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Review Article

Biomaterial Scaffolds in Regenerative Therapy of the Central Nervous System

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The central nervous system (CNS) is the most important section of the nervous system as it regulates the function of various organs. Injury to the CNS causes impairment of neurological functions in corresponding sites and further leads to long-term patient disability. CNS regeneration is difficult because of its poor response to treatment and, to date, no effective therapies have been found to rectify CNS injuries. Biomaterial scaffolds have been applied with promising results in regeneration medicine. They also show great potential in CNS regeneration for tissue repair and functional recovery. Biomaterial scaffolds are applied in CNS regeneration predominantly as hydrogels and biodegradable scaffolds. They can act as cellular supportive scaffolds to facilitate cell infiltration and proliferation. They can also be combined with cell therapy to repair CNS injury. This review discusses the categories and progression of the biomaterial scaffolds that are applied in CNS regeneration.

1. Introduction

The central nervous system (CNS), which comprises the brain and spinal cord, is the most important and complex part of the nervous system. Two of the most common causes of injury to the CNS are trauma [1] and hemorrhage [2]. For example, approximately 1.5 million individuals in the USA suffer traumatic CNS injury annually, which includes spinal cord injury (SCI) and traumatic brain injury (TBI) [3, 4]. Injury to the CNS causes significant mortality and morbidity, which results in a heavy economic burden on society. It is reported that, for 2010, the economic burden of TBI on the US economy was approximately $76.5 billion [4, 5].

Pathologically, CNS injury can directly result in the death of parenchymal cells in damaged tissue [6]. CNS injury can also cause secondary injury, such as hemorrhage, edema, and cell apoptosis due to the persisted inflammation caused by accumulated immune cells after injury [7]. In the pathological tissue, both neutrophils and macrophages adopt an inflammatory phenotype and release soluble factors, including cytokines, proteolytic enzymes, and oxidative metabolites, that exacerbate injury [8]. Leakage can also occur across the blood-brain barrier (BBB), aggravating the inflammation and damaging tissues [9–11]. The primary CNS injury in combination with its subsequent side effects may cause long-term disease and mortality [12–14]. Instinctive CNS repair processes, including accumulation of endogenous stem cells, inflammatory cells, and astrocytes; secretion of chemokines; and formation of glia scar, occur spontaneously to mitigate CNS injury [14, 15]. These mechanisms can partially rescue the residual cells and repair injured tissues. However, the endogenous repair mechanisms modify the components of the extracellular matrix (ECM) of lesions and subsequently cause further ECM degradation and remodeling [16, 17]. The chemokines (e.g., CCL-2, IL-6, and TNF-α) secreted by inflammatory cells can also aggravate local inflammatory reactions [18, 19]. These microenvironmental changes cause failure of stem cells to differentiate into nerve cells and also impede axon regrowth by survival neurons [7, 16]. Further, the glia scars formed by reactive astrocytes, microglia cells, and deposited chondroitin sulphate proteoglycans (GMPGs) separate the lesion from the surrounding tissue and hamper CNS regeneration [15, 20, 21].

Recovery from CNS injury requires rescuing of the surviving cells and axons, repairing damaged tissue, regeneration of severed axons, reconstruction of the connection between the nervous process and soma, and rehabilitation of the impaired neural functions. In recent years, with developments in stem cell biology, cell therapies have been introduced into CNS regeneration [22, 23]. Numerous studies have reported that transplantation of fetal tissue/stem cells into damaged CNS tissues can give favorable results, such as axonal regrowth and regeneration of neurons [24–26]. However, cell therapies have proven inadequate for certain CNS injuries because when a lesion is too wide cell therapy alone cannot repair it; extra physical support is needed to enable engraftment of transplanted cells and cytoarchitecture restoration [6, 24, 27, 28]. Consequently, there are currently no effective therapies for CNS injury.

Biomaterial scaffolds have been studied in tissue regeneration for decades. They have been utilized for regeneration of soft tissue, cartilage, bone, and the peripheral nerve system (PNS) with favorable results [29–32]. Biomaterial scaffolds have a three-dimensional (3D) architecture and are designed to replicate the interaction between cells and their native extracellular matrix (ECM) microenvironments [33, 34]. They can also function as a reservoir for controlled therapeutic molecule delivery or cell transplantation [35]. Recently, numerous studies have revealed that incorporation of biomaterial scaffolds has promoted CNS tissue regeneration in repair of both SCI and TBI [36, 37]. It has been shown that biomaterial scaffolds can repair CNS injury, alter the microenvironment of lesions, and promote the recovery of neural function [38, 39]. Thus, it is clear that biomaterial scaffolds are playing an increasingly important role in CNS regeneration. This review discusses the categories of biomaterial scaffolds that are applied in CNS regeneration as well as their effects.

2. Categories of Biomaterial Scaffolds Applied in CNS Regeneration

Biomaterial scaffolds are used in effort to provide specific microenvironmental cues in 3D controlled fashion to enhance cell survival, infiltration, and differentiation. Since the revelation by David and Aguayo [40] of the significance of microenvironments in CNS repair, it has been asserted that modulating hostile CNS microenvironments can improve recovery from CNS injury. Biomaterial scaffolds and biological scaffolds are the two main scaffolds utilized in CNS regeneration. Both types of scaffolds have a 3D topological structure that can closely mimic the native extracellular matrix (ECM). However, whereas biomaterial scaffolds are composed of synthesized polymers or purified natural polymers, biological scaffolds are usually in the form of decellularized mammalian tissue [38, 41–43]. Further, biomaterial scaffolds are superior to biological scaffolds in key parameters such as architecture, pattern, biocompatibility, porosity, and stiffness, and their degradation rate can be modulated more easily and precisely [44].

Biomaterial scaffolds that serve as temporary ECM provide a niche for cell infiltration and differentiation. They not only support the surrounding neural tissue but also act as a substrate for cell growth, neurite formation, and axon regeneration. They can also carry bioactive molecules that can create a relatively stable, permeable, and nutritious environment for regeneration [45–48]. Moreover, biomaterial scaffolds can also be combined with cell therapies to form "live" scaffolds. The combination of cell therapies and biomaterial scaffolds can provide physical support for transplanted cell engraftment and isolate the implanted cell from the host tissue to provide an independent microenvironment for cell differentiation and proliferation (Figure 1) [49].

Based on required structure and physical and biological properties of prospective tissue construct applied in CNS injury, the biomaterial scaffolds utilized in CNS regeneration can be further classified into hydrogels and biodegradable scaffolds. In this section, we introduce the categories of hydrogels and biodegradable scaffolds utilized in CNS regeneration.

2.1. Hydrogels. Hydrogels are an attractive scaffold substrata owing to their high water content and porous inner structure, which makes them soft and flexible and minimizes tissue damage [50–53]. Their 3D inner structure extends the surface that makes contact with infiltrated cells and expands their volume. Numerous studies have indicated that hydrogels can promote cell adhesion, axon regeneration, and myelination in CNS injury both *in vitro* and *in vivo* [54–56].

Hydrogels can be classified into polymeric covalently cross-linked hydrogels and self-assembled hydrogels according to the forming mechanism [24, 51]. In polymeric covalently cross-linked hydrogels, monomer units are linked by covalent forces, which makes hydrogels more stable in alteration of environment parameters such as pH and temperature [30]. Because they are cross-linked through covalent forces, polymeric covalently cross-linked hydrogels often appear as having an aligned inner structure. High percentage of covalent bonds between inner polymer molecules makes covalently cross-linked hydrogels less deformable but stiffer. Thus, they are usually implanted surgically [57, 58]. In self-assembled hydrogels, monomer units are organized by internal noncovalent forces, which results in them having soft and deformable mechanical characteristics. The noncovalent forces also cause self-assembled hydrogels to have randomly oriented inner structures. Self-assembled hydrogels self-assemble into hydrogels through the environmental PH or temperature changes. Thus, they can be easily injected into lesions [59, 60].

Hydrogel forming polymeric materials are classified as either natural materials or synthetic materials [61]. Natural materials are often used to produce polymeric covalently cross-linked hydrogels. They are obtained from natural resources such as hyaluronic acid from roster comb [62], fibroin [63, 64], chitosan [65], collagen from the epithelial tissue of calf [66, 67], and alginate from seaweed algae [68, 69]. Further, they are easy to acquire, contain specific molecules for cell adhesion, are biodegradable, and are highly biocompatible [70, 71]. However, natural materials also have insufficiencies such as variations between batches, which makes it hard to control the homogeneity of resulting scaffolds. In

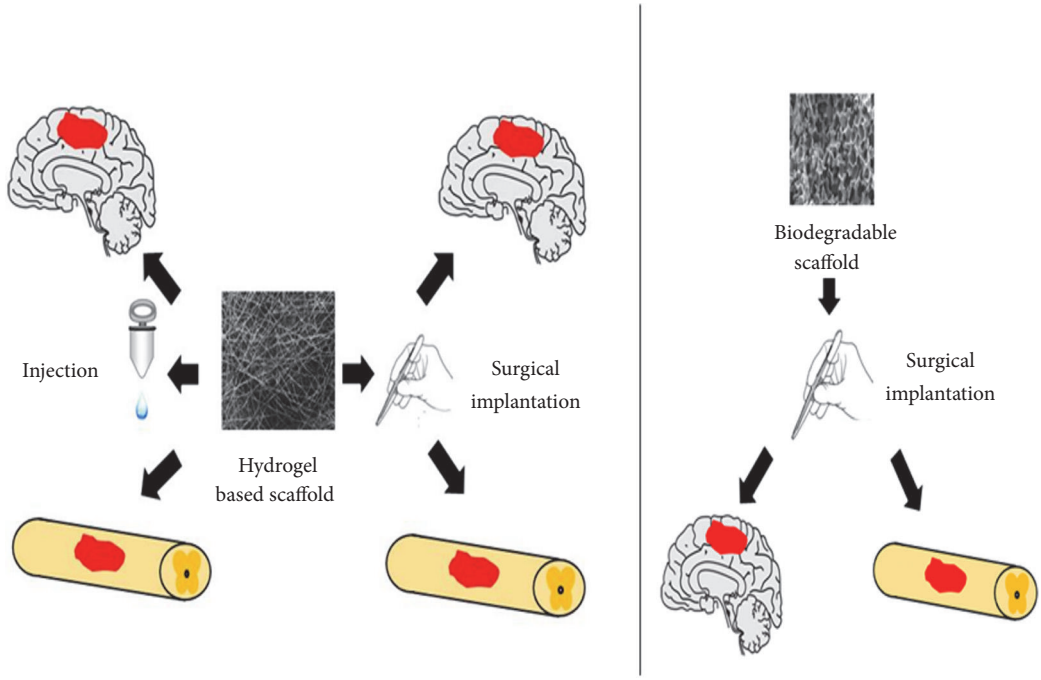

Figure 1: Application of biomaterial scaffolds in regeneration of central nervous system.

addition, the natural sources from which they are derived may contain immune reaction-causing pathogens [72].

Ethyleneglycol monomethacrylate (HEMA) and ethylene dimethacrylate (EDMA) are the first materials reportedly used to synthesize polymeric covalently cross-linked hydrogels [73, 74]. Nowadays, the hydrogels created from synthetic materials hydrogels that are widely utilized in CNS are usually synthesized from polyethylene glycol (PEG) [75], poly-N-(2-hydroxyethyl) methacrylamide (PHEMA), or poly-N-(2-hydroxypropyl) methacrylamide (PHPMA) [76–78]. Self-assembling peptides (SAPs) are the main type of self-assembled hydrogels. They have short, repeating units of amino acids and altered polar and nonpolar residues that enable them to form double-β sheet structures when dissolved in water [79, 80]. The first reported SAP was EAK16-II [81]. Subsequently, other derivatives SAPs such as RADA16 and KLDL12 family were developed as 3D scaffolds for cells [82–85]. These scaffolds can mimic the structure of ECM and functional sequences such as RGD can be added to their self-assembling sequence to improve cell adhesion, proliferation, differentiation, and maturation [86–88]. Peptide amphiphile molecules (PAs) are another important class of SAPs. These SAPs can change the interior array of hydrogels and improve their regeneration effect in the nervous system [89, 90]. Moreover, SAPs hydrogels can also carry function molecules such as homing peptides and neurotrophic factors to promote regeneration (Table 1) [88].

2.2. Biodegradable Scaffolds. Biodegradable scaffolds are biomaterials characterized by biodegradability and 3D inner architecture. Their 3D porous structures are fabricated through methods such as electrospinning, freeze-drying, microfluidic fabrication, water emulsion, thermoforming, and 3D printing [91–93]. The scaffold should be progressively replaced by the regenerating tissue, in order to last long enough to permit cell infiltration and support axon regrowth; moreover, their degraded product must be nontoxic [94]. Degradation of biodegradable scaffolds can occur by hydrolysis and enzymatic degradation, or as a result of mechanical and oxidative stress in vivo [95]. Their degradation rate can be regulated through tuning degree of acetylation, stiffness of scaffold, and changing the length of hydrolytically degradable units within the polymer crosslink [24]. Biodegradable scaffolds exhibit high biodegradability and biocompatibility that minimize their side effects on tissues and attenuate inflammation in lesions. Further, their mechanical property, porosity, shape, and conduits alignment can be easily adjusted through control of rate of cross-linking or concentration of reactants and flow rate of extruded substrata in biofabrication [96]. It has been asserted that biodegradable scaffolds are suitable for utilization in nervous tissue as they can mimic the microstructure and elastic modulus of the ECM of nerve tissues [6, 97]. Moreover, biodegradable scaffolds can carry ECM proteins, growth factors, or stem cells to generate functional scaffolds [98, 99]. Biodegradable scaffolds are desirable constructs to utilize in vivo as well as in vitro applications.

Biodegradable scaffolds can also be synthesized from natural materials or synthetic materials. The natural materials often used for this purpose include collagen [100], fibroin protein (e.g., silk fibroin) [101], chitosan, and hyaluronic acid [51, 102]. The synthetic materials that have been used to synthesize biodegradable scaffolds include poly ε-caprolactone (PCL) [103], poly L-lactic acid (PLA), and

Table 1: Natural materials scaffold applied in CNS.

Material	Description	Application in SCI	Application in brain injury
Agarose	Hydrogel	Functional recovery, tissue repair, delivering neurotrophic factor, stem cell therapy [166]	
	Biodegradable scaffold	Functional recovery, tissue repair, delivering neurotrophic factor, axonal regeneration [167]	
Alginate	Hydrogel	Functional recovery, tissue repair, delivering neurotrophic factor [69, 168]	Axonal regeneration [169]
	Biodegradable scaffold	Functional recovery, tissue repair, stem cell therapy [170]	
Cellulose	Hydrogel	Function recovery, axonal regeneration, delivering neurotrophic factor.	Tissue repair, stem cell therapy, anti-inflammation [171]
Chitosan	Hydrogel	Function recovery, axonal regeneration, anti-inflammation, stem cell therapy [172]	Function recovery, axonal regeneration, delivering neurotrophic factor and drug [173, 174]
	Biodegradable scaffold	Function recovery, axonal regeneration, anti-inflammation, delivering neurotrophic factor, stem cell therapy [175, 176]	Tissue repair, anti-inflammation, stem cell therapy [177]
Collagen	Hydrogel	Axonal regeneration, tissue repair, delivering neurotrophic factor, stem cell therapy [178]	Cell survival, axonal regeneration, stem cell therapy [179]
	Biodegradable scaffold	Function recovery, axonal regeneration, tissue repair, stem cell therapy [180–182]	Function recovery, tissue repair, stem cell therapy [183–185]
Fibrin	Hydrogel	Cell survival, axonal regeneration [186, 187]	Function recovery, cell survival, anti-inflammation, stem cell therapy [156, 188]
	Biodegradable scaffold	Cell survival and proliferation, tissue repair, anti-inflammation, stem cell therapy [189, 190]	Tissue repair, stem cell therapy [191].
Gelatin	Hydrogel	Cell survival, function recovery, axonal regeneration, tissue repair [192]	Cell survival and proliferation, stem cell therapy [193, 194]
	Biodegradable scaffold	Functional recovery, tissue repair, delivering neurotrophic factor, stem cell therapy [195, 196]	Tissue repair, anti-inflammation, stem cell therapy [197, 198]
Hyaluronic acid	Hydrogel	Function recovery, axonal regeneration, tissue repair, anti-inflammation, delivering neurotrophic factor, stem cell therapy [62, 199, 200]	Cell survival, axonal regeneration, stem cell therapy [201]
Xyloglucan	Hydrogel	Axonal regeneration, tissue repair, stem cell therapy [202]	Axonal regeneration, tissue repair, stem cell survival [203]

polyurethane [104, 105]. However, materials such as PCL are hydrophobic, which may lead to poor cell interactivity and further impede cell adhesion and proliferation [106]. To solve this problem, copolymer biodegradable scaffolds have been developed as a compromise method. This method introduces two or more different species into the polymer chain of macromolecules to promote hydrophilicity in scaffolds. The poly D,L-lactide-*co*-glycolic acid (PLGA) [107] and poly ε-caprolactone-*co*-ethyl ethylene phosphate (PCLEEP) are common copolymers that are utilized in nerve system regeneration [108]. Synthetic materials can also be combined with other synthetic materials or natural materials to create copolymers, such as PCL-PLGA scaffolds, which also combines the properties of each material and intensifies the regeneration capacity of the scaffolds (Table 2) [107]. For synthetic materials scaffolds, to achieve a specific degradation rate, oligopeptides that are sensitive to the enzymatic cleavage have been engineered into synthetic polymers. This results in the fact that hydrogels are specifically degraded by targeted enzymes involved in matrix remodeling such as matrix metalloproteases (MMPs), collagenases, and plasmin [24, 94].

Both hydrogels and biodegradable scaffold are important biomaterial scaffolds utilized in CNS regeneration. They can serve as temporary ECM to provide a niche for cell infiltration and differentiation. For future study, the choice of suitable materials for scaffold synthesis and techniques for fabricated 3D structure nontoxically should be important issues in scaffold synthesis. Besides in vivo interaction between the ECMs and scaffolds and the mechanisms of degradation still need further study.

Table 2: Synthetic materials scaffold applied in CNS.

Material	Description	Application in SCI	Application in brain injury
FGLmx	Hydrogel	Function recovery, axonal regeneration, stem cell therapy [204]	
Poly-ε-caprolactone	Hydrogel	Cell survival, delivering neurotrophic factor [205]	
	Biodegradable scaffold	Cell survival, stem cell therapy, functional recovery [206, 207]	Axonal regeneration, cell survival, functional recovery, stem cell therapy [161, 164]
Poly(ethylene glycol)	Hydrogel	Axonal regeneration, functional improvements, anti-inflammation, cell survival [208, 209]	Axonal regeneration, anti-inflammation, cell survival, delivering neurotrophic factor [210, 211]
	Biodegradable scaffold	Function recovery, axonal regeneration, anti-inflammation [212]	
Poly(hydroxyethyl methacrylate)	Hydrogel	Nerve tissue regeneration and functional recovery, stem cell therapy [121, 213]	Cell survival, axonal regeneration [214]
Poly(hydroxypropyl methacrylate)	Hydrogel	Function recovery, axonal regeneration, anti-inflammation, delivering neurotrophic factor, stem cell therapy [76, 215]	Axonal regeneration, anti-inflammation [216]
Poly(lactide-co-glycolic acid)	Biodegradable scaffold	Axonal regeneration, tissue repair, delivering neurotrophic factor, stem cell therapy [145, 217–219]	Axonal regeneration, tissue repair [220]
Polyurethane	Hydrogel	Cell survival, axonal regeneration, functional recovery, stem cell therapy [221]	Cell survival, axonal regeneration, functional recovery, stem cell therapy [221]
	Biodegradable scaffold		Cell survival, axonal regeneration, functional recovery, stem cell therapy [221]
Hydroxy ethyl methacrylate	Hydrogel	Stem cell therapy and axons repair [222]	
PuraMatrix	Hydrogel	Functional recovery, spinal repair, and neuronal regeneration [223, 224]	Stem cell therapy [225]
Imidazole-poly(organophosphazenes)	Hydrogel	Function recovery, axonal regeneration, anti-inflammation [140]	

3. Biomaterial Scaffolds in Spinal Cord Regeneration

Spinal cord injury (SCI) is characterized by long-term paralysis and sensory disturbances. SCI patients often lose the ability to work and require lifelong care [109]. Although much effort has been made by clinicians and scientists to cure this disability, the outcome for SCI patients is still unsatisfactory. In this section, we focus on the properties and mechanisms of non-cell therapy biomaterial scaffolds that have been applied in the treatment of SCI. Biomaterial scaffolds that are combined with cell therapy and applied in SCI are discussed individually in Section 5.

3.1. Application of Hydrogel in SCI. Natural polymer-derived hydrogels were first applied to SCI in 1995, when Joosten et al. used collagen hydrogels in experimental SCI model. They compared two methods of collagen hydrogels preparation, as either a fluid or preformed solid gel, in a rat SCI model. Their results showed that even though both scaffolds can reduce the gliotic response, only fluid collagen gel can induce regeneration of damaged axons [110]. Their study also resulted in a new solution for SCI. Subsequently, the effects of hydrogels made from other natural materials in the treatment of SCI have been intensively studied. It has been found that fibrin hydrogels improve tissue repair and axon regrowth [111], chitosan hydrogels promote tissue repair and neuroprotection in the SCI model, and alginate hydrogels promote axonal regrowth and elongation [112]. With the development of synthetic hydrogel techniques, raw natural material hydrogels have been designed to carry drugs and neurotrophic factors to enhance their SCI reparative effect. For example, Furuya et al. [113] injected gelatin hydrogel (GH) containing basic fibroblast growth factor (bFGF) into a rat SCI model. The bFGF-incorporated GH showed better performance in alleviating mechanical allodynia following SCI. Further, drugs such as methylprednisolone are also able to enhance axonal regeneration and reduce inflammation [114, 115]. It has been stated that excessive Ca^{2+} can hamper neurite formation and axon regrowth. To overcome this problem, McKay et al. [116] developed alginate/chitosan/genipin hydrogels, which have a high sensitivity to Ca^{2+} composites.

The developed hydrogels exhibited excellent ability to regulate astrocyte behavior and prevent Ca^{2+}-related secondary neuron damage during acute SCI.

Hydrogels made from natural materials can also deliver specific antibodies or drugs to block receptors that impede regeneration after SCI. Nogo is a myelin-associated inhibitor (MAI) that can limit axon growth and benumb functional neuronal circuits. Wen et al. developed hyaluronic acid (HA) hydrogels that blend with the anti-Nogo receptor antibody (antiNgR). Hydrogels have also been combined with PLGA microspheres containing brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF). The hydrogels were implanted into the rat SCI model and, after a few weeks, angiogenesis and axons regrowth were observed in hydrogels; the implanted rats also exhibited improved locomotor recovery [117]. These studies prove that hydrogels made from natural materials are effective in SCI treatment. They are highly biocompatible and contain a specific molecule for cell adhesion; their inner structure can mimic the extracellular matrix to provide an environment for cell proliferation.

Similar to natural hydrogels, hydrogels made from synthetic materials for the treatment of SCI can mimic the extracellular matrix to provide an environment for cell proliferation and adhesion. Further, hydrogel networks can serve as scaffolds that support regeneration until the materials are ultimately absorbed by the host. Hydrogels made from synthetic materials are more adjustable than hydrogels made from natural materials, as their key parameters can be easily controlled through modification. Poly(hydroxyethyl methacrylate) (PHEMA) was one of the earliest biomaterials utilized for tissue engineering scaffolds as they alleviate inflammation and promote axon regeneration after SCI [118]. Subsequently, biocompatible hydrogels such as polyethylene glycol (PEG) and poly-N-(2-hydroxypropyl) methacrylamide (PHPMA) hydrogels have been utilized in SCI treatment. Namba et al. [119] applied porous PEG hydrogels to SCI. They demonstrated that PEG hydrogels are simple and efficient and enable uniform seeding of neural cells throughout the entire porous scaffolds, thereby promoting axon regeneration. PHPMA hydrogels exhibit reduced macrophages/monocytes accumulation at the lesion border, and axons and myelin are both preserved in the rostral and caudal of the lesion [76]. Many aspects of hydrogels made from synthetic materials, such as phase, stiffness, biodegradability, and pattern, can also be modified to provide precise temporal control of the hydrogels and host cell interactions. For example, the hydrogels can be charged; positively charged hydrogels display higher cell infiltration and growth than negatively charged hydrogels [120].

Hydrogels made from synthetic materials can also act as a carrier to deliver growth factor to lesions and enhance their reparative effect. Chen et al. [121] incorporated basic fibroblast growth factor (bFGF) into hydroxyl ethyl methacrylate [2-(methacryloyloxy)ethyl] trimethylammonium chloride (HEMA-MOETACL) hydrogels and implanted them into the lesion of an SCI model. Their results showed that the hydrogels promoted both nerve tissue regeneration and functional recovery in the SCI model.

Adjunction of functional sequence is also a common method used to modify hydrogels. RGD [122], IKVAV [123], and laminin [124] are functional sequences that are often utilized to modify hydrogels. These functional sequences can enhance the treatment effects of scaffolds by promoting cell adhesion and proliferation in scaffolds. Woerly et al. [125] synthesized poly-N-(2-hydroxypropyl) methacrylamide (PHPMA) based hydrogels and demonstrated that they can promote axonal regeneration in an experimental SCI model. They further decorated PHPMA hydrogels with an RGD sequence and showed that the modified hydrogels can induce tissue ingrowth into the lesion cavity, and angiogenesis and axon regeneration are more effective in modified hydrogels.

SAPs and PAs are important synthetic polymers for producing self-assembling hydrogels. The self-assembling hydrogels are injectable and facilitate clinical application. Gou et al. [126] were the first to apply RADA16-I hydrogels to an experimental SCI model and prove that SAP hydrogels can promote SCI recovery. Cigognini et al. [127] further functionalized RADA16-I hydrogels with a bone marrow homing motif (BMHP1). To facilitate scaffold stability and expose more biomotifs, they inserted 4-glycine-spacer into the hydrogels. Their results indicated that RADA16-I hydrogels can increase cell infiltration, basement membrane deposition, and axon regeneration in SCI. Tysseling et al. [128] applied the functional sequence IKVAV to modified PA hydrogels and implanted them into a rat SCI model. Their results showed that, in contrast to randomized functional sequences, IKVAV PA hydrogels can improve histological and functional recovery. Their results also suggest that proper matching of functional sequence and hydrogels may be important in the synthesis of functional hydrogels.

Neuroinflammation develops within hours after SCI and TBI and can persist for months to years [11]. Delivering interventions following injury may be critical for regeneration and restraining lesion expansion [129]. Monocyte-derived macrophages are early responders to injury [130]. Both *in vitro* and *in vivo* evidences demonstrate that with specific stimulation macrophages can polarize towards functionally divergent subsets. Historically, polarized macrophages have been classified as classical (M1) macrophages, which promote inflammation, or as alternatively activated (M2) macrophages, which restrict inflammation and foster wound repair. Outside the CNS, M1 macrophages are quite rapidly (after about 1 week) replaced by M2 macrophages that successively infiltrate the lesion, where they largely contribute first to tissue repair and then remodeling via release of anti-inflammatory cytokines, stimulation of proliferation of fibroblasts and endothelial cells (angiogenesis), and production of ECM [131–134]. However, in traumatic SCI, this counterbalancing is impaired. The M2 macrophages are activated early, but disappear after about one week after lesion, while proinflammatory M1 macrophages persist indefinitely [135]. Similarly, in TBI, field alternation of M1 and M2 is also observed through numerous studies [136, 137]. Hydrogels made from both natural and synthetic materials are anti-inflammatory and alleviate gliosis after SCI, providing a favorable microenvironment for regeneration. Furthermore, it is reported they can enhance M1 macrophages modified

to M2 macrophages in SCI. Caron et al. [138] applied the functional sequence RDG to modified agarose hydrogels and implanted them into a rat SCI model. Their results showed that the hydrogels can not only repair injured spinal cord but also be able to increase and/or convert efficaciously M2 macrophages in the injured site, promoting a proregenerative environment that represents a relevant outcome in treating SCI. Chedly et al. [139] also found that chitosan favors tissue repair in part by increasing activation and/or proliferation of M2 macrophages during the early postlesion phase. Recently, experimental evidence has demonstrated that the imidazole-poly hydrogel promotes ECM remodeling by activating the metalloproteinase-9 (MMP-9) matrix found in macrophages. This indicates that hydrogels may perform complex interactions with the immune system during SCI treatment [140]. However, the mechanisms of increased proliferation of M2 macrophages after applying hydrogels are still not elucidated.

In summary, hydrogels have great potential in the treatment of SCI. They have advantages such as excellent histological and functional recovery and the fact that they can be injected into lesions. The injectability of hydrogels minimizes the risk of secondary injury when hydrogels are administrated in SCI. They can also be modified by functional sequences or delivering growth factors. However, issues such as the need to enhance their mechanical strength, durability, and stability in application and balance between fluidity and mechanical strength need to be investigated in future studies. The exact mechanisms by which hydrogels interact with SCI also require further study.

3.2. Application of Biodegradable Scaffolds in SCI. Biodegradable scaffolds are also important biomaterials that are utilized in SCI. They are often surgically implanted into lesions and are synthesized through electrospinning techniques to decrease the use of organic solvent. In the spinal cord, the axons often appear in a longitude arrangement, and the electrospinning technique can fabric materials into any desired pattern and mimic the arrangement of axons. Chitosan, gelatin, PCL, and PLGA are the scaffolds predominantly applied in SCI, as they have an effect on axon regeneration, are anti-inflammatory, and promote tissue repair [141]. The effects of gelatin and PLGA scaffolds have been compared by Du et al. Their results suggest that gelatin scaffolds are superior to PLGA scaffold in SCI treatment, possibly because PLGA scaffolds generate more acidic medium than gelatin scaffolds in the process of degradation [142].

Biodegradable scaffolds can be incorporated with hydrogels to treat SCI [24]. The goal of this approach is to combine the therapeutic ability of hydrogels with the mechanical and physical properties of biodegradable scaffolds to enhance treatment effects. Gelain et al. [143] developed PCL/PLGA nanostructured microguidance scaffolds synthesized through the electrospinning technique. They implanted the scaffolds into chronic rat SCI lesions with self-assembled RADA16-I-BMHP1. Their results indicate that scaffolds can induce both regeneration and myelination of axons in chronic SCI and the motor function can also be recovered. The biodegradable scaffolds can also carry drugs or growth factors. Furthermore, they can be designed hierarchically; growth factors or functional materials can be synthesized in different layers of the scaffold; thus, with degradation of the scaffolds, they can take effect in different phases in SCI treatment. Thomas and Shea [144] implanted electrospun poly(lactide-co-glycolide) (PLG) scaffolds to carry polysaccharides, chitosan, and heparin. They found that, in the early stage of SCI, the scaffold can have an anti-inflammatory effect, after which the scaffolds can enhance axon growth and myelination. Neurotrophins-3 are applied in SCI treatment as they can encourage axon regeneration and cell proliferation. Fan et al. [145] synthesized PLGA/recombinant human neurotrophin-3 (rhNT3) scaffolds and utilized them in a rat SCI model. Their results indicated that axonal regeneration, locomotor, and sensory recovery occurred.

Surface modification of scaffolds can enhance the effect of regeneration through promotion of cell adhesion to the scaffold. Zamani et al. [146] developed electrospun PGLA three-dimensional core-sheath scaffolds. The developed scaffolds have a nanorough sheath and an aligned core. They implanted the developed scaffolds into an experimental SCI model and the results showed that they can improve axon regeneration as well as locomotor and sensory recovery. The pattern of the scaffold is another important parameter that can affect regeneration. It has been suggested that fabricating scaffolds with smaller diameter channels promotes greater regeneration over larger diameter channels [147].

Biodegradable scaffolds are also utilized in SCI as they have good mechanical strength and tunable inner pattern and are biodegradable. However, the need for surgical implantation narrows their application in some clinical situations. In summary, biodegradable scaffolds as biomaterials that are applied in SCI have considerable potential. In future studies, the application of new materials, relationship of the inner pattern and SCI recovery, exploration of multicomponent scaffolds, and development of a mini-invasive implantation method may be the main problems explored in the development of biodegradable scaffolds.

4. Biomaterial Scaffolds in Brain Regeneration

Traumatic brain injury (TBI), brain tumors, and brain hemorrhages are common causes of brain damage. In the USA, at least 5.3 million people suffered from disability after TBI, costing approximately $76.5 billion in lost productivity in 2010 [4]. These disabilities result in social and economic burdens and need to be solved urgently. The brain is the most complex organ in the human body. It has numerous neuronal cells and their neurites are woven into a sophisticated net. After injury, activation of the immune system and a poor instinctive repair process make it difficult to regenerate injured tissue. Hence, current strategies for brain tissue regeneration are still insufficient. Recently, some studies have applied biomaterial scaffolds to brain injury. Their results indicate that biomaterial scaffolds have significant potential in the treatment of brain injury. In this section, we review biomaterial scaffolds that have been applied in the treatment of TBI and other brain injury models. Biomaterials scaffolds that are applied with cell therapy for brain repair are discussed in Section 5.

4.1. Application of Hydrogel in Brain Regeneration. The brain is protected by the cranial bone, which makes it difficult to inject materials into the brain directly. The materials applied in brain injury scenarios are often surgically implanted. Natural materials, such as hyaluronic acid (HA) [148], collagen [149], chitosan, and methylcellulose [150, 151], have been used to synthesize hydrogels that are applied in these cases. Hydrogels can fill the brain cavity, replacing the growth-prohibiting environment with a more growth-permissive one. Further, it has been reported that hydrogels can decrease inflammation through reduction of secretion of inflammatory cytokine [152]. These mechanisms might enable cells and axons to infiltrate into hydrogels and further repair injured brain tissue [148]. Similar to the hydrogels applied in SCI, the hydrogels used in the brain can also be connected with functional peptides such as IKVAV and RGD to enhance their cell adhesion and axon regrowth effects [123]. In addition, hydrogels can be modified to carry antibody or drugs to improve regeneration. The Nogo-66 antibody carried HA hydrogels to promote axon regeneration in the rats stroke model; it has also been proven that these hydrogels have the effect of functional recovery [153]. Ma et al. synthesized HA based biodegradable hydrogel scaffolds and mixed them with PLGA microspheres containing vascular endothelial growth factor (VEGF), angiopoietin-1 (Ang1), and Nogo receptor antibody (NgR-Ab). They implanted the hydrogels into a mice brain ischemic model, and their results showed that the hydrogels have good compatibility with brain tissue and inhibition to gliosis and inflammation after implantation [154]. Recently, thermosensitive and sound-sensitive hydrogels have been developed for injection in brain injury. Koivisto et al. developed biomimetic hydrogels based on gellan gum. The developed hydrogels use bioamines spermidine and spermine to function as crosslinkers for gellan gum hydrogel at +37°C [155]. These hydrogels can promote neuronal cell migration, maturation, and neurite formation. Fernández-García et al. developed in situ gelling silk fibroin hydrogels. The gelation of silk fibroin solutions can be induced by sonication. These hydrogels can be injected into a mouse brain and integration of hydrogels into the brain tissue can be controlled by the intensity and duration of sonication. Their results prove that hydrogels have good biocompatibility in the brain and can be further applied in TBI treatment [156].

Several hydrogels made from synthetic materials have also been applied in brain regeneration. In general, such hydrogels are combined with cell therapy in brain injury treatment. Hydrogels made from synthetic materials are easier to chemically modify and have a 3D inner structure and low immune responses. PHPMA-RGD hydrogels containing brain-derived neurotrophic factors have been tested in a rat TBI model, with results showing the occurrence of axon regeneration and cell infiltration [157]. Self-assembling hydrogels, such as the RADA16-I hydrogel, also show the ability to promote regeneration of brain tissue and angiogenesis [158, 159]. Hydrogels made from synthetic materials can be combined with the scaffold to increase its strength. Polymer poly-L-lactide (PLLA) electrospun fibers with fibronectin inclusion and which are dispersed in an agarose/methylcellulose hydrogen can promote cell infiltration into the lesion site following brain injury [151].

4.2. Application of Biodegradable Scaffolds in Brain Regeneration. Biodegradable scaffolds are used to carry cells in brain regeneration. Only a few studies have investigated the effect of bare biodegradable scaffolds in animal TBI models. In this section, we discuss research conducted on the materials associated with brain regeneration.

The mechanisms of biodegradable scaffolds in promoting brain regeneration are mainly concentrated on their effects in enhancing support for microenvironments, guiding axon sprouting, and cell migration. PCL based scaffolds are the most studied scaffolds in brain regeneration. Nisbet et al. implanted electrospun PCL scaffolds into the caudate putamen of an adult rat brain and discovered neurite infiltration and growth in the scaffold [160]. They stated that the characteristics of the inner structure of PCL scaffolds, such as large porosity and perpendicular alignment at the implant-tissue interface, can promote neurite growth [161]. Wong et al. further studied the relationship between PCL scaffolds' channel direction and cell infiltration. Their study revealed that pores or channels oriented towards the parenchyma will increase astrocytic infiltration and that microgrooves oriented in the desired direction of cell migration and neuronal alignment will also provide benefit for regeneration. They also discovered that fully interconnecting channels for cell migration and tissue integration can increase regeneration [162]. Wong et al. also compared the regeneration effects of PCL and PLGA scaffolds in a rat brain. They found that both polymers can alleviate astrocytic activation, prevent enlargement of the defect, and improve neural ingrowth. However, PCL induces a lower inflammatory response than PLGA [163]. Recently, studies have indicated that migration and differentiation of endogenous stem cells play an important role in brain repair. Fon et al. applied electrospun PCL scaffolds incorporated with small molecule nonpeptide ligand (BDNF-mimetic) to a rat model. Their results proved that PCL scaffolds can improve neuroblast survival and promote neuroblast migration towards lesions [164]. Our team also investigated the effect of waterborne biodegradable polyurethane (WBPU) 3D porous scaffolds on the regeneration of a rat TBI model. We found that the scaffold can improve axonal regeneration as well as functional recovery. We also found that a percentage of poly ethylene glycol (PEG) within the scaffold may affect the result of regeneration [165]. The mechanisms underlying these phenomena are still being studied.

5. Combination of Biomaterial Scaffolds and Cell Therapy

The combination of biomaterial scaffolds and cell therapy in CNS regeneration has garnered the attention of researchers in recent years. The combination of these two therapeutic methods makes it possible to achieve both cell regeneration and tissue reconstruction. The basic principle of this modality is combining exogenous cell and scaffolds to form "live" scaffolds. These "live" scaffolds can be implanted into animals through injection or surgical implantation. The parenchyma

part of CNS comprises neuron and glial cells that include astrocyte and oligodendrocyte. Neural stem/progenitor cells (NSPCs) are present in the adult CNS and are important in the maintenance and repair of CNS [226]. NSPCs can be differentiated into neuron and glial cells and hold great promise for repair of CNS [227]. However, NSPCs also have defects such as poor survival and uncontrolled differentiation. NSPCs have even been implicated as the origin of brain tumors [228, 229]. Thus, the survival factors and niches of NSPCs are critical for their application [230]. Biomaterial scaffolds have features that mimic the ECM and create a stable environment. Further, they have the potential to carry cytokines such as neural growth factor (NGF) or other functional molecules. Thus, biomaterial scaffolds are suitable for assisting with stem cell survival and differentiation [231]. In addition to NSPCs, other stem cells that have the potential to differentiate into neurocytes have also been implanted into biomaterial scaffold to help with CNS regeneration. These cells can be derived from bone marrow stem cells [138], induced pluripotent stem cells (iPSC) [232], induced pluripotent stem cells (iPSC) [233], embryonic stem cell [234], or adult stem cells [235]. The feasibility of transplantation of exogenous NSPCs has been tested by Li et al. who synthesized a methacrylamide chitosan (MAC) hydrogel system. They immobilized recombinant fusion proteins into methacrylamide chitosan (MAC) based biopolymer through a streptavidin linker. Their results indicated that the system can induce a majority of NSPCs to differentiate into the desired cell types by day 28. Their study proved that biomaterial scaffolds can regulate cells to differentiate into desired cells [236]. Biomaterial scaffolds can serve as carriers of NPSCs for injury treatment. They can create a stable microenvironment and provide the appropriate infrastructure to support cell migration into surrounding tissue [237]. In this section, we discuss progress made in the field of combination of biomaterial scaffolds and cell therapy in CNS regeneration.

In the field of SCI treatment, both hydrogels and biodegradable scaffolds have been studied in various studies. Hydrogels have been proven to improve both cell proliferation and differentiation *in vivo*. Further, they can carry growth factors or drugs to promote their effects in stem cell therapy. Mothe et al. developed a kind of hyaluronan and methyl cellulose (HAMC) hydrogels. They conjugated HAMC hydrogels with recombinant platelet-derived growth factor-A (rPDGF-A) to promote oligodendrocyte differentiation. The HAMC-rPDGF-A hydrogels were blended with adult brain-derived neural stem/progenitor cells (NSPCs), and the hydrogels were injected into a subacute, clinically relevant model of a rat SCI. They found that rats treated with HAMC-rPDGF-A hydrogels showed reduced lesion size, increased distribution of perilesional host neurons and oligodendrocytes, and better functional recovery [199]. An interesting comparison between the effects of hydrogels and biodegradable scaffolds in cell therapy has been made by Caron et al. They developed an agarose/carbomer based three-dimensional hydrogel and lyophilized sponge-like scaffolds, in which both scaffolds were loaded with mesenchymal stem cells (hMSC). Their results indicated that, compared with classic hydrogels, lyophilized sponge-like scaffolds can not only modulate inflammatory response, but also better preserve hMSC viability and stemness in an SCI mouse model [138]. This result indicates that biodegradable scaffolds may be better scaffolds in cell therapy. However, the controversy that stem cells can cause brain tumor is a long standing issue in cell therapy. Considering this problem, Führmann et al. developed a platelet-derived growth factor (PDGF-A) and RGD peptide modified hyaluronan and methylcellulose hydrogels. Their results showed that the hydrogels can enhance the survival of oligodendrocyte derived from iPSC. Moreover, they discovered that stem cells seeded in hydrogels attenuated the formation of teratoma, with the majority of stem cells differentiating to a glial phenotype. Their study indicates that hydrogels may decrease the formation of tumor after transplanting of stem cells, which is a profound result in stem cell therapy. However, more types and structures of materials need to be studied to confirm the phenomenon [238].

Biodegradable scaffolds have advantages in terms of mechanical property and biodegradability. Research on the application of biodegradable scaffolds in the treatment of SCI is concentrated on critical issues such as vitality of imbedded cells and whether they can differentiate into desired cell types. Terraf et al. utilized PCL scaffolds to carry human endometrial stem cells and applied them in a rat hemisected SCI model. According to their result, neurite outgrowth and axon regeneration can be observed and animals also showed functional recovery [239]. The strategy of combining different scaffolds to combine the advantage of each scaffold has also been used in cell therapy. Liu et al. implanted three-dimensional (3D) electrospun poly(lactide-co-glycolide)/polyethylene glycol (PLGA-PEG) scaffolds carrying iNSC into transected rat spinal cords. Their result showed iNSC survival and differentiation within the scaffolds. The cavity of the spinal cord was restored by the scaffold and functional recovery was also observed [217]. Kim et al. studied the difference in efficacy between implanted MSCs through traditional intralesional injection and through scaffold assisted implantation in a rat SCI model. They concentrated on engraftment and differentiation of transplanted cells, expression of neurotrophic factors in lesions, and functional recovery. Their results indicated higher success rate of MSCs engraftment in scaffold groups compared with the injection group. They also indicated that expression of neurotrophic factors is no different among all groups, whereas better functional recovery was exhibited in the scaffold groups. Their result proves the superiority of combining scaffolds and stem cells over traditional stem cell therapy. These results also imply that carrying neurotrophic factors in scaffolds seeded with stem cells may achieve better regeneration effects [240]. Neural growth factors (NGFs) are carried in biodegradable scaffolds that are supplied with stem cells to promote cell differentiation and proliferation. Among all NGFs, neurotrophin-3 (NT-3) is the most frequently used NGF in stem cell therapy. Johnson et al. reported that the combination of NT-3 and fibrin scaffolds can increase the total number of embryonic stem cell-derived neural progenitor cell (ESNPCs) derived neurons in NT-3 fibrin scaffolds after transplantation in a rat SCI model [241, 242]. Qiu et al. and Yang et al. both applied

NT-3/chitosan scaffolds to promote the survival and proliferation of neural stem cells (NSCs). They exhibited that scaffolds can induce NSCs to differentiate into desired phenotypes such as neurons and astrocyte [243, 244]. Duan et al. further investigated the molecular mechanism underlying the phenomenon. Through weighted gene coexpression network analysis (WGCNA), they found that enhanced new neurogenesis and angiogenesis and reduced inflammatory responses were the key mechanisms of NT3-chitosan scaffolds in treating SCI [175].

Application of biomaterial scaffolds as cell carriers and tissue supporters has also been investigated in brain injury. Hydrogel use in the brain has been proved to promote proliferation, maturation, and differentiation of stem cells with or without other trophic factors. Because hydrogels are injectable, when damage is located in the deep region of the brain, they can be injected directly into lesions to avoid damage to the superficial cortical tissue. Shi et al. developed RADA16 self-assembling peptide hydrogels that carry brain-derived neurotrophic factor (BDNF). They seeded both MSCs and astrocytes into the scaffold and applied chemokine receptor 4 to promote migration of transplanted cells. Their results indicate that transplantation of scaffolds can aid repair of moderate-sized lesion cavities caused by TBI [245]. With the development of hydrogels, visualized stem cell hydrogels have been applied in the brain to monitor their in vivo process. Moshayedi et al. developed HA based self-polymerizing hydrogels that can be tracked *in vivo* through MRI imaging. They encapsulated human neural progenitor cells (iPS-NPCs) into the hydrogels and injected the hydrogels into a mice stroke model. Their results showed that hydrogels can promote survival of iPS-NPCs after transplantation into the stroke core. In addition, the hydrogels can also increase differentiation of transplanted cells [201]. Self-assembly hydrogels modified with functional peptides such as RADA16-IKVAV also have been reported to promote proliferation and differentiation of NSCs *in vivo* [246]. With the exception of SAPs, other self-assembly hydrogels such as thermosensitive diblock copolypeptide hydrogels (DCH) have also been applied to deliver NSCs. This shows that DCH can significantly increase the survival of NSCs in healthy CNS. In mouse models, DCT has also been distributed well in nonneural lesion cores, integrated with healthy neural cells at lesion perimeters, and supported the regrowing of host nerve fibers [247].

The application of biodegradable scaffolds and cell therapy in regeneration of the brain is a newly developed field and has been increasingly noticed in recent years. Chitosan scaffolds are one of the most popular scaffolds used in brain injury. Shi et al. developed a kind of BDNF blended chitosan scaffold to carry umbilical cord mesenchymal stem cells (hUC-MSCs) through a freeze-dry technique. They found that the scaffolds can increase the differentiation rate of NSCs and the average neuron perimeter [248]. The *in vivo* process of implanted cells in the brain is important for explaining the mechanisms of repair. To achieve this goal, Hwang et al. applied poly-L-lactic acid (PLLA) scaffolds to carry NSCs that express firefly luciferase. Thus, they can monitor the process of cell proliferation *in vivo* conveniently and noninvasively. Their result showed that the signals from cells in the scaffold are both stronger and more durable than nonencapsulated cells [249]. The plasma surface between scaffold and cells can affect cell adhesion and proliferation. Zandén et al. studied the effect of different plasma surfaces of polyurethane scaffolds for attachment and proliferation of human embryonic stem cell (hESC). They found that, compared with oxygen and hydrogen plasma surface, argon plasma induced the most optimal combination of surface functionality and roughness for cell expansion [250].

In summary, in the treatment of CNS damage, using both hydrogels and biodegradable stem cell scaffolds can combine advantages of both modalities. The scaffolds can increase the survival rate of stem cells and accelerate the accumulation of ECM. They also give stem cells an isolated environment to differentiate and proliferate. Moreover, stem cells can differentiate into desired cell types to reconstruct the damaged tissue and result in functional recovery. However, many factors can affect the repair effect, such as cell type, topography, category of materials, and physical and chemical properties of materials. Thus, the optimum method of combination of materials and stem cells still needs future study.

6. Conclusion and Prospects

In this review, we summarized present development in the application of biomaterial scaffolds in central nervous system regeneration. We showed that some materials have great potential in CNS regeneration as well as the combination of materials and cell therapy in this field. Biomaterial scaffolds can reduce inflammation at injury sites and can also change the microenvironment of lesions. In addition, they can carry drugs and neurotrophic factors to enhance the effect of therapy. Moreover, combining biomaterial scaffolds and cell therapy can promote survival and differentiation of stem cells and reduce the side effect of cell therapy. Hence, biomaterial scaffolds-assisted therapy is a promising strategy in CNS regeneration. However, these effects of scaffolds are based on animal experimentation; human CNS injury is more complex and is still a great problem that needs to be solved by the overall medical world. Developing biomaterial scaffolds that are biodegradable, biocompatible, and mechanically flexible is still an important issue in CNS regeneration. Moreover, using hybrid knowledge of cell therapy, pharmaceutical therapy, and clinic technique to enhance the ability of biomaterial scaffolds in CNS regeneration is an important strategy to improve biomaterial scaffolds. Finally, degrading the speed of biomaterial scaffolds should correspond to differentiating the phase of tissue regeneration, so that they can be designed to have different functions in different stages of regeneration. With the development of materials and biology, it is reasonable to surmise that we can achieve perfect CNS regeneration in the near future.

Conflicts of Interest

The authors declare no conflicts of interest.

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