

# Applications of biomaterials in regenerative medicine

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Biomaterials play a pivotal role in the field of regenerative medicine especially in the replacement of damaged tissues and organs as well as the treatment of chronic diseases to restore normal body function [1,2]. Recent advances in biochemistry, molecular biology, engineering and material sciences have provided wider opportunities for their clinical use. In tissue regeneration, biomaterials usually act as a scaffold to provide the structural support for both cell adhesion and tissue development. They resemble an extracellular matrix (ECM), which is naturally secreted by resident cells to support the surrounding tissues and organs [3]. ECM generally consists of cell adhesion proteins (e.g., laminin and fibronectin), structural proteins (e.g., elastin and collagen), and glycans (e.g., glycosaminoglycans (GAGs) and proteoglycans) [4]. It affords not only spatial organization and physical support, but also a physiological microenvironment that sustains normal cellular functions. Additionally, ECM also contributes to biophysical cues as well as various molecular and signalling events to maintain the cell morphology and phenotype. In response to microenvironmental changes such as mechanical stimuli and all other factors that control the physiological niche (e.g., oxygen and nutrient concentrations), ECM would undergo extensive remodelling [5]. Degradation of the matrix would negatively affect cellular functions including cell growth, survival and differentiation. Therefore, biomaterials have been largely developed to mimic the native structure and composition of ECM and provide structural and functional support to the cells especially for re-growing or regenerating damaged tissues in clinical settings [6].

Natural hydrogels include (i) natural polymers such as chitosan and silk, (ii) ECM proteins such as collagen and elastin, and (iii) ECM originated from various tissues which are subject to decellularization such as dermis, intestinal submucosa and bladder matrix [7]. These materials offer several advantages such as excellent biodegradable and biocompatible, and high flexibility, which possess the capability of changing shape and size to promote the growth of engineered tissue within the surrounding tissues. While most natural hydrogels have attracted much scientific interest due to their inherent outstanding properties, synthetic hydrogels such as polyethylene glycol (PEG) offer more advantages, which include the large-scale production capability and highly tunable physical and mechanical properties, making them significantly useful for 3D cell culturing and tissue engineering [1]. The ability of tuning the properties of hydrogel advances the understanding of interactions between cells and synthetic substrates and recapitulates many of the healthy tissues and disease models. This ability would eventually improve the efficiency of tissue regeneration. Selected commercially available biomaterials are highlighted in Table 1 whereas a number of existing biomaterials for regenerative medicine applications are summarized in Table 2.

To date, multiple challenges are yet to be addressed to translate the existing synthetic biomaterials into practical applications. While

being biocompatible, most synthetic hydrogels are synthesized under harsh chemical conditions [8]. The procedures require extra care to ensure that unreacted reagents are ultimately removed to avoid cross-contaminations. Additionally, the capability of some hydrogels to achieve the dynamic and heterogenous nature of the native cellular microenvironment remains elusive [3]. To this end, a variety of manufacturing and processing techniques are being adapted for the synthesis of biomaterials with desirable features and functionality in a safely manner.

Moreover, the use of photochemical reactions to create dynamic microenvironment of hydrogel shows potential in regenerative medicine as these reactions can be conducted in a precise three-dimensional space at user-defined time [9]. The spatiotemporal control over chemical reactions can also be performed to achieve optimum functionality of hydrogel [10]. In addition, it is essential to elucidate the molecular pathways between the cells and biomaterials. Studying the mechanism and signalling pathways will review important insights into developing new biomaterials for a more defined cellular response, resulting in a more controlled and efficient tissue regeneration [11].

Even though the structural, mechanical and biochemical properties of native ECM permit the development of new types of tissue-engineered constructs, the properties of existing synthetic scaffolds fall short of the criteria for the development of a complex human tissue [12]. This is because of the inability to control all the technical parameters, which limits the study of scaffolds *in vivo*. In addition, the precise regulation of physiological processes in biomaterials remains a key challenge. It usually includes the process of bioactivation that is normally achieved through the integration of key biomolecules and signals that direct the cells and tissues *in vivo* [13]. After seeding the cells into hydrogels, the changes in cell behaviour should be monitored periodically in the synthetic microenvironment. The manipulations or signals being introduced should also be tracked while observing the changes in cellular behaviour. In fact, the resulting biomaterials must be both efficacious and cost-effective to be translated into clinical applications. This could lead to an ineluctable dichotomy between the ease and simplicity of scaffold production, and the demand for an appropriate sophistication level by integrating complex yet useful information into scaffold.

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**Received:** March 04, 2019; **Accepted:** March 18, 2019; **Published:** March 21, 2019

**Table 1.** Selected commercially available biomaterials for regenerative medicine.

Product	Tissues/ Organs	Description	Company
AlloDerm®	Skin	Acellular dermal matrix for soft-tissue augmentation and replacement	LifeCell Corp.
Apligraf®	Skin	Allogeneic fibroblasts on a bovine collagen I matrix with upper keratinocyte cell layer	Organogenesis
Dermagraft®	Skin	Allogeneic fibroblasts on a vicryl mesh scaffold	Shire Regenerative Medicine, Inc
GraftJacket®	Skin	Acellular dermal matrix for soft-tissue augmentation and chronic wound treatment	Wright Medical Technology Inc.
TransCyte®	Skin	Allogeneic fibroblasts on a nylon mesh with upper silicone layer	Shire Regenerative Medicine, Inc
Oasis® Wound Matrix	Skin	Decellularized porcine small intestinal submucosa	Cook Biotech
Integra® Bilayer Wound Matrix	Skin	Type I bovine collagen with chondroitin-6-sulfate and silicone	Integra Life Sciences
Epicel®	Skin	Autologous keratinocyte cell sheets	Genzyme
Carticel®	Cartilage	Autologous chondrocytes	Genzyme
NeoCart®	Cartilage	Autologous chondrocytes on type I bovine collagen	Histogenics
VeriCart™	Cartilage	Type I bovine collagen	Histogenics
AlloMatrix®	Bone	Demineralized bone matrix combined with calcium sulfate	Weight Medical Technology Inc.
Osteoecel® Plus	Bone	Allogeneic bone with mesenchymal stem cells	NuVasive
Pura-Matrix™	Bone	Hydrogel composed of a self-assembling peptide	3DMatrix
Osteoscaf™	Bone	Poly(lactic-co-glycolic acid) and calcium phosphate scaffold	Tissue Regeneration Therapeutics
INFUSE® bone graft	Bone	Recombinant human bone morphogenetic proteins-2 in combination with bovine type I collagen	Medtronic
Lifeline™	Blood vessels	Autologous fibroblast tubular cell sheet integrated with endothelial cells	Cytograft Tissue Engineering
Omniflow®	Blood vessels	Polyester mesh with cross-linked ovine collagen	Binova
Anginera™	Heart	Allogeneic fibroblasts on vicryl mesh	Theregen
CardioValve® SynerGraft Pulmonary Heart Valve	Heart	Decellularized allogeneic pulmonary valve	Cryolife

**Table 2.** Selected biomaterials in research and development for regenerative medicine applications

Tissues/Organs	Cell types	Types of hydrogels	Applications	References
Bone	Osteoblasts	Poly(ethylene glycol) (PEG), poly(ethylene glycol) poly (lactic acid) (PEG-PLA)	Drug delivery, cell encapsulation, scaffold for bone regeneration	[15,16]
Heart	Bone marrow cells, embryonic stem cells, cardiomyocytes	Fibrin, PEG, alginate, hyaluronic acid (HA), superabsorbent polymer (SAP)	Scaffold for heart tissue engineering	[17,18]
Cartilage	Chondrocytes	Fibrin, PEG, SAP	Drug delivery, cell encapsulation, scaffold for cartilage regeneration	[19-21]
Eye	-	HA	Corneal transplantation	[22]
Skin	Fibroblast	Collagen, fibrin, HA	Abdominal wall, ear, nose and throat reconstruction, grafting	[23,24]
Blood vessels	Stem cells, endothelial cells	PEG, alginate, HA	Vascular grafting	[25,26]

More attention should also be paid to the microfabrication technologies that afford an abundance of potential sizes, shapes, porosities, and architectures to create a complex functional engineered tissue or organ for practical use [14]. Integrating the latest biological knowledge and new structural, physical and chemical insights into biomaterials along with a deep understanding of their roles in tissue regeneration are imperative to bridge the gaps in the scientific field. The recent advances in synthetic technology will ultimately yield new generations of multi-functional biomaterials, which could potentially open new approaches in the rapid growing field of regenerative medicine.

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