapeutic cells from the host with a semipermeable barrier. By tuning the porosity of the material through polymer molecular weight, polymer chemistry, and crosslinking conditions, immune cells can be excluded while maintaining therapeutic delivery and supporting cell viability and functionality.[119] The design of cell-encapsulating microcapsules varies in terms of material selection (**Table 2**) and desired physical properties like size and permeability.[7c,132]

Alginate microcapsules are most commonly used to isolate cells within a semipermeable membrane for therapeutic delivery (**Figure 7**a). They are sufficiently porous to allow for the

Table 2. Materials for microencapsulated cell-based therapeutic delivery.

Material	Application	Therapeutic	Cell types	Design components investigated
Alginate	Diabetes	Insulin[120]	Islets,[120a–c,e–h] CM cell line,[120d] hESC-derived beta cells[120i]	Polycation coating,[120a–d,h] PEG coating,[120c,d,f] capsule size effects,[120g,h] immunosuppression[120e,f]
	Cancer	Cytokines,[121] angiogenesis inhibitors,[106a,b,107,121b,122] antibodies,[108c,d] nitric oxide generating enzymes,[106d] tumor suppressive proteins[123]	Genetically engineered cell lines	Polycation coating[106a,d,107,108c,d,121,122]
	Neurodegenerative diseases	Glucagon-like peptide-1 (GLP-1),[105a,124] ciliary neurotrophic factor (CNTF),[102b] VEGF[102c,d]	Genetically engineered cell lines,[102b–d] genetically engineered MSCs[105a,124]	Polycation coating[102c,d]
Cellulose	Cancer	Cytochrome P450 enzyme,[106c,125] antibodies[126]	Genetically engineered cell lines	
	Diabetes	Insulin	Islets,[120h] HIT-T15 cell line[127]	Capsule size effects[120h]
Agarose	Cancer	Cytochrome P450 enzyme	Genetically engineered cell line[128]	Capsule size effects[128a]
	Diabetes	Insulin	Islets[129]	
HEMA-MMA	Neurodegenerative diseases	Dopamine	PC12 cell line[130]	
PEG	Diabetes	Insulin	Islets[131]	

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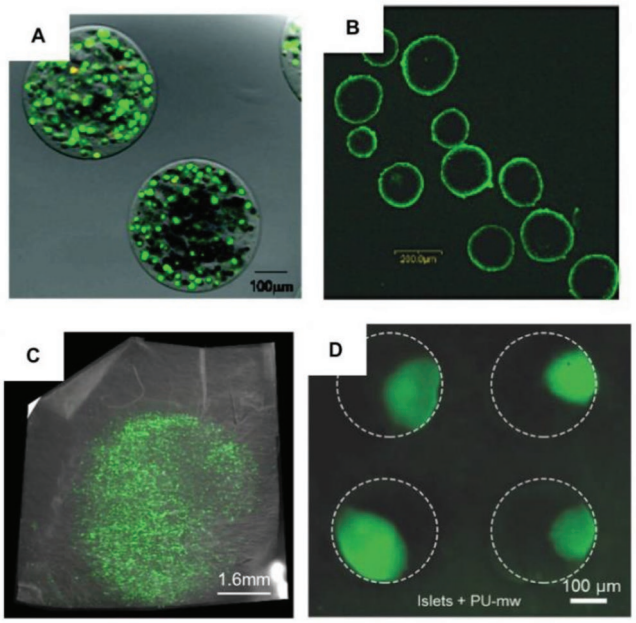

Figure 7. Cells secreting therapeutic proteins can be encapsulated in various biomaterial designs. A) Microencapsulation in alginate coated with PLL (Calcein-AM staining for viability in green). Adapted with permission.[135c] Copyright 2007, American Chemical Society. B) Conformal coating with PEG-lipid (FITC conjugated to PEG-lipid shown in green). Adapted with permission.[148a] Copyright 2007 Elsevier. C) Seeding on electrospun PLA scaffolds (cells expressing GFP, 1.6 mm scale bar). Adapted with permission.[109b] Copyright 2016, Elsevier. D) Seeding on micropatterned polyurethane scaffolds (Calcein-AM staining for viability in green). Adapted with permission.[155c] Copyright 2016, Wiley-VCH.

diffusion of nutrients and therapeutic molecules and can be tuned based on alginate type and molecular weight.[133] In order to limit pore size to reduce the infiltration of immune components, synthetic cationic polymer coatings[7a,134] such as poly-L-lysine (PLL)[135] and poly-L-ornithine[103b,120b,136] are frequently used. Other natural materials beyond alginate used in cell microencapsulation include collagen,[137] cellulose,[106c,126,127] chitosan,[138] and agarose.[129] While these materials are under investigation for a variety of therapeutic applications, alginate remains more prevalent due to its biocompatibility, mild encapsulation process, and availability.[7c]

The use of synthetic biomaterials allows for enhanced engineering of material properties and may avoid issues of natural polymer availability. While the flexibility to engineer specific properties is attractive, synthetic materials often require harsh procedures to encapsulate therapeutic cells leading to lower cell viability.[7c] PEG is one of the more commonly used synthetic polymers for cell microencapsulation.[131,139] An advantage of PEG-based microcapsules is the feasibility of surface modification to improve functionality of the encapsulated cells[140] or alter the host immune response.[141] Alternative synthetic polymers currently under investigation for microencapsulation include polyacrylates such as hydroxyethyl methacrylate-methyl methacrylate (HEMA-MMA).[142]

Beyond polymer selection, the biomaterial design must be tuned for the desired physical properties.[119] Permeability can be measured using a number of different techniques to evaluate how pore size and material chemistry impact the exclusion of particular molecules.[143] However, the ideal pore size to maintain cell functionality and exclude necessary immune molecules remains under investigation. While pore size optimization is critical for protection of therapeutic cells from some immune components, this strategy can be combined with immunomodulation for more complete isolation from immune activity.[144]

To optimize capsule size, several groups are working to make small capsules (<0.4 mm) for improved diffusion kinetics of therapeutic proteins, oxygen, and nutrients.[120h,128a] Cells in the center of microcapsules may suffer from a lack of oxygen availability, particularly in oxygen-limited transplant sites, resulting in hypoxic stress or death.[145] However, a study on the effects of implantable material size showed that alginate microcapsules with diameters of 1.5 mm or higher resulted in a significantly lower inflammatory response after implantation in both an immunocompetent mouse model and in nonhuman primates compared to conventional 0.5 mm capsules.[120g] Therefore, microcapsule size must be selected based on therapeutic site and application in order to determine the optimal balance of transport properties, inflammatory response, and transplant volume requirements.

3.2.2. Conformal Coating for Improved Transport Properties

While microcapsules have shown some success for therapeutic delivery, applying material coatings at the surface of cells may lead to further improvements in transport properties and reduced transplant volumes.[146] Cell surface coatings could allow for a greater variety of delivery sites and methods due to lower material volumes.[147] A number of strategies for coating cell surfaces with thin materials, also known as conformal coating, are in development with emphasis on the field of islet transplantation.[148]

Conformal coating strategies often involve coupling polymer layers to the cell surface, known as layer-by-layer coating, to ensure complete coverage.[149] To avoid direct interaction between potentially cytotoxic polymers and the cell membrane, PEG-lipids can be attached to the cell surface through hydrophobic interactions (Figure 7b)[150] which may be followed by layer-by-layer membrane formation.[148a,e] Conformal coatings have shown success in protecting cells from inflammatory immune activity when compared to uncoated cells. Several of these coating strategies also provide opportunity to introduce material functionalities at the cell surface for improved immunomodulation and therapeutic cell functionality.

3.2.3. Macroencapsulation for Retrievability and Controlled Membrane Design

An alternative to delivering many conformally coated cells or microcapsules is to design a single, larger device to house and protect cells. Macrodevices generally allow for improved control over pore size and membrane properties compared to microcapsules and conformal coatings. Larger devices also allow for retrieval in the event of unexpected negative effects or reduced

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cell function over time.[7a] These devices are designed in the form of semipermeable scaffolds (Figure 7c), membranes, or fibers (**Table 3**). Development of new microfabrication techniques has allowed for improvements such as precise control of membrane pore size and cell patterning in encapsulation devices (Figure 7d).[155]

For macroencapsulation, a range of materials have been used including synthetic polymers and inorganic materials. Synthetic materials are often used for macrodevice design due to their batch-to-batch consistency and for the ability to engineer their properties.[7c] Polymer scaffolds are often fabricated from PEG-based materials as they are biocompatible and allow for rapid diffusion.[117a,162] However, further materials engineering is necessary to protect cells from host immune responses in these scaffolds.[141] In contrast to microencapsulation, many macrodevices are manufactured prior to loading cells, allowing for a variety of material and solvent choices and harsher processing conditions.[7c]

Macroencapsulation in fibers enables the formation of a semipermeable chamber, often loaded with cells encapsulated in a hydrogel to maintain biocompatibility. Materials for hollow fibers are most commonly poly(acrylonitrile vinyl chloride) (PAN-PVC)[103a,158] and polyethersulfone (PES).[104a,108a] Many macrodevices consist of a cell-loaded chamber which is separated from the host by one or more semipermeable membranes. For these membranes, PCL[159,160] and polytetrafluoroethylene (PTFE)[161c] have been commonly used for their ability to be vascularized and apparent biocompatibility.[160b,163] One promising recent design for improved immunoprotection utilizes a nanoporous PCL membrane with tightly controlled pore size.[93a,160b] The nanoporous membrane keeps cytokines from reaching and damaging encapsulated cells while maintaining glucose-responsive insulin delivery from the device.

Macrodevices are frequently designed for their ability to be retrieved and refilled when needed. Retrievability is critical when therapeutic delivery is no longer required for the patient, cells show reduced functionality over time, or any unexpected negative effects are observed.[7a] Some macrodevices are designed to improve retrievability of microcapsule designs by placing capsules within larger polymer scaffolds or devices.[164] One recent device engineered for improved retrievability is the thread-reinforced alginate fiber for islets encapsulation (TRAFFIC) device.[165] Another study is working to make microneedle patches which can be easily applied and removed for the delivery of insulin-secreting cells within alginate microcapsules.[166]

3.3. Precision Biomaterials with Additional Bioactivity

Beyond material strategies for cell isolation, precision biomaterials may be designed with further functionalities in order to respond to the needs of a patient. For example, materials can be engineered to include bioactive components which promote cell functionality over the course of therapy.[117] In the context of diabetes, glucagon like peptide-1[117a,c] and insulin-like growth factor-2[117b] can be immobilized on materials for their ability to promote insulin secretion and inhibit apoptosis of islets. Other biomaterials have been designed to interact with the host in order to improve oxygen supply and to modulate the host immune system.

3.3.1. Improving Oxygen Supply

Biomaterials can be designed to address the challenge of limited oxygen supply for encapsulated cells. This hypoxia

Table 3. Materials for macroencapsulated cell-based therapeutic delivery.

Device type	Material	Application	Therapeutic	Cell type
Polymer scaffold	PLA	Cancer	Tumor necrosis factor-α-related apoptosis-inducing ligand (TRAIL)	Genetically engineered MSCs[109b]
		Diabetes	Insulin	Islets[151]
	PEG-heparin	Cancer	Antibodies	Genetically engineered MSCs[108b]
	PEG	Diabetes	Insulin	Islets,[117a] RIN-m5F cell line,[117a] MIN6 cell line[152]
	Collagen/alginate	Diabetes	Insulin	Islets[153]
	PLGA	Diabetes	Insulin	Islets[154]
	Polyurethane	Diabetes	Insulin	Islets,[155c] MSCs[155c]
Hollow fibers	PES	Cancer	Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Genetically engineered cell line[108a]
		Neurodegenerative	CNTF	Genetically engineered cell line[104a,156]
	PAN-PVC	Neurodegenerative	Dopamine,[103a] NGF,[157] CNTF[104b]	PC12 cell line,[103a] genetically engineered cell line[104b,157]
		Diabetes	Insulin	Islets[158]
Membrane devices	Polypropylene membrane	Neurodegenerative	Anti-amyloid β antibodies	Genetically engineered cell line[102a]
	PCL membrane	Neurodegenerative	Dopamine	PC12 cell line[159]
		Diabetes	Insulin	hESC-derived beta cells[160]
	Silicon membrane	Diabetes	Insulin	Islets[155a,b]
	PTFE membrane	Diabetes	Insulin	Islets[161]

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can cause detrimental effects on cell behavior or lead to cell death.[167] Cells in the core of encapsulation devices may be exposed to particularly low oxygen levels, resulting in reduced secretion of therapeutic proteins due to changes in metabolic behavior.[145,168] Strategies to improve oxygen availability include delivering oxygen to the device,[161b,169] designing oxygen-generating materials,[99b,170] and promoting vascularization by the patient after material implantation.[118,171–173]

Vascularization can be achieved through the design of precision biomaterials to recruit host vascular cells. Recent work on promoting vascularization includes vascular endothelial growth factor (VEGF) delivery from[118,172] or immobilization to[173] encapsulation materials. In one vascularization strategy, a PEG hydrogel was designed to release VEGF on-demand as host cells infiltrate and cause proteolytic degradation.[172] Functionalization with VEGF and RGD to promote host cell adhesion led to improved vascularization and encapsulated cell function. An important consideration, however, is that many of these vascularization approaches require immunosuppression to keep the device from being rejected since they promote interaction with host cells.[7a]

3.3.2. Immunomodulation

The host response to transplanted cells is a significant issue for cell-based therapeutics which can involve both blood-mediated inflammation and activation of immune cells. Blood coagulation and complement activation are early blood inflammatory responses with particular relevance to encapsulated cell therapies. These processes signal for inflammatory immune cell recruitment leading to cytotoxic inflammation.[119] These responses are mainly implicated in the blood, but proteins from these cascades are also present in fluid in the peritoneal cavity, a common transplant site for cell therapies.[174] Early cell death in islet transplantation has been linked to blood-mediated inflammatory processes, particularly when islets are exposed to blood through portal vein delivery.[175] To prevent these processes, soluble inhibitors like heparin can be given systemically to prevent protein adsorption to transplant materials. However, systemic administration comes with dangerous side effects due to the inhibition of critical processes including blood clotting.[176]

As an alternative to delivering soluble anticoagulants, biomaterials can be used to immobilize molecules onto cell surfaces to disrupt the blood-mediated inflammatory cascades.[177] Cabric et al. immobilized heparin to islets by coating their surfaces with biotin and avidin followed by heparin conjugation.[178] Cells can also be coated with PEG-lipids followed by functionalized layer-by-layer coatings to disrupt inflammation. In one study, biotinylated PEG-lipid enabled layer-by-layer coating with streptavidin and biotin-bovine serum albumin (BSA) to form a stable membrane around cells.[179] Heparin and urokinase, an enzyme involved in the breakdown of blood clots, were then attached to the surface. Complement receptor 1 (CR1) has also been conjugated to islet surfaces using the PEG-lipid approach to inhibit adsorption of complement proteins and therefore protect against complement mediated toxicity.[180]

The early response by the host immune system can involve the release of harmful inflammatory molecules and cell attachment to the implanted material, leading to the inability of the encapsulated cells to properly function. Several strategies exist for mitigating inflammatory events for encapsulated cells.[6b,114] Extending from the use of systemic immunosuppressive drugs for improved islet transplantation, anti-inflammatory molecules can be incorporated in encapsulation approaches. These molecules can be coencapsulated with therapeutic cells for localized delivery to avoid side effects associated with systemic administration.[164,181] Several materials strategies are under development to further control the activity of anti-inflammatory molecules, including loading into biodegradable microspheres[154] for extended release and incorporating in polymer coatings for localized suppression of inflammation.[120f]

Cytokines can also be locally delivered from biomaterials to lessen inflammation. For example, release of CXCL12, a protein known to inhibit inflammatory immune cell recruitment, supported encapsulated islet function long-term without systemic immunosuppression.[120e] In addition to releasing drugs and cytokines for immunomodulation, materials can be designed to present immunoregulatory molecules on their surfaces. For instance, pro-inflammatory cytokines can be sequestered at the material surface using cytokine-binding peptides to prevent harmful effects to the encapsulated cells.[141b,153a] Similarly, a peptide inhibitor of interleukin-1 (IL-1) receptor covalently attached to hydrogels was shown to improve encapsulated cell viability when exposed to toxic inflammatory cytokines.[153b]

Due to their role in response and destruction of cell transplants, several approaches aim to locally influence immune cell behavior. Certain ligands which direct T cell functions can be incorporated into biomaterials to protect encapsulated therapeutic cells.[101] For example, Fas ligand was shown to induce apoptosis in T cells when immobilized on PEG hydrogels, resulting in improved functionality of the encapsulated islets.[182] In contrast to these effector T cells, regulatory T cells (Tregs) are known to reduce inflammatory cytokine levels and suppress the inflammatory host immune response. To recruit Tregs to the cell transplant site to inhibit inflammation, certain ligands can be incorporated into encapsulating biomaterials. In one approach, JAG-1 was immobilized on the surface of islets through PEG coupling to promote Treg-mediated anti-inflammatory activity.[183] Tregs have also been codelivered with therapeutic cells for their anti-inflammatory activity.[184] Additionally, chemically modified alginates have been used for microencapsulation to reduce immune cell-mediated inflammation.[185] These materials showed limited inflammation upon implantation in both rodents and nonhuman primates and allowed for long-term blood glucose control when encapsulating stem cell-derived insulin-producing cells.[120i]

4. Biomaterials for Cell-Based Immunotherapy

Adoptive cell therapy is a strategy in cancer treatment in which immune cells with anticancer functionality are delivered to patients. Immune cells can be isolated from a patient, activated or engineered for tumor-specific activity, expanded, and delivered back to the patient for personalized therapy (**Figure 8**).

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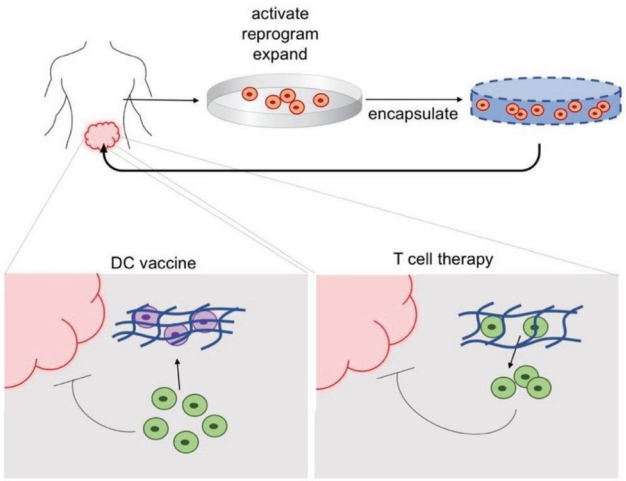

Figure 8. In cell-based immunotherapy, immune cells can be isolated from the patient, activated or engineered for tumor-specific activity and expanded. By encapsulating the immune cells in a biomaterial, they can be delivered to the site of the tumor to initiate a localized, tumor-specific immune response. With DC vaccines, DCs can recruit and activate T cells to the material for tumor cell killing. In adoptive T cell therapy, T cells can traffic out of the biomaterial and directly kill tumor cells.

Dendritic cell (DC) vaccines use DCs as therapeutics in order to present antigen to and activate effector immune cells like T and B cells. DCs can be expanded and loaded with antigens of interest ex vivo and then administered to patients.[9a] In adoptive T cell therapy, T cells can be expanded and selected for the ability to recognize relevant tumor antigen ex vivo, allowing for a large number of cells to be administered to the patient. T cells can also be engineered to express relevant T cell receptors or chimeric antigen receptors (CARs) to target certain tumor types through antigen recognition.[9b] For both DC vaccines and T cell therapy, challenges include targeting the immune cells to the tumor site and maintaining cell viability. By incorporating these cells within a biomaterial, they can be delivered to a specified location along with other factors to support their viability, proliferation, and functionality (Figure 8, **Table 4**).[193]

4.1. Dendritic Cell Vaccines

DC vaccine delivery with a biomaterial was first demonstrated with an injectable alginate hydrogel in 2008.[186] Alginate was selected for its biocompatibility, mild ionic crosslinking, and ability to bind cytokines. These hydrogels were made by mixing an alginate solution with alginate microspheres containing calcium ions for in situ gelation. By varying the amount of calcium microspheres used, the gelation time and mechanical properties could be tuned. The alginate hydrogel enables the creation of a localized inflammatory microenvironment by binding DC-secreted factors for T cell activation and recruitment. The authors further engineered the hydrogel to release cytokines for enhanced immune cell recruitment leading to suppressed melanoma tumor growth.[187] While alginate hydrogels have shown promise for DC vaccine delivery, a material which can degrade over time may be desirable for some applications. Fibrin hydrogels have been used for DC delivery due to their ability to degrade as immune cells infiltrate.[189] With biomaterial-based strategies, DCs can activate host immune cells and inhibit tumor growth even when exposed to immunosuppressive factors which typically impede vaccine efficacy. Therefore, biomaterial enabled DC vaccines may hold promise for localized cancer immunotherapy with improved efficacy and lowered systemic toxicity.

Table 4. Materials for cell-based immunotherapy.

Material	Cell type	Properties
Alginate	DCs	Injectable,[186] injectable with cytokine delivery[187]
	T cells	Implantable with cell adhesion peptides and antibody-coated microparticles for cytokine[188] or toll-like receptor ligand delivery[6a]
Fibrin	DCs	Biodegradable[189]
Chitosan	T cells	Injectable and biodegradable[190]
Agarose	Macrophages	Injectable with agarose microspheres[191]
PIC	T cells	Injectable with integrin binding peptides[192]

4.2. T Cell Therapy

Adoptive T cell therapy was first enabled by a biomaterial in 2014 with PEG-*g*-chitosan hydrogels.[190a] These in situ-forming hydrogels were designed to gel at body temperature for injectable delivery. By adjusting the amount of PEG and chitosan used in hydrogel formation, the pore size was optimized to allow for outward T cell trafficking over time. When exposed to glioblastoma cells, T cells were able to escape the hydrogel and kill the cancer cells. Implantable scaffolds can also be used for T cell therapy and could be particularly advantageous at the site of unresectable tumors or after tumor resections to reduce relapse. In order to support T cell migration and proliferation for these applications, implantable alginate hydrogels were functionalized with adhesion peptides.[188] Silica microparticles containing cytokines and adjuvants were coated with T cell antibodies and incorporated into the alginate hydrogels to promote T cell activation. In an advanced stage ovarian carcinoma mouse model, implantation of these T cell-loaded hydrogels resulted in tumor regression despite the immunosuppressive tumor microenvironment. Another recent approach for T cell delivery is a hydrogel made from tri-ethylene glycol-substituted polyisocyanopeptide (PIC) polymers with azide click handles for easy functionalization.[192] Functionalization could allow for long-term, localized presentation of stimulatory molecules instead of relying on diffusion of encapsulated molecules over time.

By supporting T cell survival and tumor site localization, biomaterials may reduce cell number requirements for administration, a major hurdle to translation of adoptive cell therapies.[194] Additionally, biomaterials can be used during the cell culture and expansion process to generate sufficient cell numbers for therapy. PIC hydrogels were used for improved expansion of activated T cells in 3D matrices as compared to typical 2D expansion[192] and scaffolds formed from lipid bilayers on mesoporous silica microrods enabled expansion by mimicking the behavior of antigen-presenting cells.[195]

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5. Conclusion

Cell therapies have been explored for a wide range of indications due to their innate ability to interact with and respond to their microenvironment. Their capacity to proliferate and differentiate has promise for use in the repair and regeneration of tissue. Their ability to secrete proteins in response to molecular cues makes them attractive for dynamic, long-term therapeutic delivery. Finally, their ability to communicate with surrounding cells allows them to orchestrate an antitumor immune response. For all of these applications, biomaterials may extend therapeutic utility by improving cell viability and functionality and localizing therapeutic action. Furthermore, precision biomaterials can be designed with additional functionalities in order to respond to the therapeutic needs of individual patients.

Biomaterial strategies have already shown great promise in supporting therapeutic cells toward clinical translation. However, clinical application can be limited by the cost and difficulty of cell isolation, expansion, and engineering prior to patient administration.[196] FDA approval can also pose a significant challenge to biomaterial-based cell therapies as both materials and cells need to meet FDA standards.[197] In particular, materials other than those already approved for use in humans have extensive requirements in quality control and safety.[198] When combining cells and materials, considerable animal and clinical testing is required which comes with high costs and lengthy development timelines.[198] New techniques in materials engineering and characterization along with improved understanding and control of therapeutic cell functionalities will therefore be critical for approval and translation. The opportunities for combination approaches are tremendous and should motivate the field to push past regulatory barriers, especially with growing interest in personalized therapeutic approaches.

In the coming years, many more cell therapies are expected to move toward clinical translation with the support of engineered biomaterials. As interest in biomaterials for personalized medicine grows,[4a,b] we expect that these approaches will become more sophisticated and personalized in nature. In particular, engineering new functionalities into cells with synthetic biology presents a variety of new therapeutic possibilities. Cells can be engineered to respond to an array of signals through complex gene circuits, resulting in therapeutic action that can be individualized to a patient.[113b] We believe that advances in cell engineering and precision biomaterial design will continue to drive new, personalized cell therapies for the treatment of a broad set of indications.

Acknowledgements

A.L.F. and L.R.V. contributed equally to this work.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

biomaterials, cell therapy, drug delivery, immunotherapy, personalized medicine, regenerative medicine

Received: March 29, 2019
Revised: July 26, 2019
Published online:

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