Carbohydrate Polymers 116 (2015) 267–277

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Polysaccharide-based strategies for heart tissue engineering

Amanda K. A. Silva[a,b], Maya Juenet[b,c], Anne Meddahi-Pellé[b,c], Didier Letourneur[b,c,*]

[a] Laboratoire Matière et Systèmes Complexes, UMR 7057 CNRS, Université Paris 7, 10 rue Alice Domon et Léonie Duquet, F-75205 Paris Cedex 13, France
[b] Inserm, U1148, Cardiovascular Bio-Engineering, X. Bichat Hospital, 46 rue H. Huchard, F-75018 Paris, France
[c] Université Paris 13, Sorbonne Paris Cité, F-93430 Villetaneuse, France

ARTICLE INFO

Article history:
Received 9 January 2014
Received in revised form 6 June 2014
Accepted 7 June 2014
Available online 16 June 2014

Chemical compounds studied in this article:
Alginate (PubChem CID: 6850754)
Dextran (PubChem CID: 71315856)
Chitosan (PubChem CID: 71853)
Hyaluronic acid (PubChem CID: 24759)
RGD peptide (PubChem CID: 104802)
Fibroblast growth factor (PubChem CID: 5486993)

Keywords:
Polysaccharides
Heart tissue engineering
Scaffolds
Cardiac patch

ABSTRACT

Polysaccharides are abundant biomolecules in nature presenting important roles in a wide variety of living systems processes. Considering the structural and biological functions of polysaccharides, their properties have raised interest for tissue engineering. Herein, we described the latest advances in cardiac tissue engineering mediated by polysaccharides. We reviewed the data already obtained *in vitro* and *in vivo* in this field with several types of polysaccharides. Cardiac injection, intramyocardial *in situ* polymerization strategies, and scaffold-based approaches involving polysaccharides for heart tissue engineering are thus discussed.

1. Introduction

Polysaccharides are long carbohydrate molecules which contain repeated monosaccharide units joined together by means of glycosidic bonds. Polysaccharides constitute the most abundant biomolecules in nature and they present essential roles in a wide variety of living systems processes (Muthana, Campbell, & Gildersleeve, 2012; Nitta & Numata, 2013; Oh, Lee, & Park, 2009). Polysaccharides are molecules that display high biocompatibility and biodegradability. They can be classified according to their origin: vegetal origin (*e.g.* pectin), algal origin (*e.g.* alginate), microbial origin (*e.g.* dextran, xanthan gum), and animal origin (chitosan, heparin) (Sinha & Kumria, 2001). Polysaccharides may also be classified as a function of their charge: cationic (chitosan), anionic (hyaluronic acid, heparin) and nonionic (dextran). Most natural polysaccharides present groups such as hydroxyl, carboxyl and amino groups (Quignard, Di Renzo, & Guibal, 2010), which easily enable their chemical modifications.

Considering the structural and biological functions of polysaccharides, it is reasonable to consider the interest in exploiting them for cardiac tissue engineering. In fact, biomaterials exhibiting both mechanical and biochemical functions may contribute to tissue engineering and are worthy of development (Chi, Yang, Chung, Chou, & Wang, 2013). Additionally, polysaccharides meet several criteria for an eligible biomaterial for tissue engineering, which include biocompatibility, biodegradation, and the ability to deliver and foster cells (Silvestri, Boffito, Sartori, & Ciardelli, 2013). It is important to highlight that the concept of the ideal biomaterial relies not only on its chemical constitution but also on macroscopic structural features. The biomaterial scaffold should present a porous structure to enable mass transport (permeability and diffusion) (Hollister, 2005). Besides, the biomaterial design should attempt to reproduce the organizational, mechanical, and elastic properties of native tissues, which is even more important for vital and highly specialized tissues, such as the cardiac one (De Mulder, Buma, & Hannink, 2009; Engelmayr et al., 2008; McDevitt, Woodhouse, Hauschka, Murry, & Stayton, 2003). Therefore, the ideal biomaterial should consist of a structure that support

* Corresponding author at: Inserm, U1148, Cardiovascular Bio-Engineering, X. Bichat Hospital, 46 rue H. Huchard, F-75018 Paris, France. Tel.: +33 1 4025 8600; fax: +33 1 4025 8602.
E-mail address: didier.letourneur@inserm.fr (D. Letourneur).

http://dx.doi.org/10.1016/j.carbpol.2014.06.010
0144-8617/

cells' attachment and growth while facilitating their organization and possibly differentiation toward a highly ordered biomimetic construct (Sokolsky-Papkov, Agashi, Olaye, Shakesheff, & Domb, 2007). The biomaterial should be also a resistant structure prone to withstand the high and permanent mechanical stresses related to cardiac contraction and relaxation. Another major role concerns the integration within the host tissue and eventual progressive replacement by the host extracellular matrix (Giraud, Guex, & Tevaearai, 2012). Additionally, biomaterials should ideally present biological properties that enhance tissue repair. Functions such as angiogenesis, cell recruitment and cardiomyocyte protection may be promising assets to contribute to the treatment of heart disease (Nelson, Ma, Fujimoto, Hashizume, & Wagner, 2011). Last but not least, tissue engineering products must be both efficient and cost-effective by combining functionality and ease of production (Place, Evans, & Stevens, 2009).

Polysaccharides are promising materials for meeting many of the above mentioned criteria for eligible biomaterials for cardiac tissue engineering. In combination with appropriate cells and bioactive molecules, polysaccharides may represent an important asset to promote heart tissue regeneration. In this regard, it is important to mention that regeneration capacity varies between different cell types and also depends on the nature of the tissue as well as the extent of injury or insult. Tissues that are in constant renewing as the skin are capable of regrowth in an important extent. In comparison, the cardiac tissue lacks mechanisms of regeneration in adults (Sokolsky-Papkov et al., 2007). The aim of this paper is to provide an overview of polysaccharide-based approaches for heart tissue engineering. Initially, the general context of tissue engineering is disclosed. It is followed by heart tissue engineering strategies related to xylan, alginate, pullulan and dextran, chitosan and hyaluronan. Finally, challenges in the field are discussed and concluding remarks are presented.

2. The context of heart tissue engineering

Cardiac infarct is followed by a sequence of wound repair processes associated with cell death, inflammation, the formation of granulation tissue (constituted by myofibroblast, macrophage, and collagen), and finally fibrosis. In response to the loss of cardiomyocytes, there is a reorganization of the extracellular matrix for compensation. This remodeling will result in cardiac wall thinning, ventricle dilatation and heart failure (Ertl & Frantz, 2005; Gajarsa & Kloner, 2011; Stefanon et al., 2013; Vilahur et al., 2011). Cardiac cell death, depending on its extent, renders the heart enable to deliver sufficient blood to meet the body's metabolic requirements leading to cardiac failure. After myocardial injury such as following important myocardial infarction, the heart regenerative capacity is overwhelmed (Giraud et al., 2012). Cardiac cell loss requires strategies to repair and regenerate the infarcted area of the myocardium (Jawad et al., 2007). Treatment options may concern approaches ranging from medication to surgical interventions. Most surgical options mainly rely on heart transplants. However, there is a chronic shortage of sources for human donors (Lam & Wu, 2012). In fact, the complex series of events involved in myocardial cell loss, and the subsequent post-myocardial infarction remodeling that result in heart failure are inefficiently addressed by current clinical strategies (Martinez & Kofidis, 2011). Current cardiac tissue engineering research aims to design tissue constructs to support, repair, replace, or enhance the function of injured or diseased myocardial tissue (Venugopal et al., 2013). Initial studies focused on the direct injection of viable cells into the infarcted myocardium tissue, a technique which is termed cellular cardiomyoplasty (Christman & Lee, 2006). The aim was to replace necrotic cardiomyocytes *via* the direct administration of cells from an aqueous cell suspension. It can be performed via intravenous, intracoronary or direct injection into the myocardium. Some improvement in cardiac performance has been observed by using cellular cardiomyoplasty. However, there are several hurdles associated with this technique. Indeed, the technique suffers from limited cell retention and poor cell survival. The results are quite disappointing considering an acute cell retention (within 24 h of delivery) in the heart that is generally <10%, irrespectively to the cell type or the administration route. In this regard, it would be important to gain deeper insight into the mechanisms underlying cell retention following coronary delivery as a function of the time (Dib et al., 2010). A main reason for that relies on the poor cell attachment ability due to the lack of extracellular matrix attached to them (Wang et al., 2008). Therefore, cells are soon washed out *via* the coronary venous system and mechanically ejected, as attested by retention rates in beating hearts markedly lower than in non-beating hearts (Malliaras & Marbán, 2011). It has been reported that cells injected into injured myocardium often relocate to the lungs, spleen, liver, kidneys and non-infarcted cardiac muscle (Hale, Dai, Dow, & Kloner, 2008; Zhang et al., 2007). The long-term engraftment of the remaining fraction of cells is also low. This raises the question concerning the real mechanisms at play. It seems difficult to state that the injected cells effectively contribute to the contractility capacity of the infarct zone. Alternatively, they seem to act mostly as a short-term reservoir of growth factors and cytokines that support the survival of host cells *via* a paracrine effect (Giraud et al., 2012; Nelson et al., 2011). In large panel of actions may be potentially induced *via* paracrine effect, such as angiogenesis (Zhou et al., 2011), pro-survival effect on cardiomyocytes (Kawaguchi et al., 2010), antifibrotic effects (Li et al., 2009), mobilization of endogenous stem cells (Bollini, Smart, & Riley, 2011) and cardioprotective action mediated by an anti-inflammatory effect (Premaratne et al., 2011).

Beyond the paracrine effect, some strategies have been developed in order to improve cell engraftment and enhance cell survival. They rely on the preconditioning of the cells prior to graft *via* heat shock, hypoxia approaches as well as exposition to pro-survival factors and enhancement of the expression of survival factors (Gerczuk & Kloner, 2012; Giraud et al., 2012).

Still concerning cell suspension injection approach, a main limitation is that such strategy relies mainly on the cells to improve cardiac function, without considering biomechanical factor that could be provided from a biomaterial (Wang & Guan, 2010). An alternative strategy involving the use of biomaterials seems to be very promising. This will be further discussed as follows.

Concerning the biomaterial approach, many of the investigated strategies for cardiac repair focused on the application of the biomaterial externally anchored to the myocardium in order to provide support. This is the case of cardiac restraint devices such as the CorCap (Acorn Cardiovascular Inc) and Heart Net (Paracor Medical Inc) that are based on Dacron and nitinol wraps, respectively, in order to mechanically support ventricular wall (Mann et al., 2007; Starling et al., 2007; Topkara, Kondareddy, & Mann, 2009). Additionally, devices such as CardioClasp (CardioClasp Inc) and Myosplint (Myocor Inc) reduce heart wall stress by constraining the dilated ventricle and decreasing intraventricular radius (Fukamachi & McCarthy, 2005; Kashem et al., 2003; Sabbah, 2003).

An alternative strategy to the cardiac restraint devices is the incorporation of the biomaterial within the heart wall in direct contact with cardiac cells. These approaches rely on natural or synthetic materials in an injectable form in combination or not with cells (Fig. 1, first, second and third panels), which are then directly injected *in vivo* (Christman et al., 2004; Zhang et al., 2010). By this way, the emerging field of tissue engineering has begun to provide promising alternatives to cellular cardiomyoplasty. The advantages of such an approach include providing a cell-friendly microenvironment to engrafted cells (Habib et al., 2011).

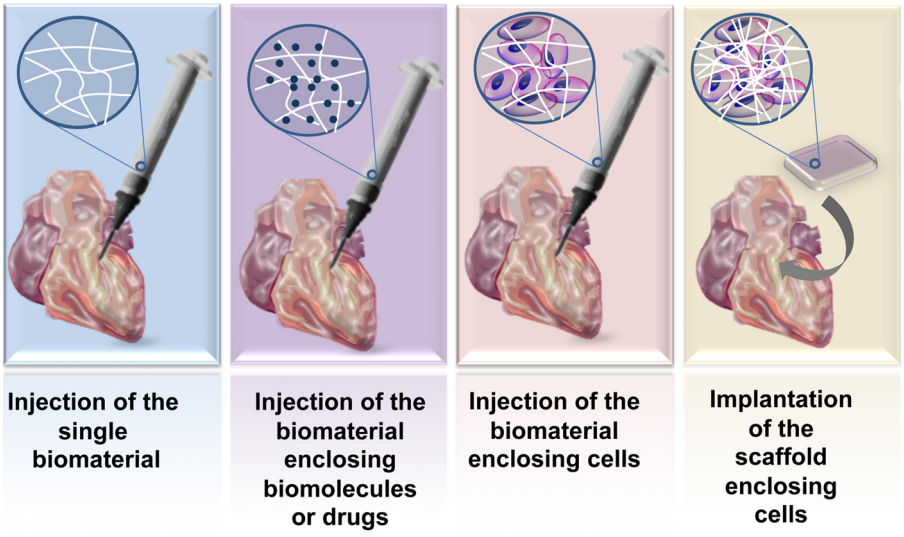

Fig. 1. Polymer-based strategies for cardiac tissue engineering.

Additionally, hydrogels can be tailored in order to deliver cells by minimally invasive catheter-based procedures while enabling high accuracy of the localization of cells at the area of interest (Vunjak-Novakovic, Lui, Tandon, & Chien, 2011). In fact, intramyocardial *in situ* polymerization represents a promising alternative to overcome both leakage and clearance-mediated cell loss and also to address the need for "conditioning" of the immediate cell environment (Davis et al., 2005; Martens et al., 2009). In a related approach, injectable acellular biomaterials can be a strategy to support the heart wall and also for preventing remodeling (Landa et al., 2008). Additionally, this approach may also be of interest for the controlled delivery of therapeutic genes and proteins to ischemic myocardium (Christman & Lee, 2006; Garbern, Minami, Stayton, & Murry, 2011; Wu et al., 2011). In spite of advances in the field, optimal design parameters, including degradation rate and profile, elastic modulus and injectability, largely remain to be fully elucidated. Another important parameter is the effect of the chemical constitution of the material itself (Nelson et al., 2011).

An alternative approach is related to the use of biomaterials to design patches *ex vivo* featuring adapted size and shape and implant them epicardially onto the infarcted tissue (Fig. 1 right panel). Such biomaterials can be loaded with cells and are expected to promote a mechanical reinforcement to the infarct scar to limit ventricular dilation (Leor & Cohen, 2004). It is interesting to highlight that patch-based strategies increase the thickness of the heart wall and by Laplace's law, this increase induces a reduction in the heart wall stress. Even if regeneration does not take place, such an effect may limit ventricular remodeling and improve disease management (Chen, Harding, Ali, Lyon, & Boccaccini, 2008). Although *in vitro*-engineered patches have demonstrated promising results, one main limitation concerns the invasiveness of the implanting technique, which requires surgical intervention. The injectable approach remains minimally invasive, and is therefore more clinically appealing (Christman & Lee, 2006).

In addition to the mechanical support, the biomaterial (in injected form or as a patch) may present intrinsic bioactivity promoting angiogenesis (Garbern et al., 2011) or cell homing (Tsur-Gang et al., 2009). In fact, the biomaterial may act as a niche favoring cellular infiltration of recruited endogenous cells that may potentially improve cardiac function (Johnson & Christman, 2013). Besides, the biomaterial may contribute to reduce border zone extension and limit infarct expansion by another mechanism. Depending on its physical properties, the biomaterial may trap necrotic and apoptotic cells originated from the infarcted area preventing the dissemination of pro-inflammatory danger-associated molecular patterns (DAMPS) into the healthy surrounding tissue (Zouein, Zgheib, Liechty, & Booz, 2012). This mechanism would reduce infarct spread *via* a decrease in surrounding molecular stress, which is highly related to contractile dysfunction due to cardiomyocyte death (Arslan, de Kleijn, & Pasterkamp, 2011). In this regard, several parameters such as degradation time, polymer crosslink density and molecular affinity play an important role in the process of DAMPS retention and alleviation of infarct spread (Venugopal et al., 2012). These different mechanisms of biomaterial contribution to cardiac tissue repair in the context of cardiac infarct processes are shown in Fig. 2.

Biologically derived, synthetic and hybrid materials have been investigated in the context of heart tissue engineering (Nelson et al., 2011). In the next section, examples of these techniques will be detailed concerning polysaccharide materials. Research on other types of polymers falls outside the scope of this review. Herein, we intend to cover the latest advances in cardiac tissue engineering mediated by polysaccharides.

3. Polysaccharide-based strategies for heart tissue engineering

3.1. Xylan

Xylan is an abundant hemicellulose whose chemical structure is mainly composed of D-glucuronic acid, L-arabinose and D-xylose (Fig. 3) (Ebringerová, Hromádková, Kačuráková, & Antal, 1994; Silva et al., 2007). *Eucalyptus globulus* wood, corn cobs, rice husks and barley husks are frequent xylan sources (Parajó, Garrote, Cruz, & Dominguez, 2004). The structural diversity and complexity of xylan depend on the source. Several extraction procedures are suitable for the isolation of xylans originated from diverse botanic sources (Ebringerová & Heinze, 2000). Naturally available xylan hydrogels are of interest considering their renewable character and nontoxic properties but also due to their biocompatibility and biodegradability. Additionally, xylans may present immunomodulatory activity (Ebringerová, Kardošová, Hromádková, Malovı′ková, & Hřı′balová, 2002).

Xylans present special gelling properties for production of hydrogels that can be used as matrices for the controlled release of bioactive agents (Chimphango, van Zyl, & Görgens, 2012). Indeed, hydrogels in general possess a degree of flexibility due to their significant water content and they are promising biomaterials

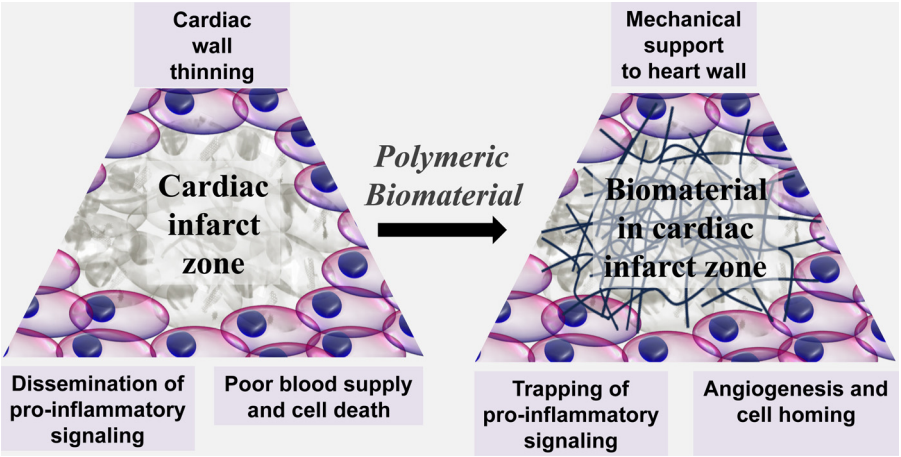

Fig. 2. Processes related to cardiac infarct (left) and the mechanisms of biomaterial interaction with these processes to promote cardiac tissue repair (right).

(Venugopal et al., 2013). Hydrogels are in fact three-dimensional polymer networks swollen by aqueous solvent, which is the major component of the gel system (Chimphango et al., 2012; Silva, Richard, Bessodes, Scherman, & Merten, 2008).

Besides forming hydrogels, xylan may be engineered to design nanofibrous scaffolds. Hybrid xylan/polyvinyl alcohol (PVA) nanofibrous electrospun scaffolds were fabricated and cross-linked with glutaraldehyde. Nanofibers were investigated for culturing rat cardiac cells for cardiac tissue engineering. Such scaffold mimicking cardiac tissue in both stiffness and anisotropy resulted in cardiac cells monolayer interconnection by intercellular junctions, which were well aligned like in native heart tissue (Venugopal et al., 2013). Scaffolds have also been shown to improve cardiomyocytes electrical excitation and formation of gap junction (Black, Meyers, Weinbaum, Shvelidze, & Tranquillo, 2009). Indeed, biomimetic materials that mimic the fibrillar architecture of the extracellular matrix (ECM) can provide necessary guidance for orientating cells (Prabhakaran, Venugopal, Kai, & Ramakrishna, 2011). Fibers may provide low-resistance pathways for electrical signal propagation mimicking the native heart tissue (Kai, Prabhakaran, Jin, & Ramakrishna, 2013). Besides, tissue constructs that mimic the structural and mechanical properties of the myocardium may

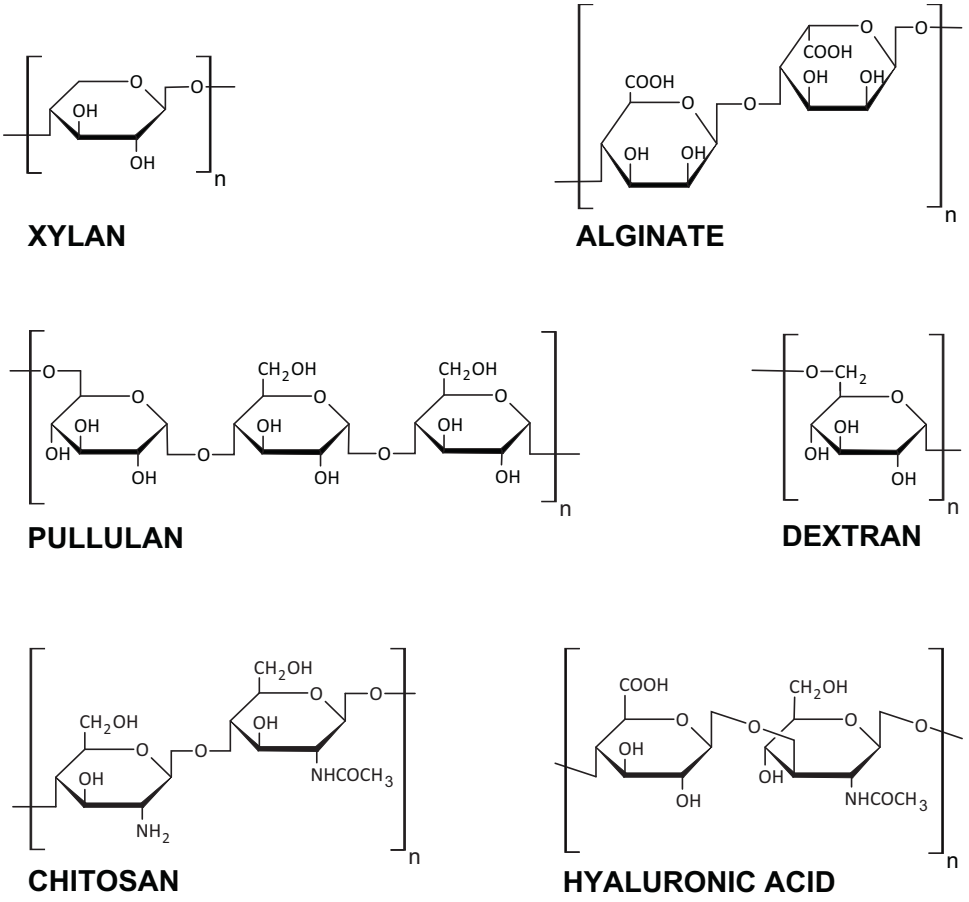

Fig. 3. Chemical structures of polysaccharides investigated for heart tissue engineering.

provide a native-like microenvironment for stimulating stem cell differentiation into a cardiac lineage (Guan et al., 2011). In the study of Venugopal et al. (2013), xylan-based nanofibers might be delivered directly into the myocardium considering their mechanical strength and swelling properties. This would avoid an open-heart surgery and the massive cell loss from the site of injection.

3.2. Alginate

Alginate is a natural polysaccharide obtained from brown seaweed. It has been widely investigated for several biomedical applications due to its biocompatibility, relatively low cost and low toxicity. Alginate is in fact a family of linear copolymers containing blocks of (1,4)-linked β-D-mannuronate (M) and α-L-guluronate (G) residues (Fig. 3). The blocks are composed of consecutive G residues (GGGGGG), consecutive M residues (MMMMMM), and alternating M and G residues (GMGMGM) (Lee & Mooney, 2012). Alginate main source is brown macroalgae, in which alginate represents the major structural component of intercellular matrix and of the cell wall (Yabur, Bashan, & Hernández-Carmona, 2007).

Although alginate presents many attractive properties, its slow and quite uncontrollable degradation can be an undesirable feature (Boontheekul, Kong, & Mooney, 2005). In order to control alginate gel degradation, partial periodate oxidation may be used. By means of oxidation, hydrolytically labile bonds in the polysaccharide were created (Boontheekul et al., 2005; Bouhadir et al., 2001).

An alternative approach to regulate alginate gel degradation is related to the control of molecular weight distribution of the polymer chains (Kong, Kaigler, Kim, & Mooney, 2004). In a combined approach, partial oxidation of alginate and the use of polymers with different molecular weight distributions is an interesting way to provide controlled degradation kinetics of gels (Boontheekul et al., 2005; Kong et al., 2004), allowing control of the release kinetics of incorporated factors (Hao et al., 2007; Silva & Mooney, 2007). Sustained growth factor delivery of vascular endothelial growth factor-A 165 and platelet-derived growth factor-BB from such alginate hydrogels enhanced the formation of mature vessels and was shown to improve cardiac function in rats (Hao et al., 2007).

Literature data has also indicated the benefits of alginate hydrogels *via* a mechanic effect. It has been described that injection in a rat model of *in situ* – forming, bioabsorbable acellular alginate hydrogel prevented cardiac remodeling and dysfunction in recent and old myocardial infarctions (Landa et al., 2008). Additionally, intracoronary injection of alginate was found to improve infarct repair and prevent adverse remodeling in a swine model (Leor et al., 2009). After implantation, the hydrogel gradually disappears, and the water-soluble alginate chains were excreted by the kidneys (Al-Shamkhani & Duncan, 1995). It was hypothesized that the injectable alginate biomaterial enabled mechanical/physical support to the infarcted cardiac tissue, a task usually fulfilled by the cardiac ECM, mainly by the collagen constituting the ECM (Brower et al., 2006). In fact, the cardiac ECM is damaged after infarction, as observed by collagen loss and reorganization. The replacement of ECM by the alginate biomaterial could be an strategy to compensate for collagen loss until cardiac healing progresses (Tsur-Gang et al., 2009).

Although mechanical effects are most commonly pointed out, the material-related biological response could potentially present a contributing effect (Nelson et al., 2011). For instance, an angiogenic effect concomitant to improved heart function was observed in rats after alginate injection alone. It indicates that the polymer itself may influence the tissue microenvironment and induce a potential therapeutic effect (Yu et al., 2009). Additionally, it was demonstrated that alginate hydrogel injection enhanced cell recruitment into the infarct, including the homing of myofibroblasts that take part in cardiac healing (Tsur-Gang et al., 2009).

In addition to the injection-based approach, the implantable scaffold-based approach was also tested for alginate. Fetal cardiac cells were cultured into 3D porous alginate scaffolds and implanted into the infarcted myocardium of rats. Following implantation, the scaffold stimulated neovascularization and attenuated heart wall dilatation and cardiac failure in treated rats when compared with controls. The approach improved the regeneration and healing of the infarcted myocardium and reduced wall stress and infarct expansion (Leor et al., 2000).

This strategy could be supplemented by the grafting of RGD peptide into alginate scaffolds. The RGD peptide is supposed to enhance cell attachment to the matrix, improved cell survival and facilitated the organization of the tissue. Indeed, the cardiomyocytes were able *in vitro* to reorganize their myofibrils and reconstructed myofibers constituted of several cardiomyocytes in a typical myofiber bundle in a way quite similar to the native cardiac tissue. In contrast, such structural organization could not be evidenced in the non-peptide grafted alginate scaffolds. In addition to cell morphology/organization results, data concerning expression levels of α-actinin, N-cadherin and connexin-43, indicated further improved *in vitro* features of the engineered cardiac tissue when RGD was grafted to alginate scaffolds (Shachar, Tsur-Gang, Dvir, Leor, & Cohen, 2011).

In a related approach, Sapir et al. investigated *in vitro* the combination of two matrix-attached peptides, the adhesion peptide G_4RGDY and heparin-binding peptide G_4SPPRRARVTY (HBP) attached to alginate for cardiac tissue regeneration. Neonatal rat cardiac cells were seeded into unmodified, single peptide or double peptide-attached alginate scaffolds. The cardiac tissue developed in the HBP/RGD-attached scaffolds demonstrated the best features of a functional muscle tissue considering data from immunostaining of cardiac cell markers, histology, Western blot of proteins and metabolic activity. Well-developed myocardial fibers could be observed by day 7. At 14 days, the HBP/RGD-attached constructs displayed an isotropic myofiber arrangement, which was not evidenced in the other constructs. The formation a contractile muscle tissue in the HBP/RGD-attached scaffolds was further demonstrated *via* the expression levels of α-actinin, N-cadherin and Connexin-43. Such strategy of attaching peptides representing different signaling in ECM-cell interactions proved to support the formation of a functional cardiac muscle tissue *in vitro* (Sapir, Kryukov, & Cohen, 2011)

3.3. Pullulan and dextran

Pullulan is a non-ionic exopolysaccharide of fungal origin. Indeed, pullulan is an exocellular homopolysaccharide produced by the strain of *Aureobasidium pullulans* (Wu, Jin, Kim, Tong, & Chen, 2009). It consists of a water-soluble, neutral linear polysaccharide consisting of α-1,6-linked maltotriose residues (Fig. 3). Pullulan is currently used in the food industry and in pharmaceutics. Due to its non-toxic, non-immunogenic, non-mutagenic and non-carcinogenic nature, there are attempts to explore this polysaccharide for several biomedical applications (Autissier, Letourneur, & Le Visage, 2007; Rekha & Sharma, 2007; Wolf, Garleb, Choe, Humphrey, & Maki, 2003).

Dextran consists of a high molecular-weight polysaccharide of microbial origin composed of glucose molecules connected in α 1–6 glucosidic linkage, in which side chains are connected in α 1–4 linkage (Fig. 3). The exact structure of each type of dextran depends on the microbial strain (Ciardelli et al., 2005; Vu, Chen, Crawford, & Ivanova, 2009). Crosslinked dextran has been widely used as a molecular sieve for purification and separation of biomolecules. It has also been used as a soluble form for biomedical applications such as plasma expander considering its biocompatibility (Cai, Yang, Bei, & Wang, 2002). Dextran is biodegradable and

biocompatible and also available in a wide variety of molecular weights. These properties make it suitable for many biomedical applications including tissue engineering (Malafaya, Silva, & Reis, 2007).

Scaffolds made of crosslinked pullulan and dextran have been investigated for cardiovascular tissue engineering (Chaouat, Le Visage, Autissier, Chaubet, & Letourneur, 2006; Lavergne et al., 2012). The scaffolds consisted on a mixture of pullulan and dextran cross-linked with sodium trimetaphosphate, containing sodium carbonate as a porogen agent. Such scaffolds presented good compatibility with respect to blood–material interactions and no anticoagulant treatment was needed. Additionally, scaffolds made of cross-linked pullulan and dextran were able to withstand pressure under physiological flow conditions in a rat model (Chaouat et al., 2006). It was also demonstrated that such biomaterial preserved the viability and the proliferation of cord-blood endothelial colony-forming cells. Indeed, pullulan and dextran scaffold enabled endothelial cell delivery while preserving cell functions, namely the capacity to form vascular structures and ability to be activated by pro-inflammatory effectors. Such biomaterial was also tested to deliver cells for cardiac repair. *In vivo* effectiveness of mesenchymal stem cells (MSCs) engraftment in rat infarcted tissue was investigated in a comparative study by testing pullulan/dextran-based porous scaffold and endocardial injection approach. The delivery of MSCs to injured rat myocardium using a polysaccharide porous scaffold resulted in improved engraftment in comparison with the endocardial injection approach. The amount of residual cells was higher for the scaffold approach compared to the injection at 1 and 2 months. Additionally, there was an observable trend toward a lower left ventricular dilatation and a reduced fibrosis in the scaffold group (Le Visage et al., 2011).

3.4. Chitosan

Chitosan is a natural polymer originated from renewable resources. Chitosan is obtained from shell of shellfish and also from the wastes of the seafood industry (Kim et al., 2008). Chitin is the source material for chitosan and represents one of the most abundant organic materials, being an important constituent of the exoskeleton in animals, especially in crustacean, insects and molluscs (Kim et al., 2008). It consists of a linear polymer composed of glucosamine and N-acetyl glucosamine units linked by β (1–4) glycosidic bonds (Fig. 3). This polysaccharide presents interesting features such as biocompatibility, biodegradability, antibacterial as well as wound-healing properties (Kim et al., 2008).

Conjugation of hydroxybutyl groups to chitosan renders the polymer water soluble and thermally responsive (Brun-Graeppi, Richard, Bessodes, Scherman, & Merten, 2010). Below its lower critical solution temperature, a solution of hydroxybutyl chitosan (HBC) can be maintained in its solvated state. Upon exposure to the temperature of 37 °C, a 3.8 wt% HBC solution rapidly forms a gel. Upon cooling, the gel is reverted to its solvated state (Dang et al., 2006). Under physiological temperature, concentrated HBC aqueous solution becomes a hydrogel within 30 s after injection (Wang et al., 2013).

The thermal responsiveness of HBC renders it an eligible polymer for injection based-approach for tissue engineering. Temperature-responsive chitosan hydrogels constitute an attractive biomaterial to deliver cells as well as bioactive factors such as growth factors and genes relevant for the repair and tissue regeneration. Once the biomaterial experiences body temperature, the polymer solution polymerize rapidly *in situ*, trapping and retaining the cells and the bioactive factors (Wang, Zhou, Liu, & Wang, 2010).

Injection of basic fibroblast growth factor (bFGF) with temperature-responsive chitosan hydrogels enhanced arteriogenesis, ventricular remodeling and cardiac function in rat infarction models (Wang, Zhang, et al., 2010). Liu et al. investigated the use of thermo-responsive chitosan hydrogel for adipose-derived MSC delivery into ischemic rat hearts. They demonstrated that chitosan hydrogel was able to improve injected cell microenvironment, enhance cell engraftment and survival, contributing to myocardial repair (Liu et al., 2012).

It is interesting to highlight that thermoresponsive chitosan itself exhibited interesting mechanical properties. This results in a beneficial effect *in vivo* that is also enhanced by the bioactivity of the polymer. In fact, injection of chitosan alone increased the microvessel density significantly within the infarcted scar (Wang et al., 2010b). Thermoresponsive chitosan in combination to embryonic stem cells was found to present supportive mechanical function, support angiogenesis and increase cardiac function after injection in a myocardial infarction rat model (Lu et al., 2008).

In a recent paper, thermoresponsive chitosan chloride was conjugated to glutathione in order to design a hydrogel able to reduce the oxidative stress injury for cardiomyocytes. In fact, myocardial infarction is associated to overproduction of reactive oxygen species, which is a hurdle for cardiac tissue engineering. The produced hydrogel was found to present antioxidant capacity and also excellent biocompatibility in order to favor the adhesion and survival of cardiomyocytes, representing then an interesting alternative to support heart tissue engineering by delivering cells while minimizing oxidative stress (Li et al., 2013).

3.5. Hyaluronan

Hyaluronan is a high-molecular-weight polysaccharide, which is an important constituent of the extracellular matrix (Laurent & Fraser, 1992). It is a linear polysaccharide constituted of a repeating disaccharide unit of (1,4)-glucuronic acid (GlcUA)-β (1,3)-N-acetylglucosamine (GlcNAc) (Fig. 3). Hyaluronan may have different sources. It can be produced by bacteria or extracted from animal tissues (Boeriu, Springer, Kooy, van den Broek, & Eggink, 2013). Large hyaluronan molecules are space filling polymers presenting regulatory as well as structural functions, while small hyaluronan fragments are involved in immunostimulation, angiogenesis and inflammation (Frenkel, 2012; Stern, Asari, & Sugahara, 2006). Hyaluronan hydrogels have the advantages of being formed in mild conditions and they enable the incorporation of angiogenic growth factors, plasmids, or cells to deliver them into ischemic tissues. Furthermore, the derivatives of hyaluronan hydrogels retain the polysaccharide angiogenic activity, which will enhance vascularization (Shen, Tanaka, & Takamori, 2009). Hyaluronan hydrogels grafted with thiols display faster degradation rates. This is assumed to be the result of relatively weak covalent cross-linking of disulfide bonds. Such faster degradation could facilitate neovascularization (Shen et al., 2009).

2-Iminothiolane grafted hyaluronan hydrogel and periodate oxidated hyaluronan hydrogel were implanted into rat adductor muscles. They showed rapid degradation rates, while inducing low inflammation and dense blood vessel formation in the areas surrounding the implanted hydrogels (Shen et al., 2009). Hyaluronan-mediated angiogenic effect *in vivo* is related to its degradation products, which stimulate endothelial cell proliferation and migration (Peattie et al., 2004).

An injectable hyaluronan-based hydrogel showed promising results when injected into mice model of myocardial infarction. Yoon and colleagues reported an increase in the thickness of the heart, a decrease in the infarcted area of the left ventricle, a higher number of arterioles and capillaries in the border zone, a reduction of apoptosis and an improvement of heart functions, such as ejection fraction (Yoon et al., 2009).

In a related study, hyaluronan-based hydrogels presenting differential moduli (~8 *versus* ~43 kPa) were injected into an ovine

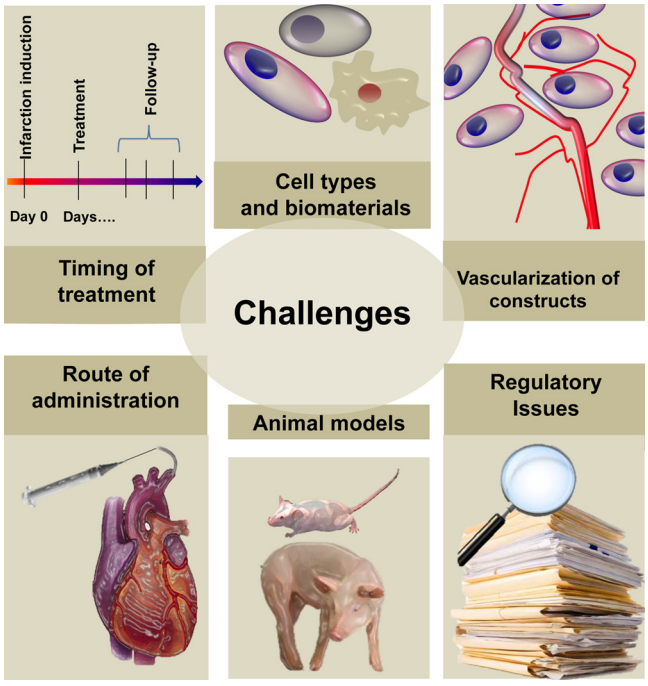

Fig. 4. Challenges in polysaccharide-based strategies for heart tissue engineering.

model of myocardial infarction. It was found that both hydrogels significantly increased the heart wall thickness compared with the control. The higher-modulus hydrogel induced a statistical reduction in the infarct area compared with the control group. The higher-modulus hydrogel also improved functional outcomes (cardiac output and ejection fraction) in a higher extent than the low-modulus and control groups (Ifkovits et al., 2010). The same team compared hyaluronan-based hydrogels presenting degradation time of about 3 weeks or 10 weeks. Both treatments resulted in increased vessel formation and cardiac output compared to controls. However, slow-degrading hyaluronan-based hydrogel was more effective at 8 weeks, implying that longer wall stabilization is needed for an improved cardiac repair (Tous et al., 2011).

In a combined approach, covalently *in situ* cross-linked hydrogels based on alginate and hyaluronic acid were designed. The mechanophysical properties of the resulting hydrogels were easily adjustable by varying degrees of derivatization, concentrations and composition of blends. *In vitro* tests with neonatal rat heart cells showed that the hydrogel allowed for the generation of a fine-tuning contractile bioartificial cardiac tissue (Dahlmann et al., 2013).

Hyaluronan hydrogels were also combined with cells for cardiac repair. Hydrogels containing cardiosphere-derived cells were injected intra-myocardially or applied epicardially in rats following myocardial infarction. The encapsulation of cell into hyaluronan hydrogel markedly increased acute myocardial retention and an improved left ventricular ejection fraction was reported. Additionally, hydrogels were highly adhesive, biodegradable and promoted the survival of cardiosphere-derived cells after administration into the heart (Chang et al., 2012).

4. Challenges

Polysaccharide-based strategies for heart tissue engineering still face many challenges. They are depicted in Fig. 4 and commented as follows.

Concerning cell-based approaches, the choice of the cell time is an issue of paramount importance that is quite challenging. Regulatory aspects and clinical availability are important points to consider in the choice of the cell source as they critically impact on translational aspects. For instance, although neonatal cardiomyocytes have been largely investigated in preclinical studies, they do not represent a quite valuable option for clinical studies due to ethical concerns and low accessibility. There are also many research investigations on embryonic stem cells. However, teratogenicity and ethical issues may hamper safe clinical use. The same applies to induced pluripotent stem cells even if they overcome some major shortcomings such as accessibility and expansion. Considering skeletal myoblasts, adverse events such as arrhythmias may occur (Giraud et al., 2012; Siepe, Akhyari, Lichtenberg, Schlensak, & Beyersdorf, 2008). Cell sourcing is therefore a complex technical and regulatory obstacle.

The optimal time window for therapy is another important challenge to be considered. Indeed, the kinetics and timing to deliver cells/biomaterials have received little attention in preclinical studies. The ideal choice of this window seems to be situated between days 3 and 7 after the infarction (Dib et al., 2010). When transplantation is performed in the first week post myocardial infarction, reduced inflammation as well as early tissue remodeling facilitates transplanted cells integration (Hu et al., 2007).

The choice of the animal model is also a main concern. It is important to mention that experimental and preclinical investigations have widely been performed in small (rodent) models. Alternatively, swine model of myocardial infarction induced by either balloon inflation or coil placement in the left anterior descending artery is considered a robust and reproducible model that simulates quite well human myocardial infarction (Dib et al., 2010).

The way of administration is also a point that deserves further attention. The biomaterial may be administered in a single or multiple injections. The injection volume is also an important parameter to be determined as well as the location of the injection (Wall, Walker, Healy, Ratcliffe, & Guccione, 2006; Wenk et al., 2009). The administration of the biomaterial to the border zone may be more appropriate to encourage regeneration than an injection in the center of the infarct (Nelson et al., 2011). The route of administration also represents a key issue. Intramyocardial, transendocardial and epicardial delivery approaches are quite frequent. The epicardial approach brings along high risk related to its invasive nature. However, it offers the benefit to provide direct visualization of the heart enabling accurate administration. Transendocardial methods *via* the use of the 3D mapping systems allow increased accuracy although the risk of perforating the myocardium is the highest. The intracoronary method is also a usual procedure, but coronary sinus delivery is considered lower risk although limited by the variability in coronary sinus anatomy. Considering all this, intravenous delivery is regarded as the most straightforward and least invasive route of administration. However, it relies on cell homing even more than the other routes of administration (Dib, Khawaja, Varner, McCarthy, & Campbell, 2011).

Vascularization aspects are equally a main concern. The contractile activity related to myogenic function requires that effective metabolic resources are supplied appropriately. In infarcted areas, oxygen and nutrition supply may fall below the minimum required levels for cell survival. *In vivo* vascularization is quite needed to avoid ischemic cell damage especially in the core zone of the engineered tissue constructs. The addition of endothelial cells in the biomaterial might favor vascularization induction (Akhyari, Kamiya, Haverich, Karck, & Lichtenberg, 2008).

Last but not least, regulatory issues represent a main challenge. There are major regulatory hurdles in the translation of polysaccharide-based tissue engineered constructs in marketed

Table 1
Patents related to polysaccharide-based approaches for heart tissue engineering.

Polysaccharide-based approaches for heart tissue engineering	Patents	References
Polysaccharide biodegradable gel matrix containing a biologically active agent and stem cells for the treatment of heart failure	EP1730265A2 WO2005093047A2 WO2005093047A3 US 20080226726 A1	Jaconi and Zammaretti-Schaer (2005a, 2005b, 2006a, 2006b)
Alginate solution to be injected in the heart to be gelled *in situ* for cardiac tissue repair	WO2004098669 A1 EP2314327 B1	Cohen and Leor (2004, 2013)
Alginate matrices with nanowires and seeded with cardiomyocytes as cardiac patches	US 20130289687 A1 WO2012094208 A1	Dvir, Kohane, Langer, and Timko (2012, 2013)
Three-dimensional aligned scaffold to grow cells in predetermined orientations for regeneration and repair of cardiac tissue	US7579189 B2 US 20050042254 A1 US7384786 B2 EP 1649008 A2 WO 2005010172 A2	Freyman, Palasis, and Ungs (2005a, 2005b, 2006, 2008, 2009)
Alginate-based vascularized support matrix to mediate the controlled release of chemical or biological agents	US20070299508 A1 US20120209403 A1 US7998735 B2 US20050056291 A1	Morrison, Messina, Knight, and Pennington (2005, 2007, 2011, 2012)
Chitosan or hyaluronan- based nanofiber scaffold seeded with cells mimicking the structure of cardiac tissue	US20130183352 A1 WO2013109642 A1	Xie (2013a, 2013b)
Chitosan or hyaluronan-based anisotropic scaffold prepared by electrospinning for cardiac tissue engineering	WO2011149836 A1 US20130131830 A1	Lelkes, Senel, Brookstein, and Govindaraj (2011, 2013)
Textured surface of chitosan to align cells for generating a cardiac patch	WO2010108025 A2 WO2010108025 A3 US20120129209 A1	Khine and Luna (2010, 2011, 2012)

products. Currently, there are several patents on polysaccharide-based approaches for cardiac tissues engineering (Table 1). This indicates an interest in translating research into commercial products. In this regard, careful attention should be paid to regulatory concerns in order to design marketed products.

Thorough consideration of the challenges going from bench to bedside is paramount in maximizing the chances that a scientific approach becomes a treatment (Pashuck & Stevens, 2012). Products derived from an autologous source would provide a straightforward route to clinical translation by reducing regulatory concerns (Seif-Naraghi, Salvatore, Schup-Magoffin, Hu, & Christman, 2010). However, for cardiac tissue engineering using polysaccharides, the source is often algae, microbial, crustacean *etc.* In addition to that, the presence of cells increases the complexity of the product. As a general rule, the regulatory difficulties concerning a particular tissue engineering product increase with the complexity of the product. For instance, a polymeric scaffold is regarded as a device, while such a scaffold endowed with growth factors and containing cells might be considered and regulated as a combination product. As a consequence, it is important to minimize complexity in the pursuit of the simplest product sufficient to match the desired clinical need in order to reduce regulatory requirements (Atala, Kasper, & Mikos, 2012). Indeed, interactions and exchanges with the regulatory body should begin at the initial stages of development in order to facilitate identification of the appropriate regulatory pathway. This is also of interest to guide the selection of the most appropriate methods for preclinical and clinical investigations in order to support regulatory requirements (Atala et al., 2012). Such concerns regard the manufacture of the product, cell purity, preclinical issues, clinical investigation and post-market requirements (Condic & Rao, 2008; Hellman, 1997), as detailed in Table 2.

Table 2
Regulatory concerns related to the manufacture, preclinical investigation, and clinical evaluation of tissue engineered products (Hellman, 1997).

Manufacture	Preclinical investigation	Clinical evaluation
Product consistency	Structural and functional activity of the biomaterial	Indications
Product stability	Biomaterial compatibility testing	Efficacy endpoints
Material sourcing	*In vitro*/animal models used	Safety monitoring
Adventitious agents	Efficacy of the tissue engineered product	Post-market reporting
Testing Process validation Toxicity testing Carcinogenicity Immunogenicity Sterility		

5. Conclusions

Heart tissue engineering intends to improve cardiac function by supporting, replacing or repairing the injured tissue. Notably, efforts have been done to propose a new alternative to cellular cardiomyoplasty, whose attempts so far have failed since most of the implanted cells die soon after transplantation or are not retained at the site of interest. Biomaterials including polysaccharides represent a new venue for cardiac repair. They may act by providing a mechanical support, by their intrinsic bioactivity and also by avoiding the spread of pro-inflammatory agents, which would induce further cardiomyocyte death and infarction expansion. Additionally, polysaccharide biomaterial may enclose cells and bioactive molecules, which have an additional contribution to for alleviation of myocardial infarction. Enclosing cells and signaling molecules such as growth factors into polysaccharide biomaterial provide an additional opportunity to enhance the effect of the biomaterial alone. Besides, in such a case, the polymer increases the cell residence time in the site of interest while improving cells survival by providing a friendly microenvironment. Several studies have been published based on polysaccharides such as xylan, alginate, pullulan and dextran, chitosan and hyaluronan and there are equally many patents on the field, as reviewed herein. However, there are still many challenges in the domain related to the choice of the cell type, the choice of the animal model, the way of administration (volume, route and timing), the angiogenic potential of the construct and also regulatory concerns. Critical issues in the near future will be the demonstration of safety and efficacy of polysaccharide-based approaches in large animal models, at long term and complying with regulatory requirements. This will ultimately lead to the transition of polysaccharide-based approaches toward clinical trials and also to the market, as a perspective.

Acknowledgements

The authors would like to thank the institutions of Inserm (National Institute for Health and Medical Research), Universities of Paris Diderot and Paris 13 for financial support, as well as the French Research National Agency (ANR TECSAN-2012-0011 Ineov), and the European Community for the NanoAthero FP-7 project (NMP-LA-2012 Grant agreement 309820).

References

Akhyari, P., Kamiya, H., Haverich, A., Karck, M., & Lichtenberg, A. (2008). Myocardial tissue engineering: The extracellular matrix. *European Journal of Cardio-Thoracic Surgery*, *34*(2), 229–241.

Al-Shamkhani, A., & Duncan, R. (1995). Radioiodination of alginate via covalently-bound tyrosinamide allows monitoring of its fate in vivo. *Journal of Bioactive and Compatible Polymers*, *10*(1), 4–13.

Arslan, F., de Kleijn, D., & Pasterkamp, G. (2011). Innate immune signaling in cardiac ischemia. *Nature Reviews Cardiology*, *8*(5), 292–300.

Atala, A., Kasper, F. K., & Mikos, A. G. (2012). Engineering complex tissues. *Science Translational Medicine*, *4*(160), 160rv12.

Autissier, A., Letourneur, D., & Le Visage, C. (2007). Pullulan-based hydrogel for smooth muscle cell culture. *Journal of Biomedical Materials Research Part A*, *82*(2), 336–342.

Black, L. D., III, Meyers, J. D., Weinbaum, J. S., Shvelidze, Y. A., & Tranquillo, R. T. (2009). Cell-induced alignment augments twitch force in fibrin gel-based engineered myocardium via gap junction modification. *Tissue Engineering Part A*, *15*(10), 3099–3108.

Boeriu, C. G., Springer, J., Kooy, F. K., van den Broek, L. A., & Eggink, G. (2013). Production methods for hyaluronan. *International Journal of Carbohydrate Chemistry*, 1–14.

Bollini, S., Smart, N., & Riley, P. R. (2011). Resident cardiac progenitor cells: At the heart of regeneration. *Journal of Molecular and Cellular Cardiology*, *50*(2), 296–303.

Boontheekul, T., Kong, H.-J., & Mooney, D. J. (2005). Controlling alginate gel degradation utilizing partial oxidation and bimodal molecular weight distribution. *Biomaterials*, *26*(15), 2455–2465.

Bouhadir, K. H., Lee, K. Y., Alsberg, E., Damm, K. L., Anderson, K. W., & Mooney, D. J. (2001). Degradation of partially oxidized alginate and its potential application for tissue engineering. *Biotechnology Progress*, *17*(5), 945–950.

Brower, G. L., Gardner, J. D., Forman, M. F., Murray, D. B., Voloshenyuk, T., Levick, S. P., et al. (2006). The relationship between myocardial extracellular matrix remodeling and ventricular function. *European Journal of Cardio-Thoracic Surgery*, *30*(4), 604–610.

Brun-Graeppi, A. K., Richard, C., Bessodes, M., Scherman, D., & Merten, O.-W. (2010). Thermoresponsive surfaces for cell culture and enzyme-free cell detachment. *Progress in Polymer Science*, *35*(11), 1311–1324.

Cai, Q., Yang, J., Bei, J., & Wang, S. (2002). A novel porous cells scaffold made of polylactide–dextran blend by combining phase-separation and particle-leaching techniques. *Biomaterials*, *23*(23), 4483–4492.

Chang, C. Y., Chan, A. T., Armstrong, P. A., Luo, H.-C., Higuchi, T., Strehin, I. A., et al. (2012). Hyaluronic acid-human blood hydrogels for stem cell transplantation. *Biomaterials*, *33*(32), 8026–8033.

Chaouat, M., Le Visage, C., Autissier, A., Chaubet, F., & Letourneur, D. (2006). The evaluation of a small-diameter polysaccharide-based arterial graft in rats. *Biomaterials*, *27*(32), 5546–5553.

Chen, Q.-Z., Harding, S. E., Ali, N. N., Lyon, A. R., & Boccaccini, A. R. (2008). Biomaterials in cardiac tissue engineering: Ten years of research survey. *Materials Science and Engineering: R: Reports*, *59*(1–6), 1–37.

Chi, N.-H., Yang, M.-C., Chung, T.-W., Chou, N.-K., & Wang, S.-S. (2013). Cardiac repair using chitosan-hyaluronan/silk fibroin patches in a rat heart model with myocardial infarction. *Carbohydrate Polymers*, *92*(1), 591–597.

Chimphango, A. F. A., van Zyl, W. H., & Görgens, J. F. (2012). In situ enzymatic aided formation of xylan hydrogels and encapsulation of horse radish peroxidase for slow release. *Carbohydrate Polymers*, *88*(3), 1109–1117.

Christman, K. L., & Lee, R. J. (2006). Biomaterials for the treatment of myocardial infarction. *Journal of the American College of Cardiology*, *48*(5), 907–913.

Christman, K. L., Vardanian, A. J., Fang, Q., Sievers, R. E., Fok, H. H., & Lee, R. J. (2004). Injectable fibrin scaffold improves cell transplant survival, reduces infarct expansion, and induces neovasculature formation in ischemic myocardium. *Journal of the American College of Cardiology*, *44*(3), 654–660.

Ciardelli, G., Chiono, V., Vozzi, G., Pracella, M., Ahluwalia, A., Barbani, N., et al. (2005). Blends of poly-(ε-caprolactone) and polysaccharides in tissue engineering applications. *Biomacromolecules*, *6*(4), 1961–1976.

Cohen, S., & Leor, J. (2004). *Injectable cross-linked polymeric preparations and uses thereof*. WO2004098669 A1.

Cohen, S., & Leor, J. (2013). *Injectable cross-linked polymeric preparations and uses thereof*. EP2314327 B1.

Condic, M. L., & Rao, M. (2008). Regulatory issues for personalized pluripotent cells. *Stem Cells*, *26*(11), 2753–2758.

Dahlmann, J., Krause, A., Möller, L., Kensah, G., Möwes, M., Diekmann, A., et al. (2013). Fully defined *in situ* cross-linkable alginate and hyaluronic acid hydrogels for myocardial tissue engineering. *Biomaterials*, *34*(4), 940–951.

Dang, J. M., Sun, D. D. N., Shin-Ya, Y., Sieber, A. N., Kostuik, J. P., & Leong, K. W. (2006). Temperature-responsive hydroxybutyl chitosan for the culture of mesenchymal stem cells and intervertebral disk cells. *Biomaterials*, *27*(3), 406–418.

Davis, M. E., Motion, J. P. M., Narmoneva, D. A., Takahashi, T., Hakuno, D., Kamm, R. D., et al. (2005). Injectable self-assembling peptide nanofibers create intramyocardial microenvironments for endothelial cells. *Circulation*, *111*(4), 442–450.

De Mulder, E. L., Buma, P., & Hannink, G. (2009). Anisotropic porous biodegradable scaffolds for musculoskeletal tissue engineering. *Materials*, *2*(4), 1674–1696.

Dib, N., Menasche, P., Bartunek, J. J., Zeiher, A. M., Terzic, A., Chronos, N. A., et al. (2010). Recommendations for successful training on methods of delivery of biologics for cardiac regeneration: A report of the international society for cardiovascular translational research. *JACC: Cardiovascular Interventions*, *3*(3), 265–275.

Dib, N., Khawaja, H., Varner, S., McCarthy, M., & Campbell, A. (2011). Cell therapy for cardiovascular disease: A comparison of methods of delivery. *Journal of Cardiovascular Translational Research*, *4*(2), 177–181.

Dvir, T., Kohane, D. S., Langer, R. S., & Timko, B. (2012). *Nanowired three dimensional tissue scaffolds*. WO2012094208 A1.

Dvir, T., Kohane, D. S., Langer, R. S., & Timko, B. (2013). *Nanowired three dimensional tissue scaffolds*. US20130289687 A1.

Ebringerová, A., & Heinze, T. (2000). Xylan and xylan derivatives–biopolymers with valuable properties. 1. Naturally occurring xylans structures, isolation procedures and properties. *Macromolecular Rapid Communications*, *21*(9), 542–556.

Ebringerová, A., Hromádková, Z., Kačuráková, M., & Antal, M. (1994). Quaternized xylans: Synthesis and structural characterization. *Carbohydrate Polymers*, *24*(4), 301–308.

Ebringerová, A., Kardošová, A., Hromádková, Z., Malovı′ková, A., & Hřı′balová, V. (2002). Immunomodulatory activity of acidic xylans in relation to their structural and molecular properties. *International Journal of Biological Macromolecules*, *30*(1), 1–6.

Engelmayr, G. C., Cheng, M., Bettinger, C. J., Borenstein, J. T., Langer, R., & Freed, L. E. (2008). Accordion-like honeycombs for tissue engineering of cardiac anisotropy. *Nature Materials*, *7*(12), 1003–1010.

Ertl, G., & Frantz, S. (2005). Healing after myocardial infarction. *Cardiovascular Research*, *66*(1), 22–32.

Frenkel, J. S. (2012). The role of hyaluronan in wound healing. *International Wound Journal*, http://dx.doi.org/10.1111/j.1742-1481X.2012.01057.x

Freyman, T., Palasis, M., & Ungs, M. (2005a). *Aligned scaffolds for improved myocardial regeneration*. US20050042254 A1.

Freyman, T., Palasis, M., & Ungs, M. (2005b). *Aligned scaffolds for improved myocardial regeneration*. WO2005010172 A2.

Freyman, T., Palasis, M., & Ungs, M. (2006). *Aligned scaffolds for improved myocardial regeneration*. EP1649008 A2.

Freyman, T., Palasis, M., & Ungs, M. (2008). *Aligned scaffolds for improved myocardial regeneration*. US7384786 B2.

Freyman, T., Palasis, M., & Ungs, M. (2009). *Aligned scaffolds for improved myocardial regeneration*. US7579189 B2.

Fukamachi, K., & McCarthy, P. M. (2005). Initial safety and feasibility clinical trial of the myosplint device? *Journal of Cardiac Surgery*, *20*(s6), S43–S47.

Gajarsa, J. J., & Kloner, R. A. (2011). Left ventricular remodeling in the post-infarction heart: A review of cellular, molecular mechanisms, and therapeutic modalities. *Heart Failure Reviews*, *16*(1), 13–21.

Garbern, J. C., Minami, E., Stayton, P. S., & Murry, C. E. (2011). Delivery of basic fibroblast growth factor with a pH-responsive, injectable hydrogel to improve angiogenesis in infarcted myocardium. *Biomaterials*, *32*(9), 2407–2416.

Gerczuk, P. Z., & Kloner, R. A. (2012). An update on cardioprotectiona review of the latest adjunctive therapies to limit myocardial infarction size in clinical trials. *Journal of the American College of Cardiology*, *59*(11), 969–978.

Giraud, M.-N., Guex, A. G., & Tevaearai, H. T. (2012). Cell therapies for heart function recovery: Focus on myocardial tissue engineering and nanotechnologies. *Cardiology Research and Practice*, *2012*.

Guan, J., Wang, F., Li, Z., Chen, J., Guo, X., Liao, J., et al. (2011). The stimulation of the cardiac differentiation of mesenchymal stem cells in tissue constructs that mimic myocardium structure and biomechanics. *Biomaterials*, *32*(24), 5568–5580.

Habib, M., Shapira-Schweitzer, K., Caspi, O., Gepstein, A., Arbel, G., Aronson, D., et al. (2011). A combined cell therapy and in-situ tissue-engineering approach for myocardial repair. *Biomaterials*, *32*(30), 7514–7523.

Hale, S. L., Dai, W., Dow, J. S., & Kloner, R. A. (2008). Mesenchymal stem cell administration at coronary artery reperfusion in the rat by two delivery routes: A quantitative assessment. *Life Sciences*, *83*(13–14), 511–515.

Hao, X., Silva, E. A., Månsson-Broberg, A., Grinnemo, K.-H., Siddiqui, A. J., Dellgren, G., et al. (2007). Angiogenic effects of sequential release of VEGF-A165 and PDGF-BB with alginate hydrogels after myocardial infarction. *Cardiovascular Research*, *75*(1), 178–185.

Hellman, K. B. (1997). Bioartificial organs as outcomes of tissue engineering scientific and regulatory issues. *Annals of the New York Academy of Sciences*, *831*(1), 1–9.

Hollister, S. J. (2005). Porous scaffold design for tissue engineering. *Nature Materials*, *4*(7), 518–524.

Hu, X., Wang, J., Chen, J., Luo, R., He, A., Xie, X., et al. (2007). Optimal temporal delivery of bone marrow mesenchymal stem cells in rats with myocardial infarction. *European Journal of Cardio-Thoracic Surgery*, *31*(3), 438–443.

Ifkovits, J. L., Tous, E., Minakawa, M., Morita, M., Robb, J. D., Koomalsingh, K. J., et al. (2010). Injectable hydrogel properties influence infarct expansion and extent

of postinfarction left ventricular remodeling in an ovine model. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(25), 11507–11512.
Jaconi, M. E., & Zammaretti-Schaer, P. (2005a). *3D-cardiac tissue engineering for the cell therapy of heart failure*. WO2005093047 A2.
Jaconi, M. E., & Zammaretti-Schaer, P. (2005b). *3D-cardiac tissue engineering for the cell therapy of heart failure*. US20080226726 A1.
Jaconi, M. E., & Zammaretti-Schaer, P. (2006a). *3D-cardiac tissue engineering for the cell therapy of heart failure*. EP1730265 A2.
Jaconi, M. E., & Zammaretti-Schaer, P. (2006b). *3D-cardiac tissue engineering for the cell therapy of heart failure*. WO2005093047 A3.
Jawad, H., Ali, N. N., Lyon, A. R., Chen, Q. Z., Harding, S. E., & Boccaccini, A. R. (2007). Myocardial tissue engineering: A review. *Journal of Tissue Engineering and Regenerative Medicine*, *1*(5), 327–342.
Johnson, T. D., & Christman, K. L. (2013). Injectable hydrogel therapies and their delivery strategies for treating myocardial infarction. *Expert Opinion on Drug Delivery*, *10*(1), 59–72.
Kai, D., Prabhakaran, M. P., Jin, G., & Ramakrishna, S. (2013). Biocompatibility evaluation of electrically conductive nanofibrous scaffolds for cardiac tissue engineering. *Journal of Materials Chemistry B*, *1*(17), 2305–2314.
Kashem, A., Kashem, S., Santamore, W. P., Crabbe, D. L., Margulies, K. B., Melvin, D. B., et al. (2003). Early and late results of left ventricular reshaping by passive cardiac-support device in canine heart failure. *Journal of Heart and Lung Transplantation*, *22*(9), 1046–1053.
Kawaguchi, N., Smith, A. J., Waring, C. D., Hasan, M. K., Miyamoto, S., Matsuoka, R., et al. (2010). c-kitpos GATA-4 high rat cardiac stem cells foster adult cardiomyocyte survival through IGF-1 paracrine signalling. *PLoS ONE*, *5*(12), e14297.
Khine, M., & Luna, J. I. (2010). *Aligning cells on wrinkled surface*. WO2010108025 A2.
Khine, M., & Luna, J. I. (2011). *Aligning cells on wrinkled surface*. WO2010108025 A3.
Khine, M., & Luna, J. I. (2012). *Aligning cells on wrinkled surface*. US20120129209 A1.
Kim, I.-Y., Seo, S.-J., Moon, H.-S., Yoo, M.-K., Park, I.-Y., Kim, B.-C., et al. (2008). Chitosan and its derivatives for tissue engineering applications. *Biotechnology Advances*, *26*(1), 1–21.
Kong, H. J., Kaigler, D., Kim, K., & Mooney, D. J. (2004). Controlling rigidity and degradation of alginate hydrogels via molecular weight distribution. *Biomacromolecules*, *5*(5), 1720–1727.
Lam, M. T., & Wu, J. C. (2012). Biomaterial applications in cardiovascular tissue repair and regeneration. *Expert Review of Cardiovascular Therapy*, *10*(8), 1039.
Landa, N., Miller, L., Feinberg, M. S., Holbova, R., Shachar, M., Freeman, I., et al. (2008). Effect of injectable alginate implant on cardiac remodeling and function after recent and old infarcts in rat. *Circulation*, *117*(11), 1388–1396.
Laurent, T. C., & Fraser, J. (1992). Hyaluronan. *FASEB Journal*, *6*(7), 2397–2404.
Lavergne, M., Derkaoui, M., Delmau, C., Letourneur, D., Uzan, G., & Le Visage, C. (2012). Porous polysaccharide-based scaffolds for human endothelial progenitor cells. *Macromolecular Bioscience*, *12*(7), 901–910.
Le Visage, C., Gournay, O., Benguirat, N., Hamidi, S., Chaussumier, L., Mougenot, N., et al. (2011). Mesenchymal stem cell delivery into rat infarcted myocardium using a porous polysaccharide-based scaffold: A quantitative comparison with endocardial injection. *Tissue Engineering Part A*, *18*(1–2), 35–44.
Lee, K. Y., & Mooney, D. J. (2012). Alginate: Properties and biomedical applications. *Progress in Polymer Science*, *37*(1), 106–126.
Lelkes, P. I., Senel, G. H., Brookstein, D., & Govindaraj, M. (2011). *Textile-templated electrospun anisotropic scaffolds for tissue engineering and regenerative medicine*. WO2011149836 A1.
Lelkes, P. I., Senel, H. G., Brookstein, D., & Govindaraj, M. (2013). *Textile-templated electrospun anisotropic scaffolds for tissue engineering and regenerative medicine*. US20130131830 A1.
Leor, J., & Cohen, S. (2004). Myocardial tissue engineering: Creating a muscle patch for a wounded heart. *Annals of the New York Academy of Sciences*, *1015*(1), 312–319.
Leor, J., Aboulafia-Etzion, S., Dar, A., Shapiro, L., Barbash, I. M., Battler, A., et al. (2000). Bioengineered cardiac grafts a new approach to repair the infarcted myocardium? *Circulation*, *102*(3), 56–61.
Leor, J., Tuvia, S., Guetta, V., Manczur, F., Castel, D., Willenz, U., et al. (2009). Intracoronary injection of in situ forming alginate hydrogel reverses left ventricular remodeling after myocardial infarction in swine. *Journal of the American College of Cardiology*, *54*(11), 1014–1023.
Li, L., Zhang, S., Zhang, Y., Yu, B., Xu, Y., & Guan, Z. (2009). Paracrine action mediate the antifibrotic effect of transplanted mesenchymal stem cells in a rat model of global heart failure. *Molecular Biology Reports*, *36*(4), 725–731.
Li, J., Shu, Y., Hao, T., Wang, Y., Qian, Y., Duan, C., et al. (2013). A chitosan–glutathione based injectable hydrogel for suppression of oxidative stress damage in cardiomyocytes. *Biomaterials*, *34*(36), 9071–9081.
Liu, Z., Wang, H., Wang, Y., Lin, Q., Yao, A., Cao, F., et al. (2012). The influence of chitosan hydrogel on stem cell engraftment, survival and homing in the ischemic myocardial microenvironment. *Biomaterials*, *33*(11), 3093–3106.
Lu, W.-N., Lü, S.-H., Wang, H.-B., Li, D.-X., Duan, C.-M., Liu, Z.-Q., et al. (2008). Functional improvement of infarcted heart by co-injection of embryonic stem cells with temperature-responsive chitosan hydrogel. *Tissue Engineering Part A*, *15*(6), 1437–1447.
Malafaya, P. B., Silva, G. A., & Reis, R. L. (2007). Natural–origin polymers as carriers and scaffolds for biomolecules and cell delivery in tissue engineering applications. *Advanced Drug Delivery Reviews*, *59*(4), 207–233.
Malliaras, K., & Marbán, E. (2011). Cardiac cell therapy: Where we've been, where we are, and where we should be headed. *British Medical Bulletin*, *98*(1), 161–185.
Mann, D. L., Acker, M. A., Jessup, M., Sabbah, H. N., Starling, R. C., & Kubo, S. H. (2007). Clinical evaluation of the CorCap Cardiac Support Device in patients with dilated cardiomyopathy. *The Annals of Thoracic Surgery*, *84*(4), 1226–1235.
Martens, T. P., Godier, A. F., Parks, J. J., Wan, L. Q., Koeckert, M. S., Eng, G. M., et al. (2009). Percutaneous cell delivery into the heart using hydrogels polymerizing in situ. *Cell Transplantation*, *18*(3), 297–304.
Martinez, E. C., & Kofidis, T. (2011). Adult stem cells for cardiac tissue engineering. *Journal of Molecular and Cellular Cardiology*, *50*(2), 312–319.
McDevitt, T. C., Woodhouse, K. A., Hauschka, S. D., Murry, C. E., & Stayton, P. S. (2003). Spatially organized layers of cardiomyocytes on biodegradable polyurethane films for myocardial repair. *Journal of Biomedical Materials Research Part A*, *66A*(3), 586–595.
Morrison, W., Messina, A., Knight, K., & Pennington, A. (2005). *Vascularized tissue graft*. US20050056291 A1.
Morrison, W., Messina, A., Knight, K., & Pennington, A. (2007). *Vascularized tissue graft*. US20070299508 A1.
Morrison, W. A., Messina, A., Knight, K. R., & Penington, A. J. (2011). *Vascularized tissue graft*. US7998735 B2.
Morrison, W., Messina, A., Knight, K., & Pennington, A. (2012). *Vascularized tissue graft*. US20120209403 A1.
Muthana, S. M., Campbell, C. T., & Gildersleeve, J. C. (2012). Modifications of glycans: Biological significance and therapeutic opportunities. *ACS Chemical Biology*, *7*(1), 31–43.
Nelson, D. M., Ma, Z., Fujimoto, K. L., Hashizume, R., & Wagner, W. R. (2011). Intramyocardial biomaterial injection therapy in the treatment of heart failure: Materials, outcomes and challenges. *Acta Biomaterialia*, *7*(1), 1–15.
Nitta, S. K., & Numata, K. (2013). Biopolymer-based nanoparticles for drug/gene delivery and tissue engineering. *International Journal of Molecular Sciences*, *14*(1), 1629–1654.
Oh, J. K., Lee, D. I., & Park, J. M. (2009). Biopolymer-based microgels/nanogels for drug delivery applications. *Progress in Polymer Science*, *34*(12), 1261–1282.
Parajó, J., Garrote, G., Cruz, J., & Dominguez, H. (2004). Production of xylooligosaccharides by autohydrolysis of lignocellulosic materials. *Trends in Food Science & Technology*, *15*(3), 115–120.
Pashuck, E. T., & Stevens, M. M. (2012). Designing regenerative biomaterial therapies for the clinic. *Science Translational Medicine*, *4*(160), 160sr164.
Peattie, R. A., Nayate, A. P., Firpo, M. A., Shelby, J., Fisher, R. J., & Prestwich, G. D. (2004). Stimulation of in vivo angiogenesis by cytokine-loaded hyaluronic acid hydrogel implants. *Biomaterials*, *25*(14), 2789–2798.
Place, E. S., Evans, N. D., & Stevens, M. M. (2009). Complexity in biomaterials for tissue engineering. *Nature Materials*, *8*(6), 457–470.
Prabhakaran, M. P., Venugopal, J., Kai, D., & Ramakrishna, S. (2011). Biomimetic material strategies for cardiac tissue engineering. *Materials Science and Engineering C*, *31*(3), 503–513.
Premaratne, G. U., Ma, L.-P., Fujita, M., Lin, X., Bollano, E., & Fu, M. (2011). Stromal vascular fraction transplantation as an alternative therapy for ischemic heart failure: Anti-inflammatory role. *Journal of Cardiothoracic Surgery*, *6*(43), 8090–8096.
Quignard, F., Di Renzo, F., & Guibal, E. (2010). From natural polysaccharides to materials for catalysis, adsorption, and remediation. *Topics in Current Chemistry*, *294*, 165–197.
Rekha, M., & Sharma, C. P. (2007). Pullulan as a promising biomaterial for biomedical applications: A perspective. *Trends in Biomaterials and Artificial Organs*, *20*(2), 116–121.
Sabbah, H. N. (2003). The cardiac support device and the myosplint: Treating heart failure by targeting left ventricular size and shape. *The Annals of Thoracic Surgery*, *75*(6), S13–S19.
Sapir, Y., Kryukov, O., & Cohen, S. (2011). Integration of multiple cell-matrix interactions into alginate scaffolds for promoting cardiac tissue regeneration. *Biomaterials*, *32*(7), 1838–1847.
Seif-Naraghi, S. B., Salvatore, M. A., Schup-Magoffin, P. J., Hu, D. P., & Christman, K. L. (2010). Design and characterization of an injectable pericardial matrix gel: A potentially autologous scaffold for cardiac tissue engineering. *Tissue Engineering Part A*, *16*(6), 2017–2027.
Shachar, M., Tsur-Gang, O., Dvir, T., Leor, J., & Cohen, S. (2011). The effect of immobilized RGD peptide in alginate scaffolds on cardiac tissue engineering. *Acta Biomaterialia*, *7*(1), 152–162.
Shen, X., Tanaka, K., & Takamori, A. (2009). Coronary arteries angiogenesis in ischemic myocardium: Biocompatibility and biodegradability of various hydrogels. *Artificial Organs*, *33*(10), 781–787.
Siepe, M., Akhyari, P., Lichtenberg, A., Schlensak, C., & Beyersdorf, F. (2008). Stem cells used for cardiovascular tissue engineering. *European Journal of Cardio-Thoracic Surgery*, *34*(2), 242–247.
Silva, E., & Mooney, D. (2007). Spatiotemporal control of vascular endothelial growth factor delivery from injectable hydrogels enhances angiogenesis. *Journal of Thrombosis and Haemostasis*, *5*(3), 590–598.
Silva, A. K. A., da Silva, É. L., Oliveira, E. E., Nagashima, T., Jr., Soares, L. A. L., Medeiros, A. C., et al. (2007). Synthesis and characterization of xylan-coated magnetite microparticles. *International Journal of Pharmaceutics*, *334*(1–2), 42–47.
Silva, A. K. A., Richard, C., Bessodes, M., Scherman, D., & Merten, O.-W. (2008). Growth factor delivery approaches in hydrogels. *Biomacromolecules*, *10*(1), 9–18.
Silvestri, A., Boffito, M., Sartori, S., & Ciardelli, G. (2013). Biomimetic materials and scaffolds for myocardial tissue regeneration. *Macromolecular Bioscience*, *13*(8), 984–1019.
Sinha, V., & Kumria, R. (2001). Polysaccharides in colon-specific drug delivery. *International Journal of Pharmaceutics*, *224*(1), 19–38.

Sokolsky-Papkov, M., Agashi, K., Olaye, A., Shakesheff, K., & Domb, A. J. (2007). Polymer carriers for drug delivery in tissue engineering. *Advanced Drug Delivery Reviews*, *59*(4–5), 187–206.

Starling, R. C., Jessup, M., Oh, J. K., Sabbah, H. N., Acker, M. A., Mann, D. L., et al. (2007). Sustained benefits of the CorCap Cardiac Support Device on left ventricular remodeling: Three year follow-up results from the Acorn clinical trial. *The Annals of Thoracic Surgery*, *84*(4), 1236–1242.

Stefanon, I., Valero-Muñoz, M., Fernandes, A. A., Ribeiro, R. F., Jr., Rodríguez, C., Miana, M., et al. (2013). Left and right ventricle late remodeling following myocardial infarction in rats. *PLoS ONE*, *8*(5), e64986.

Stern, R., Asari, A. A., & Sugahara, K. N. (2006). Hyaluronan fragments: An information-rich system. *European Journal of Cell Biology*, *85*(8), 699–715.

Topkara, V. K., Kondareddy, S., & Mann, D. L. (2009). Modulation of left ventricular dilation remodeling with epicardial restraint devices in postmyocardial infarction heart failure. *Current Heart Failure Reports*, *6*(4), 229–235.

Tous, E., Ifkovits, J. L., Koomalsingh, K. J., Shuto, T., Soeda, T., Kondo, N., et al. (2011). Influence of injectable hyaluronic acid hydrogel degradation behavior on infarction-induced ventricular remodeling. *Biomacromolecules*, *12*(11), 4127–4135.

Tsur-Gang, O., Ruvinov, E., Landa, N., Holbova, R., Feinberg, M. S., Leor, J., et al. (2009). The effects of peptide-based modification of alginate on left ventricular remodeling and function after myocardial infarction. *Biomaterials*, *30*(2), 189–195.

Venugopal, J. R., Prabhakaran, M. P., Mukherjee, S., Ravichandran, R., Dan, K., & Ramakrishna, S. (2012). Biomaterial strategies for alleviation of myocardial infarction. *Journal of the Royal Society Interface*, *9*(66), 1–19.

Venugopal, J., Rajeswari, R., Shayanti, M., Sridhar, R., Sundarrajan, S., Balamurugan, R., et al. (2013). Xylan polysaccharides fabricated into nanofibrous substrate for myocardial infarction. *Materials Science and Engineering C*, *33*(3), 1325–1331.

Vilahur, G., Juan-Babot, O., Peña, E., Oñate, B., Casaní, L., & Badimon, L. (2011). Molecular and cellular mechanisms involved in cardiac remodeling after acute myocardial infarction. *Journal of Molecular and Cellular Cardiology*, *50*(3), 522–533.

Vu, B., Chen, M., Crawford, R. J., & Ivanova, E. P. (2009). Bacterial extracellular polysaccharides involved in biofilm formation. *Molecules*, *14*(7), 2535–2554.

Vunjak-Novakovic, G., Lui, K. O., Tandon, N., & Chien, K. R. (2011). Bioengineering heart muscle: A paradigm for regenerative medicine. *Annual Review of Biomedical Engineering*, *13*, 245–267.

Wall, S. T., Walker, J. C., Healy, K. E., Ratcliffe, M. B., & Guccione, J. M. (2006). Theoretical impact of the injection of material into the myocardium a finite element model simulation. *Circulation*, *114*(24), 2627–2635.

Wang, F., & Guan, J. (2010). Cellular cardiomyoplasty and cardiac tissue engineering for myocardial therapy. *Advanced Drug Delivery Reviews*, *62*(7–8), 784–797.

Wang, C.-C., Chen, C.-H., Lin, W.-W., Hwang, S.-M., Hsieh, P. C. H., Lai, P.-H., et al. (2008). Direct intramyocardial injection of mesenchymal stem cell sheet fragments improves cardiac functions after infarction. *Cardiovascular Research*, *77*(3), 515–524.

Wang, H., Zhang, X., Li, Y., Ma, Y., Zhang, Y., Liu, Z., et al. (2010). Improved myocardial performance in infarcted rat heart by co-injection of basic fibroblast growth factor with temperature-responsive chitosan hydrogel. *Journal of Heart and Lung Transplantation*, *29*(8), 881–887.

Wang, H., Zhou, J., Liu, Z., & Wang, C. (2010). Injectable cardiac tissue engineering for the treatment of myocardial infarction. *Journal of Cellular and Molecular Medicine*, *14*(5), 1044–1055.

Wang, Q., Kong, M., An, Y., Liu, Y., Li, J., Zhou, X., et al. (2013). Hydroxybutyl chitosan thermo-sensitive hydrogel: A potential drug delivery system. *Journal of Materials Science*, *48*(16), 5614–5623.

Wenk, J. F., Sabbah, H. N., Burger, M., Ratcliffe, M. B., Guccione, J. M., Stander, N., et al. (2009). A method for automatically optimizing medical devices for treating heart failure: Designing polymeric injection patterns. *Journal of Biomechanical Engineering*, *131*(12), 121011.

Wolf, B. W., Garleb, K. A., Choe, Y. S., Humphrey, P. M., & Maki, K. C. (2003). Pullulan is a slowly digested carbohydrate in humans. *Journal of Nutrition*, *133*(4), 1051–1055.

Wu, S., Jin, Z., Kim, J. M., Tong, Q., & Chen, H. (2009). Downstream processing of pullulan from fermentation broth. *Carbohydrate Polymers*, *77*(4), 750–753.

Wu, J., Zeng, F., Huang, X.-P., Chung, J. C. Y., Konecny, F., Weisel, R. D., et al. (2011). Infarct stabilization and cardiac repair with a VEGF-conjugated, injectable hydrogel. *Biomaterials*, *32*(2), 579–586.

Xie, J. (2013a). *Nanofiber scaffolds and methods for repairing damaged cardiac tissue*. WO2013109642 A1.

Xie, J. (2013b). *Nanofiber scaffolds and methods for repairing damaged cardiac tissue*. US20130183352 A1.

Yabur, R., Bashan, Y., & Hernández-Carmona, G. (2007). Alginate from the macroalgae *Sargassum sinicola* as a novel source for microbial immobilization material in wastewater treatment and plant growth promotion. *Journal of Applied Phycology*, *19*(1), 43–53.

Yoon, S. J., Fang, Y. H., Lim, C. H., Kim, B. S., Son, H. S., Park, Y., et al. (2009). Regeneration of ischemic heart using hyaluronic acid-based injectable hydrogel. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, *91B*(1), 163–171.

Yu, J., Gu, Y., Du, K. T., Mihardja, S., Sievers, R. E., & Lee, R. J. (2009). The effect of injected RGD modified alginate on angiogenesis and left ventricular function in a chronic rat infarct model. *Biomaterials*, *30*(5), 751–756.

Zhang, H., Song, P., Tang, Y., Zhang, X.-L., Zhao, S.-H., Wei, Y.-J., et al. (2007). Injection of bone marrow mesenchymal stem cells in the borderline area of infarcted myocardium: Heart status and cell distribution. *Journal of Thoracic and Cardiovascular Surgery*, *134*(5), 1234–1240, e1231.

Zhang, X., Wang, H., Ma, X., Adila, A., Wang, B., Liu, F., et al. (2010). Preservation of the cardiac function in infarcted rat hearts by the transplantation of adipose-derived stem cells with injectable fibrin scaffolds. *Experimental Biology and Medicine*, *235*(12), 1505–1515.

Zhou, Y., Wang, S., Yu, Z., Hoyt, R. F., Jr., Qu, X., & Horvath, K. A. (2011). Marrow stromal cells differentiate into vasculature after allogeneic transplantation into ischemic myocardium. *The Annals of Thoracic Surgery*, *91*(4), 1206–1212.

Zouein, F. A., Zgheib, C., Liechty, K. W., & Booz, G. W. (2012). Post-infarct biomaterials, left ventricular remodeling, and heart failure: Is good good enough? *Congestive Heart Failure*, *18*(5), 284–290.