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Review

Biomaterial scaffolds used for the regeneration of spinal cord injury (SCI)

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Summary. This review presents a summary of various types of scaffold biomaterials used alone or together with therapeutic drugs and cells to regenerate spinal cord injury (SCI). The inhibitory environment and loss of axonal connections after SCI give rise to critical obstacles to regeneration of lost tissues and neuronal functions. Biomaterial scaffolds can provide a bridge to connect lost tissues, an adhesion site for implanted or host cells, and sustained release of therapeutic drugs in the injured spinal cord. In addition, they not only provide a structural platform, but can play active roles by inhibiting apoptosis of cells, inflammation and scar formation, and inducing neurogenesis, axonal growth and angiogenesis. Many synthetic and natural biomaterial scaffolds have been extensively investigated and tested *in vitro* and in animal SCI models for these purposes. We summarized the literature on the biomaterials commonly used for spinal cord regeneration in terms of historical backgrounds and current approaches.

Key words: Spinal cord injury (SCI), Biomaterials, Scaffolds, Stem cells, Tissue engineering, Drug delivery

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Introduction

Therapeutic approaches to spinal cord injury (SCI) have long been focused on the acute or subacute phase after injury. These approaches include mostly administration of neuroprotective agents and neurotrophic factors that can prevent the action of inhibitory cues and enhance innate regeneration activity. Unfortunately, however, most of these efforts have been in vain and showed no beneficial effect on the regeneration of SCI in animal and/or clinical studies (Hyun and Kim, 2010). The restoration of spinal cord function in the chronic phase especially requires a therapy that allows for the reconstruction of grey and white matters that consist of various tissues and cell types including neurons, astrocytes, oligodendrocytes, blood vessels, extras cellular matrices, and myelinated nerve fibers (Bixby and Harris, 1991; Venstrom and Reichardt, 1993).

Cell therapy and tissue engineering are emerging technologies for replacing and/or regenerating injured tissues, including neural tissues in the central nervous system (CNS) (Rao, 2013). They use a variety of cell types both from somatic neural tissues and with stem cell origin, and inject them directly in the injury site or nearby surrounding tissues (Tabesh et al., 2009). These approaches usually aim at several beneficial roles of stem cells; 1) controlling the secondary injury of spinal cord, 2) reducing the adverse effect of axon growth inhibitors such as myelin-based molecules and glial scars, and 3) bridging physically the cavity, which facilitates interconnection of regenerating axons from the rostral and caudal tissues (Ankeny et al., 2004). Cell therapy has mostly been applied to acute or subacute

SCI and a few cases used in chronic SCI did not show significant therapeutic effect, probably due to glial scars covering the defect area and blocking the regeneration of spinal tissue and neural axons. Therefore, chronic SCI has been a target of tissue engineering approaches aimed at restoring the anatomic structure and function of damaged tissues or organs by combining scaffolds, cells and other factors such as bioactive molecules, and mechanical forces (Atala, 2000; Ibarra et al., 2000). In this sense, MSCs with diverse paracrine functions have been recently highlighted as a promising cell source for CNS repair and regeneration, including the SCI (Kim et al., 2013).

Many studies revealed, however, that therapeutic cells applied to the injury site of spinal cord are in an unfavorable environment and not sufficiently competent by themselves for regenerating or replacing injured spinal cords (Fawcett and Asher, 1999; Fricker et al., 1999; Shihabuddin et al., 2000). Biological scaffolds are used to overcome this problem and provide many other biological functions as well. Notable studies with promising biomaterial scaffolds for regeneration of SCI are described in more detail in Section 2.

Scaffolds used in the regeneration of spinal cord

A variety of scaffolds made of synthetic (e.g. poly(lactic-co-glycolic acid) and poly-ε-caprolactone) and natural biomaterials (e.g. agarose, collagen, and fibrin) have been investigated for regenerating SCI (Tables 1, 2). Scaffolds provide spatial signals to modulate the organization of the cells as well as that of the extracellular matrix derived from them (Atala, 2000; Ibarra et al., 2000). They should be highly porous to allow cell seeding at high densities and biocompatible with no harm to either therapeutic cells or host tissues. They are also generally required to be biodegradable, non-toxic, and similar in their physicochemical properties to the surrounding tissues. In addition, it is desirable that they are cheap to manufacture and easily manipulated to various types and conformations, including surface modification with other molecules to potentially increase their interaction with the host tissue (Madigan et al., 2009).

Scaffolds are used in various forms for regeneration of SCI, such as hydrogels, sponges, tubules with single or multi-channels and membranes. Efforts to find out novel biomaterials such as graphene and silk fibroin are also under active investigation (Ryu and Kim, 2013; Subrata Kar et al., 2013). In animal studies, scaffolds in hydrogels and membranes are commonly used in acute and subacute models of SCI that are produced using vascular clips or physical impacts (weight drops and water percussion) and mimic acute SCI pathology of open cord laceration and closed compression injuries in patients. While deep tears or transections are rare in human injury, complete (thoracic) or partial (dorsal or unilateral) transections in animal models are useful in a controlled study of axonal regeneration and tissue engineering of spinal cord (Talac et al., 2004). Scaffolds in sponges and tubular types are commonly used in these approaches to sustain conformation of spinal cord tissues and traverse the glial scar (Nomura et al., 2006a,b) (Fig. 1).

Natural scaffolds

Natural scaffolds have advantages over synthetic ones in their high biocompatibility and functionality, while being limited in mechanical strength and flexibility in manipulation. A variety of natural biomaterials commonly made of proteins and carbohydrates have been used for the cell delivery and

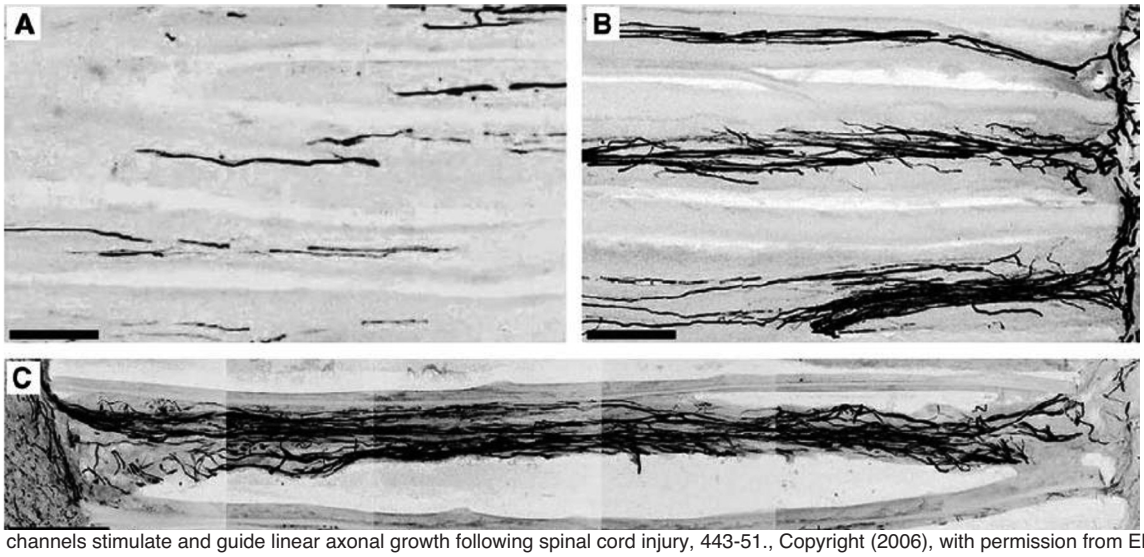


Fig. 1. Nissl stain shows penetration and remarkably linear alignment of axons within channels of freeze-dried agarose scaffolds. The scaffolds unloaded **(A)** and loaded with recombinant human BDNF **(B)**. An ideal example of linear axonal growth and guidance **(C)**. "Reprinted from Biomaterials, 27(3), Stokols S and Tuszynski MH, Freeze-dried agarose scaffolds with uniaxial channels stimulate and guide linear axonal growth following spinal cord injury, 443-51., Copyright (2006), with permission from Elsevier."

tissue engineering to regenerate spinal cord tissues.

Alginate

Alginate is a linear polysaccharide produced by brown algae, and composed of (1→4) linked β-D-mannuronic acid (M) and α-L-glucuronic acid (G) residues. Due to its biocompatibility and bioresoption properties, alginate has been widely used to fill in the damaged spinal cord (Suzuki et al., 2002). Freeze-dried alginate sponge or gel acted as a guide for the amputated axons and reduced astrocytosis between the grafted alginate and the host spinal cord after spinal cord transection in young rats (Kataoka et al., 2004). Alginate was also used to encapsulate hMSCs and sustained hMSC viability and constitutive secretion of regulatory cytokines and growth factors to attenuate macrophage activation *in vitro* and promote tissue regeneration *in vivo* (Barminko et al., 2011). BDNF-producing fibroblasts encapsulated within alginate survived well in the injured spinal cord tissue and contributed to some functional recovery after implantation (Tobias et al., 2005). However, due to its high degradation rate and cytotoxicity, strategies have been adopted to overcome these limitations, such as by incorporating Poly(lactic-co-glycolic acid) (PLGA) microspheres in alginate hydrogels (Ashton et al., 2007). In addition, most of the commercial alginate products include significant amounts of toxic impurities and need ultra-purification prior to cell transplantation (Zimmermann et al., 2001).

Agarose

Agarose is a linear polysaccharide extracted from sea weed and a thermal gelling hydrogel. It has been widely used as a delivery vehicle for drugs or macromolecules. Freeze-dried agarose scaffolds containing nerve growth factor (NGF) showed a favorable effect on axonal regeneration after CNS injury (Stokols and Tuszynski, 2006). It was also used to guide cell adhesion and neurite outgrowth *in vitro* (Luo and Shoichet, 2004). Recently, the sugar trehalose and agarose hydrogel-based delivery system was utilized to facilitate sustained local delivery of thermostabilized chondroitinase ABC (chABC) *in vivo* and, in combination with neutrophin-3 (NT-3), showed locomotor recovery with axonal regeneration of injured spinal cord in rats (Lee et al., 2010). Agarose was also used to deliver bone marrow stromal cells over-expressing NT-3 into the injured spinal cord in rats, which showed a substantial increase in linear growth of long-tract axons across the lesion site (Gros et al., 2010).

Chitosan

Chitin is a co-polymer of N-acetyl-glucosamine and N-glucosamine units. Chitosan is a natural substance similar in structure to cellulose, a plant fiber, and is prepared from chitin by N-deacetylation (Khor and Lim, 2003). The physicochemical properties of chitosan depend on their biological sources. They inherently

Table 1. The major natural biomaterials in use in animal model of spinal cord injury.

Natural biomaterials		Application for spinal cord repair	References
Agarose /Alginate	Encapsulation	Microencapsulation of hMSC or ChABC.	Barminko et al., 2011
	Tubular	Induction of long-tract axons with MSCs and NT-3 or BDNF.	Stokols et al., 2006; Gros et al., 2010; Lee et al., 2010
	Hydrogel	Local delivery of BDNF.	Jain et al., 2006
Chitosan	Tubular	Extra and intramedullary tissue bridge conduits with neural stem/progenitor cells or MSCs.	Nomura et al., 2008; Bozkurt et al., 2010; Chen et al., 2011
	Sponge	Laminin-incorporated nerve conduits.	Cheng et al., 2007
Collagen	Tubular	Using a collagen scaffold containing a collagen binding BDNF and an EGFR neutralizing Ab.	Liu et al., 2001; Spilker et al., 2001; Han et al., 2010
	Sponge	Transplantation of MSCs, Human ESC-derived neural precursor cells and olfactory ensheathing cells	Yoshii et al., 2004; Hatami et al., 2009; Deumens et al., 2013
	Hydrogel	Alignment of astrocytes in 3D collagen gel and axon stretch-growth technology.	Iwata et al., 2006; East et al., 2010
Fibrin	Hydrogel	Controlled release of NT-3 and PDGF from scaffolds containing NPCs. Transplantation of human umbilical MSCs and human BMSCs.	Itosaka et al., 2009; Johnson et al., 2010a-c; Zurita et al., 2010; Liu et al., 2013
Fibronectin	Hydrogel	Neurotrophin/drug delivery	Phillips et al., 2004
Hyaluronic acid	Hydrogel	Modified with nogo-66 receptor Ab and Poly-L-lysine or matrix metalloproteinase-sensitive.	Park et al., 2010; Wei et al., 2010; Khaing et al., 2011; Li et al., 2013
Xyloglucan	Hydrogel	The repair using themoresponsive hydrogel.	Nisbet et al., 2009

affect the size and morphology of pores in scaffolds, which consequently determines their physicochemical properties, such as water absorption, mechanical strength, biodegradation rates and cellular activities (Nwe et al., 2009). Because of its non-toxic and ideal biodegradation properties, chitosan scaffolds have been used to bridge sciatic nerve injury (Itoh et al., 2003; Rosales-Cortes et al., 2003). Chitosan has by itself a neuroprotective effect and enhances physiological recovery of traumatic SCI (Cho et al., 2010). Neural stem cells loaded on chitosan channels showed enhanced survival rates and efficient regeneration of injured spinal cord when transplanted in complete spinal cord transection and subacute SCI models of rats (Nomura et al., 2008; Bozkurt et al., 2010). However, they showed functional recovery only when co-treated with growth factors and soluble Nogo-66 receptor to block myelin-based inhibitors in the complete transection model and with dibutyryl cyclic-AMP in the subacute model, respectively (Kim et al., 2011; Guo et al., 2012). In contrast, transplantation of bone marrow stromal cells loaded on chitosan conduits was shown to enhance both nerve regeneration and functional recovery in an acute SCI model in rats (Chen et al., 2011). A hydrogel form of chitosan cross-linked with poly(ethylene oxide) (chitosan-PEO) has been fabricated and showed high compatibility and functionality on neuronal cell culture *in vitro* but needs further verification in SCI models (Kim et al., 2012).

Collagen

Collagen is one of the major ECM proteins found in mammals, accounting for 25–30% of the total protein in human. Collagen has binding sites for cell adhesion and supports well cell migration, proliferation and differentiation. In addition, it has a relatively high mechanical strength as a natural biomaterial, being similar to that of native soft tissues. These ideal properties and bioactive functions of collagen made it one of the most popular natural biomaterials investigated for therapeutic purposes (Yoshii et al., 2004). Early use of collagen scaffolds in SCI mainly focused on delivery of neurotrophic factors such as NGF, NT-3 and BDNF (Houweling et al., 1998a,b). Collagen scaffolds were used in various forms of hydrogel, sponge and guidance conduit to deliver therapeutic cells into injured spinal cord. A combination therapy of collagen gels with several neurotrophic factors such as BDNF and NT-3, stimulated axonal regeneration, including axons from the corticospinal tract, after dorsal spinal cord transection, and promoted partial functional recovery (East et al., 2010; Han et al., 2010). Neural precursor cells derived from ESCs were transplanted in collagen scaffold and showed enhanced remyelination and functional improvements in a rat model of acute SCI (Hatami et al., 2009). Schwann cells suspended in laminin-collagen composite gels showed enhanced cell survival, improved vascularization and axonal growth in a contusion model

Table 2. The major synthetic biomaterials in use in animal model of spinal cord injury.

Synthetic biomaterials		Application for spinal cord repair	References
PCL	Tubular	3d plotting and printing, a rapid prototyping technology, was used in scaffold fabrication. In addition, SCI treated with SAP, BDNF and ChABC.	Silva et al., 2010, 2013; Gelain et al., 2011; Donoghue et al., 2013
	Sponge	Transplantation of genetically modified NSCs to secrete NT-3.	Hwang et al., 2011
PHB	Sponge	PHB-HV-based 3D scaffold	Ribeiro-Samy et al., 2013
	Sheet	Transplantation of Schwann cells on PHB with laminin coating.	Novikova et al., 2008
PLA	Sponge	Microporous scaffolds seeded with genetically modified Schwann cells.	Hurtado et al., 2006, 2011; Cai et al., 2007
PLGA	Tubular	Transplantation of NT-3 gene-modified Schwann cells and TrkC gene-modified MSC. Local gene delivery or NT-3 delivery.	De Laporte et al., 2009; He et al., 2009; Krych et al., 2009; Fan et al., 2011
	Sponge	Transplantation of NSCs, Schwann cells and/or MSCs. Evaluation of PLGA seeded with human NSCs in the African green monkey or in canine.	Rooney et al., 2008a,b; Chen et al., 2009; De Laporte et al., 2009; Olson et al., 2009; Rauch et al., 2009; Yang et al., 2009; Pritchard et al., 2010; Du et al., 2013
	Film	NSCs seeded on micropatterned films or Scavenger-releasing films.	Yucel et al., 2010
	Hydrogel	NT-3 delivery	Stanwick et al., 2012
PEG	Hydrogel	Local delivery BDNF or FGF2 with or without cells.	Kang et al., 2010; Conova et al., 2011; Kouhzaei et al., 2013; Li et al., 2013; Shi, 2013
PHEMA	Hydrogel	Scaffolds used for cell adhesion, axonal growth and angiogenesis.	Hejcl et al., 2009, 2013; Ruzicka et al., 2013; Valdes-Sanchez et al., 2013
PHPMA	Hydrogel	Hydrogel seeded with MSCs.	Hejcl et al., 2010; Pertici et al., 2013

in rats (Patel et al., 2010). Human NSCs and canine neural-induced adipose-derived MSCs mixed in matrigel showed axonal regeneration and functional recovery in canine SCI models at 12 and 8 weeks, respectively (Lee et al., 2009; Park et al., 2012). When injected using matrigel, MSCs from different sources of the adipose tissue, bone marrow, umbilical cord blood (UCB) and Wharton's jelly all showed functional recovery, increased neuronal survival and reduced inflammation in the canine SCI model (Ryu et al., 2012). Among them, UCB-derived MSCs showed the best outcome. Other studies utilized the collagen conduit that can guide longitudinal infiltration of cells and axon growth. Astrocytes alignment mapped within collagen gels supported neurite growth along the alignment, and could be transformed into the spinal cord conduit by plastic compression *in vitro* (East et al., 2010). A combined cell therapy using Schwann cells in matrigel-filled guidance channels, olfactory ensheathing glia and chondroitinase ABC improved bladder function to void efficiently at 5 weeks after complete thoracic SCI model in rats (Fouad et al., 2009). In contrast to these promising results of cell therapy using collagen scaffolds, a frustrating result was also reported. Transplantation of olfactory ensheathing cells (OEC) in a collagen-based multichannel scaffold has shown no significant improvement in motor function or relieve of allodynia in a unilateral low-thoracic hemisection model of SCI in rats (Deumens et al., 2013). The authors conclude that it was probably due to the relatively large defect size. However it is questionable because their SCI model has been commonly used in many previous studies showing positive results with or without cell transplantation.

Fibrin

Fibrin is the major component of a blood clot. It acts as a binding molecule for the interactions between cells. In injured tissue, some cells bind to fibrin through its surface receptors, which helps them to perform different biologic roles. Many studies have demonstrated the utility of injectable and biodegradable fibrin in tissue regeneration, occasionally being used with growth factors (e.g. aFGF and NT-3) or in combination with other matrices (Taylor et al., 2006; Zurita et al., 2010). When injected into injured spinal cord in rats at a subacute phase (2 weeks post-injury), fibrin promoted neural fiber sprouting and increased migration of neural support cells into the lesion site (Johnson et al., 2010a-c). Fibrin was also used to transplant ectomesenchymal stem cells (EMSCs) into hemisected spinal cord of rats and enhanced their survival and migration to promote behavioral and histological improvement (Liu and et al., 2013). When embryonic stem cells (ESCs)-derived neural progenitor cells (NPCs) were embedded in fibrin scaffolds containing NT-3 and PDGF, cell survival and proliferation was much increased at 2 weeks after transplantation into injured spinal cord in rats (Johnson et al., 2010a-c). Fibrin scaffold containing growth factor cocktails also supported well long-distance axonal growth and inter-connection of neural stem cells (NSCs) implanted into severe spinal cord injury in rats (Lu et al., 2012). These findings suggest that fibrin might be one of the most promising candidates for a potential, minimally invasive scaffold to regenerate injured spinal cord (Itosaka et al., 2009).

Hyaluronic acid

Hyaluronic acid (HA) is a natural polysaccharide consisting of repeating disaccharide units in linear structure: glucuronic acid and N-acetylglucosamine. It has an important role in many tissue repair processes (Wang et al., 1998). Several *in vivo* and *in vitro* experiments show that hyaluronan-based conduits are completely biodegradable, non-cytotoxic, and biocompatible (Avitabile et al., 2001). Cells do not readily adhere to HA but the modification to its surface properties can improve its efficacy. HA can reduce the extent of scar formation by inhibiting lymphocyte migration, proliferation and chemotaxis. High MW HA hydrogel and the one modified with nogo-66 receptor antibody reduced astrocytes activation and decreased CSPG deposition *in vivo* (Wei et al., 2010). Injection of BDNF-incorporated HA hydrogel in the rat SCI model prevented the development of an inflammatory reaction and increased motor function (Park et al., 2010). However, due to its weak mechanical properties and high degradation rate, HA needs incorporation of other polymers to be used for cell delivery. For example, thiol-functionalized HA was cross-linked with thiol-functionalized gelatin by poly-(ethylene glycol) diacrylate (PEGDA) to improve cell adhesion and mechanical properties and used successfully to deliver oligodendrocyte progenitor cells (OPCs) and enhance remyelination of adult spinal cord after demyelination using ethidium bromide (EB) (Li et al., 2013).

Self-assembling peptides

Self-assembling peptides (SAPs) are nanomaterials that form a scaffold by themselves in solution that mimics the properties of the natural ECM. They are reabsorbable, allow biofunctionalizations and can be fabricated easily into an injectable type. They are composed of short, repeating units of amino acids that form nanofibrous scaffolds in response to thermal or pH changes (Cigognini et al., 2011). An injectable SAP RADA16-I (Ac-RADARADARADARADA-COHN2) was functionalized with a bone marrow homing motif (BMHP1, PFSSTKT), which significantly enhanced survival and differentiation of adult mouse neural stem cells and schwann cells *in vitro* (Gelain et al., 2006) and improved functional and histological recovery of acute SCI in rats (Cigognini et al., 2011). A SAP K2(QL)6K2 was shown to promote neurological recovery of SCI by inhibiting inflammation and glial scar formation (Liu et al., 2013). Therefore, the SAP-based injectable scaffolds

have a high potential and wide range of utility for the regeneration of SCI, which will be developed in the near future.

Synthetic scaffolds

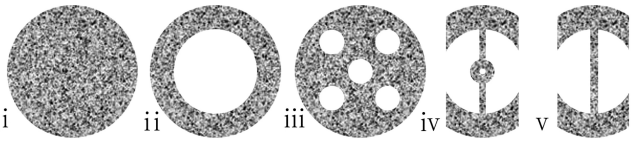
Synthetic polymers have many advantages as scaffolds (Table 2). They can be manipulated to have a wide range of mechanical and physicochemical properties. Different synthetic polymers can be easily blended together to produce a new biomaterial with unique properties (Willerth and Sakiyama-Elbert, 2007; Madigan et al., 2009). However, they are prone to cause an immune response in the human body and have a limitation in FDA approval for practical use.

Poly-ε-caprolactone (PCL)

PCL is a bioresorbable and biocompatible aliphatic polyester that is commonly used in many medical products, including wound dressings (Venugopal et al., 2005). PCL is degraded easily by hydrolysis of its ester bonds in physiological conditions and therefore has been used extensively to construct an implantable biomaterial. It is particularly useful for manufacturing implantable devices for long periods of time, because its degradation rate is even slower than that of polylactide *in vivo*. A recent study using an *in vitro* model showed that PCL was much better than other synthetic biomaterials such as polycarbonate (PCB), poly(methyl) methacrylate (PMMA), polystyrene (PS), poly-L-lactide (PLLA) and polydimethylsiloxane (PDMS) in supporting myelination of neurons, although its ability to support neurite growth itself was quite similar to them (Donoghue et al., 2013). In a T8-T9 spinal hemisection model of rats, implantation of a composite scaffold using starch and PCL itself stabilized the injured spinal cord and improved motor deficits (Silva et al., 2013). The novel open-path designs of PCL conduits allowed greater penetration of GFAP-positive cells from both stumps and caused less scarring than the other architectures, including the cylinder, tube and channel, when they were implanted into the T8 complete transection of rat spinal cord (Wong et al., 2008) (Fig. 2). An electrospun fiber of PCL and SAPs was also used to fabricate a hollow guidance channel (Gelain et al., 2011). The PCL/SAPs guidance channel promoted regeneration of nerve fibers throughout the whole channels, and improved vascular network formation and locomotor recovery, when implanted in combination with pro-regenerative cytokines into the cavity of chronic, post-contusive lesions of the thoracic spinal cord. Delivery of NSCs and NT3 using PCL scaffold was recently shown to promote regeneration of injured spinal cord and improved locomotor recovery in a rat hemisection model (Hwang et al., 2011). However, delivery of MSCs in a PCL conduit promoted peripheral nerve regeneration but not that of spinal cord neurons (Frattini et al., 2012). From the studies above, we can understand that PCL can be easily fabricated into scaffolds with various architectures and used alone or in combination with trophic factor and/or therapeutic cells to regenerate injured spinal cords.

Poly-lactic acid (PLA)

PLA is a member of the α-hydroxy acid class of compounds and also a biodegradable aliphatic polyester like PCL. It has been widely used as a temporary extracellular matrix in tissue engineering. PLA is structurally unstable, fragmenting and collapsing, but proved to support the extension of axons and vascular growth into the graft. The PLA scaffolds were fabricated in a diverse array of architectures including hydrogels, macroporous sponges with inner channels, micro- or nano-fibers, and multi-walled conduits, and mostly used without therapeutic cells or drugs to regenerate SCI (Deng et al., 2006; Cai et al., 2007; Li and Shi, 2007; Hurtado et al., 2011). These approaches have shown promising results by bridging spinal cord gaps, allowing infiltration of host astrocytes or Schwann cells and finally promoting axonal regeneration and functional recovery in some cases. However, it is generally regarded that implantation of scaffolds alone is not enough to promote meaningful recovery of injured spinal cord, particularly in human patients. A macroporous PLA scaffold with longitudinal pores was used to deliver BDNF but failed to improve axonal regeneration of injured spinal cord in rats (Patist et al., 2004). A single channel tubular PLA scaffold containing Schwann cells guided well axonal regeneration in the completely transected adult rat spinal cord, which appeared to be comparable to that seen with a Schwann cell-loaded non-degradable polyacrylonitrile/



	Tissue ingrowth and continuity	Myelinated fibers	Astrocyte immigration	Axonal infiltration
Cylinder(i)	-	-	-	-
Tube(ii)	+	-	-	+
Channel(iii)	+	-	+	+
Open-path with core (iv)	++	+++	++	+++
Open-path without core (v)	++	++	+	++

Fig. 2. Open-path designs of nerve conduits allowed greater penetration of GFAP+ cells from both stumps and caused less scarring than the conventional implant designs. It also provided contact guidance and allowed nerve fibers to extend across the entire defect length (Wong et al., 2008).

polyvinylchloride (PAN/PVC) channel (Oudega et al., 2001). However, freeze-dried PLA macroporous guidance scaffold with NT3-expressing rat Schwann cells showed poor survival of implanted cells and functional improvement of the hind limbs was not observed in a complete transection model of rat thoracic spinal cord (Hurtado et al., 2006). Therefore, the PLA scaffolds were not always successful in axonal regeneration SCI in animal models and probably need further optimization.

Poly-lactic-co-glycolic acid (PLGA)

PLGA is synthesized by random co-polymerization of two different monomers of glycolic acid and lactic acid. PLGA is one of the most extensively investigated biomaterials used alone or to deliver therapeutic cells and drugs for spinal cord regeneration. The degradation rate of PLGA can be manipulated to some extent by altering the ratios of the PLA and PGA in the composite, which also affects their physicochemical properties (bending, swelling, deformation, degradation and permeability) (de Ruiter et al., 2008).

PLGA hydrogels and nerve conduits were used traditionally to deliver neurotrophic factors to injured spinal cord (Yang et al., 2005; Burdick et al., 2006). PLGA microspheres were used later for drug delivery to treat SCI in animal models (Goraltchouk et al., 2006; Tan et al., 2007). In recent studies, PLGA nanoparticles were fabricated to encapsulate various therapeutic drugs, which showed some beneficial effects on spinal cord regeneration and functional recovery, when implanted alone or embedded in other hydrogels (Chvatal et al., 2008; Wang et al., 2008; Baumann et al., 2010; Stanwick et al., 2012).

PLGA scaffolds were also investigated extensively in the animal models of SCI to deliver therapeutic cells such as MSCs, NSCs and Schawann cells (Teng et al., 2002; Moore et al., 2006; Krych et al., 2009; Kim et al., 2010; Kang et al., 2012). PLGA scaffold containing NSCs showed remarkable improvement in the spinal cord function in a rat hemisection injury model (Teng et al., 2002) and a possibility of spinal cord regeneration in a canine model (Kim et al., 2010). A recent study using human MSCs-loaded PLGA scaffold showed significant improvement in behavior analysis and in motor-evoked potentials (MEPs) in a rat complete transection model (Kang et al., 2012). Co-implantation of NSCs with other cell types such as Schawann cells or endothelial cells in a PLGA scaffold was suggested as a promising strategy to increase therapeutic benefits in animal studies (Olson et al., 2009; Rauch et al., 2009; Xiong et al., 2012).

PLGA scaffolds can also be fabricated in diverse architectures and compositions. For example, a PLGA conduit with smaller diameter channels was shown to promote regeneration of injured spinal cord better than that with larger channels, when they were implanted with Schwann cells (Krych et al., 2009). PLGA was sometimes combined with other biomaterials to fabricate cell delivery implants. It was fabricated into a cylindrical scaffold in combination with small intestinal submucosa (SIS) for MSCs delivery (Kang et al., 2011), a thin film to ensheath a gelatin sponge scaffold containing MSCs (Zeng et al., 2011), and a conduit filled with olfactory ensheathing cells (OECs) and extracellular matrix gel (Li et al., 2010).

As shown above, PLGA has been extensively investigated with diverse uses because it has an ideal physicochemical property as a scaffold biomaterial. PLGA was approved by the US FDA for its clinical use for drug delivery, diagnosis and other applications but without including cells. Degradation of PLGA is known to decrease pH value in the surrounding environment, which might hamper its therapeutic potential to regenerate injured spinal cord (Du et al., 2013). Therefore, this problem has to be solved before it is approved by US FDA as a cell delivery vehicle.

Poly-β-hydroxybutirate (PHB)

PHB is a high molecular weight biopolyester originally detected in microorganisms. It is a biodegradable and biocompatible polymer. It degrades slowly in the human body after implantation, and converts to a non-toxic metabolite secreted in urine. A tubular conduit made of PHB was used with cultured adult Schwann cells to promote axonal regeneration in a SCI model (Novikova et al., 2008). A PHB fiber coated with alginate hydrogel and fibronectin was also used by itself or with neurotrophic factors (BDNF or NT3) to regenerate injured spinal cord in a rat model (Novikov et al., 2002). However, it has not been a preferred choice for neural regeneration due to its brittle mechanical property. Recently, poly (3-hydroxybutyrate-co-e-hydroxyvalerate) (PHB-HV), a derivate of PHB, was reported to have ideal properties for tissue engineering of spinal cord in terms of biodegradability, biocompatibility, thermoplasticity and piezoelectricity (Ribeiro-Samy et al., 2013).

Polyethylene glycol (PEG)

PEG is a water-soluble surfactant polymer. PEG shows an immune-protecting effect on the injected area by keeping out cell infiltration. PEG was commonly used in as an injectable hydrogel to deliver cells and drugs. A cross-linked hydrogel composed of a poly(N-isopropylacrylaminde) (PNIPAAAm) and PEG was permissive to axonal growth and was used successfully to deliver cell transplants or BDNF into injured spinal cord (Grous et al., 2013). PEG was also used as an adjunct to fabricate other biomaterial scaffolds. A co-hydrogel of hyaluronic acid and gelatin was fabricated by cross-linking using PEG, which enhanced survival of OPCs transplants and remyelination of injured spinal cord (Li et al., 2013). Single-walled carbon nanotubes coated with PEG were used as an implant to bridge injured spinal cord and promote locomotor recovery

(Roman et al., 2011).

Interestingly, PEG itself is known to have a protective effect on spinal cord defects by rapidly resealing neuronal membrane and decreasing mitochondria-derived oxidative stress (Nehrt et al., 2010; Kouhzaei et al., 2013; Shi, 2013). A self-assembled monomethoxy copolymer micelle composed of PEG and poly(d,l-lactic acid) was recently shown to repair injured spinal cord, even when it was implanted intravenously into the injured spinal cord (Shi et al., 2010).

Poly(2-hydroxyethyl methacrylate) (pHEMA)

pHEMA hydrogel consists of cross-linked networks of hydrophilic co-polymers that swell in water and provide 3D substrates for cell attachment and growth. pHEMA is particularly attractive for biomedical engineering applications, because of its ideal physical properties and high biocompatibility. pHEMA can be easily manipulated through formulation chemistry and has been used in many medical applications, e.g. contact lenses, kerato prostheses and as orbital implants. It is also non-biodegradable and therefore does not produce intermediary breakdown products that can be toxic to cells and may adversely affect the regeneration process (Bakshi et al., 2004).

pHEMA shows low interfacial tension with biological fluids and can be formulated in a hydrogel to have mechanical properties similar to those of the spinal cord (Bakshi et al., 2004; Hejcl et al., 2009). pHEMA or p(HEMA-MMA) hydrogel, a co-polymer of HEMA and methyl methacrylate (MMA), was shown to promote regeneration of brainstem motor axons in a rat complete spinal cord transection model (Tsai et al., 2004). It was also modified to have a better mechanical strength and function as a guidance material for SCI by incorporating coiled channels made of PCL or other natural extracellular matrixes such as collagen, fibrin, Matrigel and methylcellulose (Nomura et al., 2006; Tsai et al., 2006). Surface-modified pHEMA with positively charged functional group promoted better axonal growth and spinal cord regeneration than the unmodified or negatively-modified pHEMA (Bakshi et al., 2004; Hejcl et al., 2009).

pHEMA and its derivatives were recently used extensively to deliver various therapeutic cells. Delivery of MSCs using pHEMA promoted regeneration of hemisected rat spinal cord, and p(HEMA-MOETACI), a co-polymer of HEMA and [2-(methacryloxyl)ethyl] trimethylammonium chloride (MOETACI), was better in MSCs delivery (Sykova et al., 2006; Hejcl et al., 2013). Caprolactone 2-(methacryloyloxy) ethyl ester (CLMA), a co-polymer of HEMA and c-caprolactone, was used successfully to deliver ependymal stem/progenitor cells (epSPCs) and regenerate SCI in combination with FM19G11, a hypoxia-inducible factor (HIF) modulator and activator of stem cell function (Valdes-Sanchez et al., 2014). In contrast, pHEMA-5HT, a serotonin-modified pHEMA, was used to deliver SPC-01_GFP3, a spinal progenitor cell line expressing green fluorescent protein (GFP), but only showed short-term recovery of SCI within 1 month (Ruzicka et al., 2013).

Poly [N-2-(hydroxypropyl) methacrylamide] (PHPMA)

PHPMA is a hydrophilic co-polymer that has similar physicochemical property to pHEMA. PHPMA hydrogel was shown to have neuroinductive and neuroconductive effects on injured spinal cord by facilitating regeneration of spinal cord tissues with glial cells, blood vessels and axonal infiltration (Woerly et al., 1998, 1999; Pertici et al., 2013). PHPMA hydrogel with a Arg-Gly-Asp (RGD) modification was developed to treat SCI (Woerly et al., 2001) and is now commercialized under the name of NeuroGelTM.

Concluding remark

This review summarized recent studies to develop biomaterial scaffolds for cell or drug delivery and tissue engineering to treat SCI. The key designs of these spinal cord implants were hydrogels and guidance conduits or channels. Hydrogels have advantages in that they can be made similar to the spinal cord tissues in mechanical property, easily implanted by simple injection and fit well in shape with the surrounding tissues. Natural biomaterials are commonly used to produce the hydrogel because they are more biocompatible than synthetic ones and has mechanical properties suitable for the hydrogel than for solid scaffolds (Phillips et al., 2004; Itosaka et al., 2009; Khaing et al., 2011). The guidance conduits and channels appear to be better at promoting axonal regeneration in the injured spinal cord. However, they require higher mechanical strength to maintain the channel structure, surgical operation to implant them and sometimes further fabrications to fit them in the injury site. Synthetic biomaterials are commonly used for the channel type scaffolds, because they are strong in mechanical property and easy to manipulate in diverse shapes and structures, for example using electro spinning and rapid prototyping (Wong et al., 2008). Three dimensional sponges with simple pores are a conventional choice and not used frequently now, unless they are made of novel biomaterials or equipped with additional properties by combining two different biomaterials or other functional molecules. So, recent approaches are rather focusing on a diverse array of modifications and combination of two or three biomaterials. Many different cell types are used for spinal cord regeneration including but not limited to MSCs, Schwann cells, OECs, NSCs, ESCs and sometimes iPSCs. Most of them were suggested to be efficient in neuronal regeneration of injured spinal cord by reducing neuronal damage, and promoting neurite outgrowth and remyelination (Hatami et al., 2009; Itosaka et al., 2009; Olson et al., 2009; Qian et al., 2009; Hwang et al., 2011; Zhang et al., 2012). A combination

of two different cell types has shown added benefits by enhancing the plasticity and functional recovery as can be seen in the paracrine effect of MSCs to increase NSCs survival and migration into the injury site (Oh et al., 2011; Hawryluk et al., 2012). However, the clinical utility of therapeutic cells in SCI patients needs further verification and probably functional improvement. Growth factors most frequently used together with the biomaterial scaffolds to treat SCI were NT-3, BDNF, FGF-2 and GDNF. Other soluble factors such as chondroitinase ABC and neutralizing antibodies against CSPG and myelin debris were also often used. Therapeutic drugs are certainly thought to play a critical role but not sufficient enough by themselves in spinal cord regeneration. Therefore, a combinatorial approach using cells, scaffolds and drugs appears to be a promising strategy for spinal cord regeneration.

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References

Ankeny D.P., McTigue D.M. and Jakeman L.B. (2004). Bone marrow transplants provide tissue protection and directional guidance for axons after contusive spinal cord injury in rats. Exp. Neurol. 190, 17-31.

Ashton R.S., Banerjee A., Punyani S., Schaffer D.V. and Kane R.S. (2007). Scaffolds based on degradable alginate hydrogels and poly(lactide-co-glycolide) microspheres for stem cell culture. Biomaterials 28, 5518-5525.

Atala A. (2000). Tissue engineering of artificial organs. J. Endourol. 14, 49-57.

Avitabile T., Marano F., Castiglione F., Bucolo C., Cro M., Ambrosio L., Ferrauto C. and Reibaldi A. (2001). Biocompatibility and biodegradation of intravitreal hyaluronan implants in rabbits. Biomaterials 22, 195-200.

Bakshi A., Fisher O., Dagci T., Himes B.T., Fischer I. and Lowman A. (2004). Mechanically engineered hydrogel scaffolds for axonal growth and angiogenesis after transplantation in spinal cord injury. J. Neurosurg. Spine 1, 322-329.

Barminko J., Kim J.H., Otsuka S., Gray A., Schloss R., Grumet M. and Yarmush M.L. (2011). Encapsulated mesenchymal stromal cells for *in vivo* transplantation. Biotechnol. Bioeng. 108, 2747-2758.

Baumann M.D., Kang C.E., Tator C.H. and Shoichet M.S. (2010). Intrathecal delivery of a polymeric nanocomposite hydrogel after spinal cord injury. Biomaterials 31, 7631-7639.

Bixby J.L. and Harris W.A. (1991). Molecular mechanisms of axon growth and guidance. Annu. Rev. Cell Biol. 7, 117-159.

Bozkurt G., Mothe A.J., Zahir T., Kim H., Shoichet M.S. and Tator C.H. (2010). Chitosan channels containing spinal cord-derived stem/progenitor cells for repair of subacute spinal cord injury in the rat. Neurosurgery 67, 1733-1744.

Burdick J.A., Ward M., Liang E., Young M.J. and Langer R. (2006). Stimulation of neurite outgrowth by neurotrophins delivered from degradable hydrogels. Biomaterials 27. 452-459.

Cai J., Ziemba K.S., Smith G.M. and Jin Y. (2007). Evaluation of cellular organization and axonal regeneration through linear PLA foam implants in acute and chronic spinal cord injury. J. Biomed. Mater. Res. A. 83, 512-520.

Chen B.K., Knight A.M., de Ruiter G.C., Spinner R.J., Yaszemski M.J., Currier B.L. and Windebank A.J. (2009). Axon regeneration through scaffold into distal spinal cord after transection. J. Neurotrauma. 26, 1759-1771.

Chen X., Yang Y., Yao J., Lin W., Li Y., Chen Y., Gao Y., Gu X. and Wang X. (2011). Bone marrow stromal cells-loaded chitosan conduits promote repair of complete transection injury in rat spinal cord. J. Mater. Sci. Mater. Med. 22, 2347-2356.

Cheng H., Huang Y.C., Chang P.T. and Huang Y.Y. (2007). Laminin-incorporated nerve conduits made by plasma treatment for repairing spinal cord injury. Biochem. Biophys. Res. Commun. 357, 938-944.

Cho Y., Shi R. and Borgens R.B. (2010). Chitosan produces potent neuroprotection and physiological recovery following traumatic spinal cord injury. J. Exp. Biol. 213, 1513-1520.

Chvatal S.A., Kim Y.T., Bratt-Leal A.M., Lee H. and Bellamkonda R.V. (2008). Spatial distribution and acute anti-inflammatory effects of Methylprednisolone after sustained local delivery to the contused spinal cord. Biomaterials 29, 1967-1975.

Cigognini D., Satta A., Colleoni B., Silva D., Donega M., Antonini S. and Gelain F. (2011). Evaluation of early and late effects into the acute spinal cord injury of an injectable functionalized self-assembling scaffold. PLoS One 6. e19782.

Conova L., Vernengo J., Jin Y., Himes B.T., Neuhuber B., Fischer I. and Lowman A. (2011). A pilot study of poly(N-isopropylacrylamide)-g-polyethylene glycol and poly(N-isopropylacrylamide)-g-methylcellulose branched copolymers as injectable scaffolds for local delivery of neurotrophins and cellular transplants into the injured spinal cord. J. Neurosurg. Spine 15, 594-604.

De Laporte L., Yan A.L. and Shea L.D. (2009). Local gene delivery from ECM-coated poly(lactide-co-glycolide) multiple channel bridges after spinal cord injury. Biomaterials 30, 2361-2368.

De Laporte L., Yang Y., Zelivyanskaya M.L., Cummings B.J., Anderson A.J. and Shea L.D. (2009). Plasmid releasing multiple channel bridges for transgene expression after spinal cord injury. Mol. Ther. 17, 318-326.

De Ruiter G.C., Onyeneho I.A., Liang E.T., Moore M.J., Knight A.M., Malessy M.J., Spinner R.J., Lu L., Currier B.L., Yaszemski M.J. and Windebank A.J. (2008). Methods for *in vitro* characterization of multichannel nerve tubes. J. Biomed. Mater. Res. A 84, 643-651.

Deng Q.Y., Li S.R., Cai W.Q. and Su B.Y. (2006). Poly-lactic acid and agarose gelatin play an active role in the recovery of spinal cord injury. Neurosci. Bull. 22, 73-78.

Deumens R., Van Gorp S.F., Bozkurt A., Beckmann C., Fuhrmann T., Montzka K., Tolba R., Kobayashi E., Heschel I., Weis J. and Brook G.A. (2013). Motor outcome and allodynia are largely unaffected by novel olfactory ensheathing cell grafts to repair low-thoracic lesion gaps in the adult rat spinal cord. Behav. Brain Res. 237, 185-189.

Donoghue P.S., Lamond R., Boomkamp S.D., Sun T., Gadegaard N., Riehle M.O. and Barnett S.C. (2013). The development of a epsilon-polycaprolactone scaffold for central nervous system repair. Tissue Eng. Part A 19, 497-507.

Du B.L., Zeng C.G., Zhang W., Quan D.P., Ling E.A. and Zeng Y.S. (2013). A comparative study of gelatin sponge scaffolds and PLGA scaffolds transplanted to completely transected spinal cord of rat. J. Biomed. Mater. Res. A 102, 1715-1725.

East E., de Oliveira D.B., Golding J.P. and Phillips J.B. (2010).

Alignment of astrocytes increases neuronal growth in three-dimensional collagen gels and is maintained following plastic compression to form a spinal cord repair conduit. Tissue Eng. Part A 16, 3173-3184.

Fan J., Zhang H., He J., Xiao Z., Chen B., Xiaodan J., Dai J. and Xu R. (2011). Neural regrowth induced by PLGA nerve conduits and neurotrophin-3 in rats with complete spinal cord transection. J. Biomed. Mater. Res. B Appl. Biomater. 97, 271-277.

Fawcett J.W. and Asher R.A. (1999). The glial scar and central nervous system repair. Brain Res. Bull. 49, 377-391.

Fouad K., Pearse D.D., Tetzlaff W. and Vavrek R. (2009). Transplantation and repair: combined cell implantation and chondroitinase delivery prevents deterioration of bladder function in rats with complete spinal cord injury. Spinal Cord 47, 727-732.

Frattini F., Lopes F.R., Almeida F.M., Rodrigues R.F., Boldrini L.C., Tomaz M.A., Baptista A.F., Melo P.A. and Martinez A.M. (2012). Mesenchymal stem cells in a polycaprolactone conduit promote sciatic nerve regeneration and sensory neuron survival after nerve injury. Tissue Eng. Part A 18, 2030-2039.

Fricker R.A., Carpenter M.K., Winkler C., Greco C., Gates M.A. and Bjorklund A. (1999). Site-specific migration and neuronal differentiation of human neural progenitor cells after transplantation in the adult rat brain. J. Neurosci. 19, 5990-6005.

Gelain F., Bottai D., Vescovi A. and Zhang S. (2006). Designer self-assembling peptide nanofiber scaffolds for adult mouse neural stem cell 3-dimensional cultures. PLoS One 1. e119.

Gelain F., Panseri S., Antonini S., Cunha C., Donega M., Lowery J., Taraballi F., Cerri G., Montagna M., Baldissera F. and Vescovi A. (2011). Transplantation of nanostructured composite scaffolds results in the regeneration of chronically injured spinal cords. ACS Nano 5, 227-236.

Goraltchouk A., Scanga V., Morshead C.M. and Shoichet M.S. (2006). Incorporation of protein-eluting microspheres into biodegradable nerve guidance channels for controlled release. J. Control Release. 110, 400-407.

Gros T., Sakamoto J.S., Blesch A., Havton L.A. and Tuszynski M.H. (2010). Regeneration of long-tract axons through sites of spinal cord injury using templated agarose scaffolds. Biomaterials 31, 6719-6729.

Grous L.C., Vernengo J., Jin Y., Himes B.T., Shumsky J.S., Fischer I. and Lowman A. (2013). Implications of poly(N-isopropylacrylamide)-g-poly(ethylene glycol) with codissolved brain-derived neurotrophic factor injectable scaffold on motor function recovery rate following cervical dorsolateral funiculotomy in the rat. J. Neurosurg. Spine 18, 641-652.

Guo X., Zahir T., Mothe A., Shoichet M.S., Morshead C.M., Katayama Y. and Tator C.H. (2012). The effect of growth factors and soluble Nogo-66 receptor protein on transplanted neural stem/progenitor survival and axonal regeneration after complete transection of rat spinal cord. Cell Transplant. 21, 1177-1197.

Han Q., Jin W., Xiao Z., Ni H., Wang J., Kong J., Wu J., Liang W., Chen L., Zhao Y., Chen B. and Dai J. (2010). The promotion of neural regeneration in an extreme rat spinal cord injury model using a collagen scaffold containing a collagen binding neuroprotective protein and an EGFR neutralizing antibody. Biomaterials 31, 9212-9220.

Hatami M., Mehrjardi N.Z., Kiani S., Hemmesi K., Azizi H., Shahverdi A. and Baharvand H. (2009). Human embryonic stem cell-derived neural precursor transplants in collagen scaffolds promote recovery in injured rat spinal cord. Cytotherapy 11, 618-630.

Hawryluk G.W., Mothe A., Wang J., Wang S., Tator C. and Fehlings M.G. (2012). An *in vivo* characterization of trophic factor production following neural precursor cell or bone marrow stromal cell transplantation for spinal cord injury. Stem Cells Dev. 21, 2222-2238.

He L., Zhang Y., Zeng C., Ngiam M., Liao S., Quan D., Zeng Y., Lu J. and Ramakrishna S. (2009). Manufacture of PLGA multiple-channel conduits with precise hierarchical pore architectures and *in vitro/vivo* evaluation for spinal cord injury. Tissue Eng. Part C Methods 15, 243-255.

Hejcl A., Lesny P., Pradny M., Sedy J., Zamecnik J., Jendelova P., Michalek J. and Sykova E. (2009). Macroporous hydrogels based on 2-hydroxyethyl methacrylate. Part 6: 3D hydrogels with positive and negative surface charges and polyelectrolyte complexes in spinal cord injury repair. J. Mater. Sci. Mater. Med. 20, 1571-1577.

Hejcl A., Sedy J., Kapcalova M., Toro D.A., Amemori T., Lesny P., Likavcanova-Masinova K., Krumbholcova E., Pradny M., Michalek J., Burian M., Hajek M., Jendelova P. and Sykova E. (2010). HPMA-RGD hydrogels seeded with mesenchymal stem cells improve functional outcome in chronic spinal cord injury. Stem Cells Dev. 19, 1535-1546.

Hejcl A., Ruzicka J., Kapcalova M., Turnovcova K., Krumbholcova E., Pradny M., Michalek J., Cihlar J., Jendelova P. and Sykova E. (2013). Adjusting the chemical and physical properties of hydrogels leads to improved stem cell survival and tissue ingrowth in spinal cord injury reconstruction: a comparative study of four methacrylate hydrogels. Stem Cells Dev. 22, 2794-2805.

Houweling D.A., Lankhorst A.J., Gispen W.H., Bar P.R. and Joosten E.A. (1998a). Collagen containing neurotrophin-3 (NT-3) attracts regrowing injured corticospinal axons in the adult rat spinal cord and promotes partial functional recovery. Exp. Neurol. 153, 49-59.

Houweling D.A., van Asseldonk J.T., Lankhorst A.J., Hamers F.P., Martin D., Bar P.R. and Joosten E.A. (1998b). Local application of collagen containing brain-derived neurotrophic factor decreases the loss of function after spinal cord injury in the adult rat. Neurosci. Lett. 251, 193-196.

Hurtado A., Moon L.D., Maquet V., Blits B., Jerome R. and Oudega M. (2006). Poly (D,L-lactic acid) macroporous guidance scaffolds seeded with Schwann cells genetically modified to secrete a bi-functional neurotrophin implanted in the completely transected adult rat thoracic spinal cord. Biomaterials 27, 430-442.

Hurtado A., Cregg J.M., Wang H.B., Wendell D.F., Oudega M., Gilbert R.J. and McDonald J.W. (2011). Robust CNS regeneration after complete spinal cord transection using aligned poly-L-lactic acid microfibers. Biomaterials 32, 6068-6079.

Hwang D.H., Kim H.M., Kang Y.M., Joo I.S., Cho C.S., Yoon B.W., Kim S.U. and Kim B.G. (2011). Combination of multifaceted strategies to maximize the therapeutic benefits of neural stem cell transplantation for spinal cord repair. Cell Transplant. 20, 1361-1379.

Hyun J.K. and Kim H.W. (2010). Clinical and experimental advances in regeneration of spinal cord injury. J. Tissue Eng. 2010, 650857.

Ibarra C., Koski J.A. and Warren R.F. (2000). Tissue engineering meniscus: cells and matrix. Orthop. Clin. North Am. 31, 411-418.

Itoh S., Suzuki M., Yamaguchi I., Takakuda K., Kobayashi H., Shinomiya K. and Tanaka J. (2003). Development of a nerve scaffold using a tendon chitosan tube. Artif. Organs 27, 1079-1088.

Itosaka H., Kuroda S., Shichinohe H., Yasuda H., Yano S., Kamei S., Kawamura R., Hida K. and Iwasaki Y. (2009). Fibrin matrix provides

a suitable scaffold for bone marrow stromal cells transplanted into injured spinal cord: a novel material for CNS tissue engineering. Neuropathology 29, 248-257.

Iwata A., Browne K.D., Pfister B.J., Gruner J.A. and Smith D.H. (2006). Long-term survival and outgrowth of mechanically engineered nervous tissue constructs implanted into spinal cord lesions. Tissue Eng. 12, 101-110.

Jain A., Kim Y.T., McKeon R.J. and Bellamkonda R.V. (2006). In situ gelling hydrogels for conformal repair of spinal cord defects, and local delivery of BDNF after spinal cord injury. Biomaterials 27, 497-504.

Johnson P.J., Parker S.R. and Sakiyama-Elbert S.E. (2010a). Fibrin-based tissue engineering scaffolds enhance neural fiber sprouting and delay the accumulation of reactive astrocytes at the lesion in a subacute model of spinal cord injury. J. Biomed. Mater. Res. A 92, 152-163.

Johnson P.J., Tatara A., McCreedy D.A., Shiu A. and Sakiyama-Elbert S.E. (2010b). Tissue-engineered fibrin scaffolds containing neural progenitors enhance functional recovery in a subacute model of SCI. Soft Matter. 6, 5127-5137.

Johnson P.J., Tatara A., Shiu A. and Sakiyama-Elbert S.E. (2010c). Controlled release of neurotrophin-3 and platelet-derived growth factor from fibrin scaffolds containing neural progenitor cells enhances survival and differentiation into neurons in a subacute model of SCI. Cell Transplant. 19. 89-101.

Kang C.E., Tator C.H. and Shoichet M.S. (2010). Poly(ethylene glycol) modification enhances penetration of fibroblast growth factor 2 to injured spinal cord tissue from an intrathecal delivery system. J. Control Release 144, 25-31.

Kang K.N., Lee J.Y., Kim da Y., Lee B.N., Ahn H.H., Lee B., Khang G., Park S.R., Min B.H., Kim J.H., Lee H.B. and Kim M.S. (2011). Regeneration of completely transected spinal cord using scaffold of poly(D,L-lactide-co-glycolide)/small intestinal submucosa seeded with rat bone marrow stem cells. Tissue Eng. Part A 17, 2143-2152.

Kang K.N., Kim da Y., Yoon S.M., Lee J.Y., Lee B.N., Kwon J.S., Seo H.W., Lee I.W., Shin H.C., Kim Y.M., Kim H.S., Kim J.H., Min B.H., Lee H.B. and Kim M.S. (2012). Tissue engineered regeneration of completely transected spinal cord using human mesenchymal stem cells. Biomaterials 33, 4828-4835.

Kataoka K., Suzuki Y., Kitada M., Hashimoto T., Chou H., Bai H., Ohta M., Wu S., Suzuki K. and Ide C. (2004). Alginate enhances elongation of early regenerating axons in spinal cord of young rats. Tissue Eng. 10, 493-504.

Khaing Z.Z., Milman B.D., Vanscoy J.E., Seidlits S.K., Grill R.J. and Schmidt C.E. (2011). High molecular weight hyaluronic acid limits astrocyte activation and scar formation after spinal cord injury. J. Neural Eng. 8, 046033.

Khor E. and Lim L.Y. (2003). Implantable applications of chitin and chitosan. Biomaterials 24, 2339-2349.

Kim B.G., Kang Y.M., Phi J.H., Kim Y.H., Hwang D.H., Choi J.Y., Ryu S., Elastal A.E., Paek S.H., Wang K.C., Lee S.H., Kim S.U. and Yoon B.W. (2010). Implantation of polymer scaffolds seeded with neural stem cells in a canine spinal cord injury model. Cytotherapy 12, 841-845.

Kim H., Zahir T., Tator C.H. and Shoichet M.S. (2011). Effects of dibutyryl cyclic-AMP on survival and neuronal differentiation of neural stem/progenitor cells transplanted into spinal cord injured rats. PLoS One 6, e21744.

Kim S.M., Jo S.Y., Shin E.K., Kim D.Y. and Noh I.S. (2012). Evaluations of nerve cell compatibility of self cross-linking chitosan-poly(ethylene oxide) hydrogel. Tissue Eng. Regen. Med. 9, 84-91.

Kim M.H., Kim K.H., Park S.R. and Choi B.H. (2013). Mesenchymal stem cells for treatment of neurological disorders: a paracrine effect. Tissue Eng. Regen. Med. 10, 234-245.

Kouhzaei S., Rad I., Mousavidoust S. and Mobasheri H. (2013). Protective effect of low molecular weight polyethylene glycol on the repair of experimentally damaged neural membranes in rat's spinal cord. Neurol. Res. 35, 415-423.

Krych A.J., Rooney G.E., Chen B., Schermerhorn T.C., Ameenuddin S., Gross L., Moore M.J., Currier B.L., Spinner R.J., Friedman J.A., Yaszemski M.J. and Windebank A.J. (2009). Relationship between scaffold channel diameter and number of regenerating axons in the transected rat spinal cord. Acta Biomater. 5, 2551-2559.

Lee S.H., Chung Y.N., Kim Y.H., Kim Y.J., Park J.P., Kwon D.K., Kwon O.S., Heo J.H., Ryu S., Kang H.J., Paek S.H., Wang K.C., Kim S.U. and Yoon B.W. (2009). Effects of human neural stem cell transplantation in canine spinal cord hemisection. Neurol. Res. 31, 996-1002.

Lee H., McKeon R.J. and Bellamkonda R.V. (2010). Sustained delivery of thermostabilized chABC enhances axonal sprouting and functional recovery after spinal cord injury. Proc. Natl. Acad. Sci. USA 107, 3340-3345.

Li J. and Shi R. (2007). Fabrication of patterned multi-walled poly-l-lactic acid conduits for nerve regeneration. J. Neurosci. Methods. 165, 257-264.

Li B.C., Jiao S.S., Xu C., You H. and Chen J.M. (2010). PLGA conduit seeded with olfactory ensheathing cells for bridging sciatic nerve defect of rats. J. Biomed. Mater. Res. A 94, 769-780.

Li X., Liu X., Cui L., Brunson C., Zhao W., Bhat N.R., Zhang N. and Wen X. (2013). Engineering an in situ crosslinkable hydrogel for enhanced remyelination. FASEB J. 27, 1127-1136.

Liu S., Said G. and Tadie M. (2001). Regrowth of the rostral spinal axons into the caudal ventral roots through a collagen tube implanted into hemisected adult rat spinal cord. Neurosurgery 49, 143-150; discussion 150-141.

Liu J., Chen Q., Zhang Z., Zheng Y., Sun X., Cao X., Gong A., Cui Y., He Q. and Jiang P. (2013). Fibrin scaffolds containing ectomesenchymal stem cells enhance behavioral and histological improvement in a rat model of spinal cord injury. Cells Tissues Organs 198, 35-46.

Liu Y., Ye H., Satkunendrarajah K., Yao G.S., Bayon Y. and Fehlings M.G. (2013). A self-assembling peptide reduces glial scarring, attenuates post-traumatic inflammation and promotes neurological recovery following spinal cord injury. Acta Biomater. 9, 8075-8088.

Lu P., Wang Y., Graham L., McHale K., Gao M., Wu D., Brock J., Blesch A., Rosenzweig E.S., Havton L.A., Zheng B., Conner J.M., Marsala M. and Tuszynski M.H. (2012). Long-distance growth and connectivity of neural stem cells after severe spinal cord injury. Cell 150, 1264-1273.

Luo Y. and Shoichet M.S. (2004). A photolabile hydrogel for guided three-dimensional cell growth and migration. Nat. Mater. 3, 249-253.

Madigan N.N., McMahon S., O'Brien T., Yaszemski M.J. and Windebank A.J. (2009). Current tissue engineering and novel therapeutic approaches to axonal regeneration following spinal cord injury using polymer scaffolds. Respir. Physiol. Neurobiol. 169, 183-199.

Moore M.J., Friedman J.A., Lewellyn E.B., Mantila S.M., Krych A.J., Ameenuddin S., Knight A.M., Lu L., Currier B.L., Spinner R.J.,

Marsh R.W., Windebank A.J. and Yaszemski M.J. (2006). Multiple-channel scaffolds to promote spinal cord axon regeneration. Biomaterials 27, 419-429.

Nehrt A., Hamann K., Ouyang H. and Shi R. (2010). Polyethylene glycol enhances axolemmal resealing following transection in cultured cells and in ex vivo spinal cord. J. Neurotrauma. 27, 151-161.

Nisbet D.R., Moses D., Gengenbach T.R., Forsythe J.S., Finkelstein D.I. and Horne M.K. (2009). Enhancing neurite outgrowth from primary neurones and neural stem cells using thermoresponsive hydrogel scaffolds for the repair of spinal cord injury. J. Biomed. Mater. Res. A 89, 24-35.

Nomura H., Katayama Y., Shoichet M.S. and Tator C.H. (2006a). Complete spinal cord transection treated by implantation of a reinforced synthetic hydrogel channel results in syringomyelia and caudal migration of the rostral stump. Neurosurgery 59, 183-192; discussion 183-192.

Nomura H., Tator C.H. and Shoichet M.S. (2006b). Bioengineered strategies for spinal cord repair. J. Neurotrauma. 23, 496-507.

Nomura H., Zahir T., Kim H., Katayama Y., Kulbatski I., Morshead C.M., Shoichet M.S. and Tator C.H. (2008). Extramedullary chitosan channels promote survival of transplanted neural stem and progenitor cells and create a tissue bridge after complete spinal cord transection. Tissue Eng. Part A 14, 649-665.

Novikov L.N., Novikova L.N., Mosahebi A., Wiberg M., Terenghi G. and Kellerth J.O. (2002). A novel biodegradable implant for neuronal rescue and regeneration after spinal cord injury. Biomaterials 23, 3369-3376.

Novikova L.N., Pettersson J., Brohlin M., Wiberg M. and Novikov L.N. (2008). Biodegradable poly-beta-hydroxybutyrate scaffold seeded with Schwann cells to promote spinal cord repair. Biomaterials 29, 1198-1206.

Nwe N., Furuike T. and Tamura H. (2009). The mechanical and biological properties of chitosan scaffolds for tissue regeneration templates are significantly enhanced by chitosan from Gongronella butleri. Materials 2, 374-398.

Oh J.S., Kim K.N., An S.S., Pennant W.A., Kim H.J., Gwak SJ.., Yoon do H., Lim M.H., Choi B.H. and Ha Y. (2011). Cotransplantation of mouse neural stem cells (mNSCs) with adipose tissue-derived mesenchymal stem cells improves mNSC survival in a rat spinal cord injury model. Cell Transplant. 20, 837-849.

Olson H.E., Rooney G.E., Gross L., Nesbitt J.J., Galvin K.E., Knight A., Chen B., Yaszemski M.J. and Windebank A.J. (2009). Neural stem cell- and Schwann cell-loaded biodegradable polymer scaffolds support axonal regeneration in the transected spinal cord. Tissue Eng. Part A 15, 1797-1805.

Oudega M., Gautier S.E., Chapon P., Fragoso M., Bates M.L., Parel J.M. and Bunge M.B. (2001). Axonal regeneration into Schwann cell grafts within resorbable poly(alpha-hydroxyacid) guidance channels in the adult rat spinal cord. Biomaterials 22, 1125-1136.

Park J., Lim E., Back S., Na H., Park Y. and Sun K. (2010). Nerve regeneration following spinal cord injury using matrix metalloproteinase-sensitive, hyaluronic acid-based biomimetic hydrogel scaffold containing brain-derived neurotrophic factor. J. Biomed. Mater. Res. A 93, 1091-1099.

Park S.S., Lee Y.J., Lee S.H., Lee D., Choi K., Kim W.H., Kweon O.K. and Han H.J. (2012). Functional recovery after spinal cord injury in dogs treated with a combination of Matrigel and neural-induced adipose-derived mesenchymal Stem cells. Cytotherapy 14, 584-597.

Patel V., Joseph G., Patel A., Patel S., Bustin D., Mawson D., Tuesta L.M., Puentes R., Ghosh M. and Pearse D.D. (2010). Suspension matrices for improved Schwann-cell survival after implantation into the injured rat spinal cord. J. Neurotrauma. 27, 789-801.

Patist C.M., Mulder M.B., Gautier S.E., Maquet V., Jerome R. and Oudega M. (2004). Freeze-dried poly(D,L-lactic acid) macroporous guidance scaffolds impregnated with brain-derived neurotrophic factor in the transected adult rat thoracic spinal cord. Biomaterials 25, 1569-1582.

Pertici V., Amendola J., Laurin J., Gigmes D., Madaschi L., Carelli S., Marqueste T., Gorio A. and Decherchi P. (2013). The use of poly(N-[2-hydroxypropyl]-methacrylamide) hydrogel to repair a T10 spinal cord hemisection in rat: a behavioural, electrophysiological and anatomical examination. ASN Neuro. 5, 149-166.

Phillips J.B., King V.R., Ward Z., Porter R.A., Priestley J.V. and Brown R.A. (2004). Fluid shear in viscous fibronectin gels allows aggregation of fibrous materials for CNS tissue engineering. Biomaterials 25, 2769-2779.

Pritchard C.D., Slotkin J.R., Yu D., Dai H., Lawrence M.S., Bronson R.T., Reynolds F.M., Teng Y.D., Woodard E.J. and Langer R.S. (2010). Establishing a model spinal cord injury in the African green monkey for the preclinical evaluation of biodegradable polymer scaffolds seeded with human neural stem cells. J. Neurosci. Methods 188, 258-269.

Qian L.M., Zhang Z.J., Gong A.H., Qin R.J., Sun X.L., Cao X.D., Liu J.B., Jiang P. and Chen Y.C. (2009). A novel biosynthetic hybrid scaffold seeded with olfactory ensheathing cells for treatment of spinal cord injuries. Chin. Med. J. (Engl). 122, 2032-2040.

Rao M. (2013). Stem cells for therapy. Tissue Eng. Regen. Med. 10, 223-229.

Rauch M.F., Hynes S.R., Bertram J., Redmond A., Robinson R., Williams C., Xu H., Madri J.A. and Lavik E.B. (2009). Engineering angiogenesis following spinal cord injury: a coculture of neural progenitor and endothelial cells in a degradable polymer implant leads to an increase in vessel density and formation of the blood-spinal cord barrier. Eur. J. Neurosci. 29, 132-145.

Ribeiro-Samy S., Silva N.A., Correlo V.M., Fraga J.S., Pinto L., Teixeira-Castro A., Leite-Almeida H., Almeida A., Gimble J.M., Sousa N., Salgado A.J. and Reis R.L. (2013). Development and characterization of a PHB-HV-based 3D scaffold for a tissue engineering and cell-therapy combinatorial approach for spinal cord injury regeneration. Macromol. Biosci. 13, 1576-1592.

Roman J.A., Niedzielko T.L., Haddon R.C., Parpura V. and Floyd C.L. (2011). Single-walled carbon nanotubes chemically functionalized with polyethylene glycol promote tissue repair in a rat model of spinal cord injury. J. Neurotrauma. 28, 2349-2362.

Rooney G.E., Moran C., McMahon S.S., Ritter T., Maenz M., Flugel A., Dockery P., O'Brien T., Howard L., Windebank A.J. and Barry F.P. (2008a). Gene-modified mesenchymal stem cells express functionally active nerve growth factor on an engineered poly lactic glycolic acid (PLGA) substrate. Tissue Eng. Part A 14, 681-690.

Rooney G.E., Vaishya S., Ameenuddin S., Currier B.L., Schiefer T.K., Knight A., Chen B., Mishra P.K., Spinner R.J., Macura S.I., Yaszemski M.J. and Windebank A.J. (2008b). Rigid fixation of the spinal column improves scaffold alignment and prevents scoliosis in the transected rat spinal cord. Spine (Phila Pa 1976) 33, E914-919.

Rosales-Cortes M., Peregrina-Sandoval J., Banuelos-Pineda J., Castellanos-Martinez E.E., Gomez-Pinedo U.A. and Albarran-Rodriguez E. (2003). Regeneration of the axotomised sciatic nerve in dogs using the tubulisation technique with Chitosan biomaterial

preloaded with progesterone. Rev Neurol. 36, 1137-1141 (in spanish).

Ruzicka J., Romanyuk N., Hejcl A., Vetrik M., Hruby M., Cocks G., Cihlar J., Pradny M., Price J., Sykova E. and Jendelova P. (2013). Treating spinal cord injury in rats with a combination of human fetal neural stem cells and hydrogels modified with serotonin. Acta Neurobiol. Exp. (Wars) 73, 102-115.

Ryu S.M. and Kim B.S. (2013). Culture of neural cells and stem cells on graphene. Tissue Eng. Regne. Med. 10. 39-46.

Ryu H.H., Kang B.J., Park S.S., Kim Y., Sung G.J., Woo H.M., Kim W.H. and Kweon O.K. (2012). Comparison of mesenchymal stem cells derived from fat, bone marrow, Wharton's jelly, and umbilical cord blood for treating spinal cord injuries in dogs. J. Vet. Med. Sci. 74, 1617-1630.

Shi R. (2013). Polyethylene glycol repairs membrane damage and enhances functional recovery: a tissue engineering approach to spinal cord injury. Neurosci. Bull. 29, 460-466.

Shi Y., Kim S., Huff T.B., Borgens R.B., Park K., Shi R. and Cheng J.X. (2010). Effective repair of traumatically injured spinal cord by nanoscale block copolymer micelles. Nat. Nanotechnol. 5, 80-87.

Shihabuddin L.S., Horner P.J., Ray J. and Gage F.H. (2000). Adult spinal cord stem cells generate neurons after transplantation in the adult dentate gyrus. J. Neurosci. 20, 8727-8735.

Silva N.A., Salgado A.J., Sousa R.A., Oliveira J.T., Pedro A.J., Leite-Almeida H., Cerqueira R., Almeida A., Mastronardi F., Mano J.F., Neves N.M., Sousa N. and Reis R.L. (2010). Development and characterization of a novel hybrid tissue engineering-based scaffold for spinal cord injury repair. Tissue Eng. Part A 16, 45-54.

Silva N.A., Sousa R.A., Fraga J.S., Fontes M., Leite-Almeida H., Cerqueira R., Almeida A., Sousa N., Reis .RL. and Salgado A.J. (2013). Benefits of spine stabilization with biodegradable scaffolds in spinal cord injured rats. Tissue Eng. Part C Methods 19, 101-108.

Spilker M.H., Yannas I.V., Kostyk S.K., Norregaard T.V., Hsu H.P. and Spector M. (2001). The effects of tubulation on healing and scar formation after transection of the adult rat spinal cord. Restor. Neurol. Neurosci. 18, 23-38.

Stanwick J.C., Baumann M.D. and Shoichet M.S. (2012). Enhanced neurotrophin-3 bioactivity and release from a nanoparticle-loaded composite hydrogel. J. Control Release 160, 666-675.

Stokols S. and Tuszynski M.H. (2006). Freeze-dried agarose scaffolds with uniaxial channels stimulate and guide linear axonal growth following spinal cord injury. Biomaterials 27, 443-451.

Stokols S., Sakamoto J., Breckon C., Holt T., Weiss J. and Tuszynski M.H. (2006). Templated agarose scaffolds support linear axonal regeneration. Tissue Eng. 12, 2777-2787.

Subrata Kar S.T, Shilpa Pal, Sunita Nayak, Pallavi Paranjape, Kundu S.C. (2013). Silk gland fibroin from indian muga silkworm Antheraea assama as potential biomaterial. Tissue Eng. Regen. Med 10, 200-210.

Suzuki Y., Kitaura M., Wu S., Kataoka K., Suzuki K., Endo K., Nishimura Y. and Ide C. (2002). Electrophysiological and horseradish peroxidase-tracing studies of nerve regeneration through alginate-filled gap in adult rat spinal cord. Neurosci. Lett. 318, 121-124.

Sykova E., Jendelova P., Urdzikova L., Lesny P. and Hejcl A. (2006). Bone marrow stem cells and polymer hydrogels--two strategies for spinal cord injury repair. Cell Mol. Neurobiol. 26, 1113-1129.

Tabesh H., Amoabediny G., Nik N.S., Heydari M., Yosefifard M., Siadat S.O. and Mottaghy K. (2009). The role of biodegradable engineered scaffolds seeded with Schwann cells for spinal cord regeneration. Neurochem. Int. 54, 73-83.

Talac R., Friedman J.A., Moore M.J., Lu L., Jabbari E., Windebank A.J., Currier B.L. and Yaszemski M.J. (2004). Animal models of spinal cord injury for evaluation of tissue engineering treatment strategies. Biomaterials 25, 1505-1510.

Tan E.Y., Law J.W., Wang C.H. and Lee A.Y. (2007). Development of a cell transducible RhoA inhibitor TAT-C3 transferase and its encapsulation in biocompatible microspheres to promote survival and enhance regeneration of severed neurons. Pharm. Res. 24, 2297-2308.

Taylor S.J., Rosenzweig E.S., McDonald J.W. 3rd. and Sakiyama-Elbert S.E. (2006). Delivery of neurotrophin-3 from fibrin enhances neuronal fiber sprouting after spinal cord injury. J. Control Release 113, 226-235.

Teng Y.D., Lavik E.B., Qu X., Park K.I., Ourednik J., Zurakowski D., Langer R. and Snyder E.Y. (2002). Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells. Proc. Natl. Acad. Sci. USA 99, 3024-3029.

Tobias C.A., Han S.S., Shumsky J.S., Kim D., Tumolo M., Dhoot N.O., Wheatley M.A., Fischer I., Tessler A. and Murray M. (2005). Alginate encapsulated BDNF-producing fibroblast grafts permit recovery of function after spinal cord injury in the absence of immune suppression. J. Neurotrauma. 22, 138-156.

Tsai E.C., Dalton P.D., Shoichet M.S. and Tator C.H. (2004). Synthetic hydrogel guidance channels facilitate regeneration of adult rat brainstem motor axons after complete spinal cord transection. J. Neurotrauma. 21, 789-804.

Tsai E.C., Dalton P.D., Shoichet M.S. and Tator C.H. (2006). Matrix inclusion within synthetic hydrogel guidance channels improves specific supraspinal and local axonal regeneration after complete spinal cord transection. Biomaterials 27, 519-533.

Valdes-Sanchez T., Rodriguez-Jimenez F.J., Garcia-Cruz D.M., Escobar-Ivirico J.L., Alastrue-Agudo A., Erceg S., Monleon M. and Moreno-Manzano V. (2014). Methacrylate-endcapped caprolactone and FM19G11 provide a proper niche for spinal cord-derived neural cells. J. Tissue Eng. Regen. Med. (in press).

Venstrom K.A. and Reichardt L.F. (1993). Extracellular matrix. 2: Role of extracellular matrix molecules and their receptors in the nervous system. FASEB J. 7, 996-1003.

Venugopal J., Zhang Y.Z. and Ramakrishna S. (2005). Fabrication of modified and functionalized polycaprolactone nanofibre scaffolds for vascular tissue engineering. Nanotechnology 16, 2138-2142.

Wang K.K., Nemeth I.R., Seckel B.R., Chakalis-Haley D.P., Swann D.A., Kuo J.W., Bryan D.J. and Cetrulo C.L. Jr (1998). Hyaluronic acid enhances peripheral nerve regeneration *in vivo*. Microsurgery 18, 270-275.

Wang Y.C., Wu Y.T., Huang H.Y., Lin H.I., Lo L.W., Tzeng S.F. and Yang C.S. (2008). Sustained intraspinal delivery of neurotrophic factor encapsulated in biodegradable nanoparticles following contusive spinal cord injury. Biomaterials 29. 4546-4553.

Wei Y.T., He Y., Xu C.L., Wang Y., Liu B.F., Wang X.M., Sun X.D., Cui F.Z. and Xu Q.Y. (2010). Hyaluronic acid hydrogel modified with nogo-66 receptor antibody and poly-L-lysine to promote axon regrowth after spinal cord injury. J. Biomed. Mater. Res. B Appl. Biomater. 95, 110-117.

Willerth S.M. and Sakiyama-Elbert SE. (2007). Approaches to neural tissue engineering using scaffolds for drug delivery. Adv. Drug Deliv. Rev. 59, 325-338.

Woerly S., Pinet E., De Robertis L., Bousmina M., Laroche G., Roitback T., Vargova L. and Sykova E. (1998). Heterogeneous PHPMA hydrogels for tissue repair and axonal regeneration in the injured spinal cord. J. Biomater. Sci. Polym. Ed. 9, 681-711.

Woerly S., Petrov P., Sykova E., Roitbak T., Simonova Z. and Harvey A.R. (1999). Neural tissue formation within porous hydrogels implanted in brain and spinal cord lesions: ultrastructural, immunohistochemical, and diffusion studies. Tissue Eng. 5, 467-488.

Woerly S., Pinet E., de Robertis L., Van Diep D. and Bousmina M. (2001). Spinal cord repair with PHPMA hydrogel containing RGD peptides (NeuroGel). Biomaterials 22, 1095-1111.

Wong D.Y., Leveque J.C., Brumblay H., Krebsbach P.H., Hollister S.J. and Lamarca F. (2008). Macro-architectures in spinal cord scaffold implants influence regeneration. J. Neurotrauma. 25, 1027-1037.

Xiong Y., Zhu J.X., Fang Z.Y., Zeng C.G., Zhang C., Qi G.L., Li M.H., Zhang W., Quan D.P. and Wan J. (2012). Coseeded Schwann cells myelinate neurites from differentiated neural stem cells in neurotrophin-3-loaded PLGA carriers. Int. J. Nanomedicine 7, 1977-1989.

Yang Y., De Laporte L., Rives C.B., Jang J.H., Lin W.C., Shull K.R. and Shea L.D. (2005). Neurotrophin releasing single and multiple lumen nerve conduits. J. Contr. Rel. 104, 433-446.

Yang Y., De Laporte L., Zelivyanskaya M.L., Whittlesey K.J., Anderson A.J., Cummings B.J. and Shea L.D. (2009). Multiple channel bridges for spinal cord injury: cellular characterization of host response. Tissue Eng. Pt. A 15, 3283-3295.

Yoshii S., Oka M., Shima M., Taniguchi A., Taki Y. and Akagi M. (2004). Restoration of function after spinal cord transection using a collagen bridge. J. Biomed. Mater. Res. A 70, 569-575.

Yucel D., Kose G.T. and Hasirci V. (2010). Tissue engineered, guided nerve tube consisting of aligned neural stem cells and astrocytes. Biomacromolecules 11, 3584-3591.

Zeng X., Zeng Y.S., Ma Y.H., Lu L.Y., Du B.L., Zhang W., Li Y. and Chan W.Y. (2011). Bone marrow mesenchymal stem cells in a three-dimensional gelatin sponge scaffold attenuate inflammation, promote angiogenesis, and reduce cavity formation in experimental spinal cord injury. Cell Transplant. 20, 1881-1899.

Zhang Y.Q., He L.M., Xing B., Zeng X., Zeng C.G., Zhang W., Quan D.P. and Zeng Y.S. (2012). Neurotrophin-3 gene-modified Schwann cells promote TrkC gene-modified mesenchymal stem cells to differentiate into neuron-like cells in poly(lactic-acid-co-glycolic acid) multiple-channel conduit. Cells Tissues Organs 195, 313-322.

Zimmermann U., Thurmer F., Jork A., Weber M., Mimietz S., Hillgartner M., Brunnenmeier F., Zimmermann H., Westphal I., Fuhr G., Noth U., Haase A., Steinert A. and Hendrich C. (2001). A novel class of amitogenic alginate microcapsules for long-term immunoisolated transplantation. Ann. N. Y. Acad. Sci. 944, 199-215.

Zurita M., Otero L., Aguayo C., Bonilla C., Ferreira E., Parajon A. and Vaquero J. (2010). Cell therapy for spinal cord repair: optimization of biologic scaffolds for survival and neural differentiation of human bone marrow stromal cells. Cytotherapy 12, 522-537.

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