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## REVIEW

# Biomaterials for the central nervous system

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Biomaterials are widely used to help treat neurological disorders and/or improve functional recovery in the central nervous system (CNS). This article reviews the application of biomaterials in (i) shunting systems for hydrocephalus, (ii) cortical neural prosthetics, (iii) drug delivery in the CNS, (iv) hydrogel scaffolds for CNS repair, and (v) neural stem cell encapsulation for neurotrauma. The biological and material requirements for the biomaterials in these applications are discussed. The difficulties that the biomaterials might face in each application and the possible solutions are also reviewed in this article.

**Keywords:** biomaterials; nerve repair; neural prosthetics

## 1. INTRODUCTION

A wide variety of biomaterials are used in the central nervous system (CNS): drugs or gene carriers for treatment of neurological disorders and brain tumours, scaffolds for promoting tissue regeneration, neural electrodes for restoration of lost neurological functions or shunt systems for hydrocephalus. The biomaterials used in the CNS include silicone, lipids, natural polymers and synthetic polymers in various forms based on their applications. Biomaterials can be categorized as biodegradable or non-biodegradable, depending on their fate after implantation or injection. Some applications, such as neural electrodes or CNS shunts, require the biomaterials to remain functional indefinitely. Other applications, such as drug carriers or tissue scaffolds, require the biomaterials to degrade after their function is fulfilled.

All these biomaterials must be biocompatible, meaning that they must elicit an appropriate host response in a specific application (Williams 1987). In the CNS, neurons have signalling functions (Kandel *et al.* 2000), so neuronal death may impair the normal operation of the CNS and disable patients. Serious inflammatory response can cause neuronal death and the formation of neuroinhibitory glial scar. Since the neurons are difficult to be replaced, it is preferable that the biomaterials elicit a minimal inflammatory response. This is especially true with electrodes, whose ability to record or modulate electrical activity is minimized if neurons in their immediate vicinity are compromised.

This article reviews the application of biomaterials in (i) shunting systems for hydrocephalus, (ii) cortical neural prosthetics (CNP), (iii) drug delivery in the

CNS, (iv) hydrogel scaffolds for CNS repair, and (v) neural stem cell encapsulation for neurotrauma. It discusses the biological and material requirements for the biomaterials in each application, along with difficulties they might face, and reviews possible solutions.

## 2. CNS SHUNTS FOR HYDROCEPHALUS

### 2.1. Hydrocephalus and CNS shunt system

Hydrocephalus is a condition in which excessive accumulation of cerebrospinal fluid (CSF) in the brain increases intracranial pressure. The most common and effective treatment of hydrocephalus is the CSF shunt system, which has been used for over 50 years (VandeVord *et al.* 2004; Liang *et al.* 2006). These shunts relieve pressure by draining excess CSF from the cerebral ventricles or subarachnoid spaces into a less constrained area of the body, such as the peritoneal cavity or the right atrium of the heart (Bayston *et al.* 2004; Garton 2004; VandeVord *et al.* 2004).

The CSF shunts typically consist of a proximal catheter, which runs from the cerebral ventricles' subarachnoid spaces to a valve that connects to a distal catheter and regulates the drainage of CSF. The distal catheter is a long thin silicone tube that is placed subcutaneously and terminates in a distal body cavity where the CSF can be reabsorbed into the body (Garton & Piatt 2004; Browd *et al.* 2006a; de Aquino *et al.* 2006). The most common site of distal CSF drainage is the peritoneal cavity. Other popular sites include the pleural cavity, the right atrium of the heart, the gall bladder and the internal jugular vein (Kalousdian *et al.* 1998; Garton & Piatt 2004). CSF shunt devices are manufactured almost solely from medical grade silicone, owing to its chemical stability, minimal biological reactivity, low toxicity and

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noncarcinogenicity (Agnew *et al.* 1962; Del Bigio 1998; Kalousdian *et al.* 1998). Currently, silicone is used to make the following shunt components: catheters, access chambers, valve mechanisms, suture clamps and external valve housings (Drake & Sainte-Rose 1995).

## 2.2. Biological responses to silicone shunts

Although CSF shunt systems are effective in treating hydrocephalus, shunt dysfunction is a common problem. Recent trials estimated the failure rate for all implanted shunts to be 40–50% during the first 2 years after surgery (Browd *et al.* 2006b). Complications can be due to obstruction, mechanical failure, infection or excess drainage (Kalousdian *et al.* 1998; Sgouros & Dipple 2004; Browd *et al.* 2006a). Shunt obstructions and infections often occur soon after implantation (11 months on average), while mechanical complications can occur years later (90 months on average; Boch *et al.* 1998).

The most common CSF shunt complication is obstruction, affecting 40% of shunts during the first year after implantation and 80% within 10 years (Sgouros & Dipple 2004). The two most common locations for the shunt obstruction are the ventricular catheter tip and the shunt valve (Browd *et al.* 2006a). The proximal catheter is multi-perforated in order to enable the CSF to pass through; these drain holes allow for tissue ingrowth into the lumen of catheters. Shunt obstruction caused by tissue ingrowth through the drain holes has been widely reported, and choroid plexus and glial tissue account for the majority of offending tissues (Collins *et al.* 1978; Del Bigio & Fedoroff 1992; Del Bigio 1998; Ginsberg *et al.* 2000). In addition, scanning electron microscopy studies have shown biofilm formation on both inner and outer surface of the shunts (Guevara *et al.* 1987; Koga *et al.* 1992; Fux *et al.* 2006). Ventricular catheter obstruction is mostly caused by ingrowth of choroid plexus and gliopendymal tissue into the lumen of the tube (Del Bigio 1998; Sgouros & Dipple 2004; Browd *et al.* 2006a). A significant number of catheters also contain ependymal cells, necrotic brain tissue, connective tissue and remnants of clotted blood, as well as inflammatory cells, including lymphocytes, macrophages, multinucleate giant cells and neutrophils (Del Bigio 1998). Valve obstructions can be caused by infiltration of particulate debris, blood cells, fibroblasts and infectious organisms (Del Bigio 1998; Browd *et al.* 2006a). Silicone rubber does not support astroglial cell growth owing to poor cell adhesion (Del Bigio & Fedoroff 1992). Therefore, it is suggested that ingrowth of gliovascular tissue is due to firm continuous physical contact between the shunt catheter and ventricular wall (Bruni & Del Bigio 1986; Del Bigio & Fedoroff 1992; Del Bigio 1998). Excess CSF drainage causes collapse of the ventricle walls onto the shunt, which promotes the growth of viable tissue into ventricular catheter (Go *et al.* 1981; Del Bigio 1998). Inflammatory tissue response to implanted shunts also contributes to the catheter obstruction (Sekhar *et al.* 1982; Del Bigio 1998). Insertion of a ventricular catheter causes cell death, tissue injury and disruption of blood–brain barrier (BBB), which in turn causes

release of cytokines and neurotoxic free radicals, invasion of blood-borne macrophages, adhesion of blood components (platelet and serum proteins) to the shunt catheter and oedema (Fitch & Silver 1997; Del Bigio 1998). These events potentiate the inflammatory tissue response (Del Bigio 1998). The obstructed catheters are often associated with acute and chronic inflammatory cell infiltrate and multinucleate foreign body giant cells (Schmidt *et al.* 1993; Del Bigio 1998). Modifying the silicone surface of the shunt may reduce tissue reaction and bacteria adhesion.

The incidence of infection after shunt operation is approximately 5–10% in large trials and usually occurs within the first few months (Kalousdian *et al.* 1998; Sgouros & Dipple 2004; Browd *et al.* 2006a). Most infections in CSF shunts are caused by bacteria entering the incision from skin during the insertion procedure (Govender *et al.* 2003; Bayston *et al.* 2004, 2005). Bacteria adhere to the inner and outer surfaces of shunt tubing and colonize, leading to biofilm development (Del Bigio 1998; Bayston *et al.* 2004). Bacteria adhesion is aided by microscopic surface irregularities as well as surface hydrophobicity (Del Bigio 1998; Cagavi *et al.* 2004; Bayston *et al.* 2005; Fux *et al.* 2006). Some evidence suggests that protein adsorption enhances bacterial adhesion, but others have shown the opposite (Del Bigio 1998). Most shunt infections are due to staphylococcus species, which account for close to 90% of the shunt infections (Kalousdian *et al.* 1998; Govender *et al.* 2003; Cagavi *et al.* 2004). Bacteria adhering to outer surfaces of the shunt catheters can be cleared by the cellular immune system, but the inner surface is isolated from the immune system and provides an environment for bacterial colonization, eventually leading to shunt failure (Bayston *et al.* 2004, 2005). Antibiotic treatment of the shunt infections often fails (Furno *et al.* 2004; Livni *et al.* 2004), so attempts have been made to prevent bacteria adhesion and colonization by modifying the shunt material (Kohnen *et al.* 2003; Cagavi *et al.* 2004; Bayston *et al.* 2005; Liang *et al.* 2006).

Strategies to prevent infection can be divided into two categories: surface modification with hydrophilic polymer, heparin or anti-microbial agent and impregnation of the material with antimicrobial agents. Surface modification with hydrophilic polymer coatings has been used to reduce bacterial adhesion. The rationale for this approach is that hydrophilic surfaces reduce bacterial adhesion, and hydrated hydrophilic polymers have fewer adhesion-promoting surface irregularities (Cagavi *et al.* 2004; Bayston *et al.* 2005). The results demonstrate that hydrophilic coating can reduce bacterial adhesion but not colonization (Cagavi *et al.* 2004). The results from studies on the effects of heparinized surfaces on bacterial or cell adhesion have been contradictory or inconclusive (Liang *et al.* 2006). Coating the device surface with antimicrobial agents failed to remain effective for an extended period, possibly due to diffusion or inactivation of the agents (Furno *et al.* 2004; Liang *et al.* 2006).

Impregnation of polymers with antimicrobials has been suggested to be superior over coating because it allows for sustained release of antimicrobial agents and protects both the inner and outer surfaces of the

catheter (Furno *et al.* 2004). Impregnation of drugs into polymer matrix is commonly done by immersing silicone elastomer in a chloroform-based antibiotic solution (Kohnen *et al.* 2003; Bayston *et al.* 2004; Liang *et al.* 2006). The impregnated silicone elastomer kills bacteria already attached and limits further colonization and spreading (Kohnen *et al.* 2003; Bayston *et al.* 2004). A recent study reported a cast-moulding approach for drug impregnation into silicone to prolong drug release and avoid the use of chloroform (Liang *et al.* 2006). In this method, drug is loaded into silicone precursor before curing. The initial burst release is greatly reduced when compared with the immersion method, so it is likely to allow for longer lasting drug release.

### 2.3. Summary

The CSF shunt systems are the most common treatment for hydrocephalus, but have a high failure rate. The most severe problems for ventricular catheters are shunt obstruction and infection. Prolonging shunt longevity relies on the improvement in catheter materials. Developing antimicrobial-impregnated catheters and modifying catheter surfaces to reduce cell and bacterial adhesion are promising strategies to reduce ventricular catheter failure.

## 3. CORTICAL NEURAL PROSTHETICS

### 3.1. Application of cortical neural prosthetics in pathological disorders

CNPs are a subset of neural prosthetics and include both stimulating and recording electrodes. Stimulation-based devices are used to restore hearing and alleviate the symptoms of Parkinson's disease in the CNS (Benabid *et al.* 2000; Colletti *et al.* 2001). Recording-based devices, or brain-computer interfaces, are used to control a mechanical device, which the brain may incorporate into its representation of the body. By reading signals from an array of neurons and translating them into action, these devices are designed for the purpose of allowing paralysed patients to control a motorized wheelchair or a prosthetic limb through thought (Donoghue 2002; Pesaran *et al.* 2006).

Recording-based CNPs hold great promise for patients with impaired movement due to stroke, cervical spine injuries or neurodegenerative diseases such as multiple sclerosis and amyotrophic lateral sclerosis, but are still in the research stage due to problems with long-term recording stability (Donoghue 2002; Ludwig *et al.* 2006; Santhanam *et al.* 2006). These devices lose the ability to record neural activity within a few days or weeks after implantation (Edell *et al.* 1992; Liu *et al.* 1999; Cui *et al.* 2003; Nicolelis *et al.* 2003). A possible contributing factor to the loss of signal is the formation of glial scar around the electrodes, which is part of the inflammatory reaction to a foreign body in the CNS. The glial scar acts as a barrier that inhibits axon re-growth and may possibly interfere with signalling by insulating electrodes from nearby neurons (Turner *et al.* 1999; Cui *et al.* 2003;

Properzi *et al.* 2003; Biran *et al.* 2005). Alternately, the glial scar could be representative of a general inflammatory response that compromises the functional state of the neuronal circuitry around the electrodes. Either way, inflammatory response around implanted electrodes contributes significantly to failure to achieve stable long-term recordings from the cortex although several groups are attempting to overcome these challenges as described below.

### 3.2. Multiple recording electrode types

Investigators are currently developing multichannel microelectrode arrays for long-term cortical neuronal recordings. Many types of microelectrode arrays have been developed, including microwires (Nicolelis *et al.* 1999; Williams *et al.* 1999; Kralik *et al.* 2001), silicon micromachined microprobes (SMMs; Drake *et al.* 1988; Campbell *et al.* 1991; Jones *et al.* 1992; Hetke & Anderson 2002; Kipke *et al.* 2003; Ludwig *et al.* 2006) and polymer substrate probes (Rousche *et al.* 2001; Schneider & Stieglitz 2004). Microwires and SMMs receive the most attention because they are easy to process and fabricate.

The first chronic recording electrodes were microwires. Microwire electrodes are fine wires of 20–50 µm in diameter (Williams *et al.* 1999; Kralik *et al.* 2001). They are made of conductive metals including platinum, gold, tungsten, iridium and stainless steel and are insulated with Teflon or polyimide (Williams *et al.* 1999; Nicolelis *et al.* 2003). The tips of the wires are not insulated and are used for recording neuronal signals (Polikov *et al.* 2005). Arranging the wires in an array by soldering them to a small connector provides access to more neurons, which is better for neuroprosthetic control (Nicolelis *et al.* 1999; Williams *et al.* 1999).

Compared with SMMs, microwire electrodes are easier to fabricate and have lower impedance, but tend to lose signal when recording long term (weeks). One cause of long-term recording failure in microelectrode arrays is the increase of electrode impedance over time due to tissue reaction (Cui *et al.* 2003; Kim & Martin 2006). Impedance is proportional to both thermal noise and signal loss, and consequently improves signal transport across the neural interface and increases sensitivity to neural activity (Robinson *et al.* 1968; Cui *et al.* 2001; Ludwig *et al.* 2006). Low impedance ought to allow long-term recording stability, but the number of functional electrodes declines with time (Nicolelis *et al.* 2003). Electrode impedance is correlated with tissue reactivity around implanted electrodes (Williams *et al.* 2007).

Microwire electrodes record from the tips of the wires and the arrays are glued to the skull, so the depth of the electrode tips relative to the skull is fixed. If the cortical surface moves after surgery, the electrode tip may move to a different cortical layer or into the white matter and fail to record neural signals of interest (Schwartz 2004). As a result, individual neurons cannot be 'tracked' longer than approximately six weeks (Nicolelis *et al.* 1997; Williams *et al.* 1999; Rousche *et al.* 2001).



SMMs are the next generation of electrode arrays. Silicon photolithographic processing provides unsurpassed control over electrode size, shape, texture and spacing, and allows multiple recording sites to be placed on a single electrode shank (Kewley *et al.* 1997; Nicolelis *et al.* 2003). A number of silicon-based micro-electrode arrays have been developed, and two designs have attained prominence in the field (Schwartz 2004; Vetter *et al.* 2004; Polikov *et al.* 2005).

A vertically implanted array developed by the University of Michigan Center for Neural Communication Technology is commonly referred to as 'the Michigan probe'. The Michigan probes have several important advantages over microwires, including batch fabrication, high reproducibility of geometrical and electrical characteristics, precise and repeatable relative electrode locations, high-density recording sites and the ability to integrate circuits directly on the probes (Kewley *et al.* 1997; Vetter *et al.* 2004). The Michigan probe shanks are 15  $\mu\text{m}$  thick and 100–500  $\mu\text{m}$  wide and range in length from 3 mm to 1 cm. Compared with microwire arrays, the Michigan probes offer better access to neurons of interest. Because the multiple recordings sites are placed from top to bottom along the planar probe, at least some of the sites will be situated at cortical depths ideal for extracellular recording (Schwartz 2004). However, the scar tissue encapsulation, which raises the electrode impedance and isolates neurons from the electrodes, is a more severe problem for the Michigan probes owing to their high electrode impedance. In addition, the planar design renders the Michigan probes fragile, which raises the difficulty for handling, post-processing and further modification.

The other favoured design comes from the University of Utah. The Utah Electrode Array (UEA) was developed by Normann and co-workers (Campbell *et al.* 1991; Rousche & Normann 1998) and is now commercially available through Cyberkinetics. It is fabricated from a single block of silicon. Etching, doping and heat treatment result in a three-dimensional  $5 \times 5$  or  $10 \times 10$  array of needles on a  $4 \times 4$  mm square, with a recording site at the tip of each needle or shank. The shank's length ranges from 1 to 1.5 mm depending on the target cortical depth, and its diameter ranges from 100  $\mu\text{m}$  at the base to less than 1  $\mu\text{m}$  at the tip in these designs (Rousche & Normann 1998; Schwartz 2004). This design has the advantage of placing a relatively large number of recording sites in a compact volume of cortex. However, with a single recording site at a fixed cortical depth, the UEAs suffer from the same positioning problem as microwires, leading to eventual recording failure (Schwartz 2004).

This common drawback of the microwire electrodes and UEAs reduces the attractiveness of these two types of electrodes for chronic implants. The advantages of the Michigan probe over the other two types of electrode arrays are that it has better access to neurons and flexible designs. However, these advantages are offset by the problem of scar tissue encapsulation, which raises the electrode impedance. The Michigan probes are usually capable of successfully recording action potentials for the first one to three weeks after

implantation, after which time the signal degrades (Schwartz 2004). An alternative technology proposed by Llinas *et al.* (2005) used nanoelectrodes to record brain activities from capillary vessels without violating the brain parenchyma, which minimizes the invasiveness of electrode implantation and recording. This technology offers another potential strategy to explore in the future.

### 3.3. Factors affecting tissue reaction to the implanted neural electrodes

Factors affecting brain tissue reaction to the implanted neural electrodes include the mechanical trauma during insertion, foreign body reaction, implantation method and physical properties of the electrodes (size, shape and surface characteristics).

When inserting a neural probe into the brain, neurons and glial cells are killed or injured, blood vessels are disrupted and the BBB is damaged. This mechanical trauma and the presence of foreign material initiates the cellular and molecular cascades of the CNS wound healing response. The tissue injury and breakdown of the BBB causes release of cytokines and neurotoxic free radicals, as well as invasion of blood-borne macrophages (Fitch & Silver 1997). Insertion-induced accumulation of fluid and necrotic nervous tissue cause oedema, increasing the pressure around the probe. The main cell types involved in the inflammatory and wound healing response to the brain injury and materials implanted in the CNS are microglia/blood-borne macrophages, oligodendrocyte precursors (OPCs) and astrocytes (Fawcett & Asher 1999; Norton 1999; Hampton *et al.* 2004), which respond very rapidly (Fawcett & Asher 1999; Kato & Walz 2000; Hampton *et al.* 2004). Following injury to the adult CNS, a large number of these cells are recruited to the injury site. The microglia/macrophages are activated upon adherence to the material surface (Anderson 2001) and release neurotoxic molecules such as free radicals and nitric oxide, as well as proinflammatory cytokines including interleukin-1, tumour necrosis factor- $\alpha$  and interleukin-6 (Brucoleri *et al.* 1998; Hays 1998; Kyrkanides *et al.* 2001; Takeuchi *et al.* 2001), which subsequently activate the astrocytes (Merrill & Benveniste 1996; John *et al.* 2005). Astrocyte activation is also mediated by blood-borne factors including growth factors and hormone, albumin, thrombin, angiotensin II and cAMP (Logan & Berry 2002). The reactive astrocytes undergo hypertrophy, proliferation and upregulate trophic factors, cytokines, as well as extracellular matrix (ECM; Fawcett & Asher 1999).

Chondroitin sulphate proteoglycans (CSPGs) are important inhibitory molecules in glial scar (Fawcett & Asher 1999; Properzi & Fawcett 2004). Astrocytes produce neurocan, phosphacan and brevican, microglia/macrophages produce NG2 and OPCs produce neurocan, NG2 and versican (Fawcett & Asher 1999; Tang *et al.* 2003; Hampton *et al.* 2004; Properzi & Fawcett 2004; Tatsumi *et al.* 2005). It has recently been suggested that part of NG2-positive cells proliferating in the injury site differentiate into the glial scar astrocytes (Alonso 2005; Tatsumi *et al.* 2005). The

CSPGs and other glial scar-associated inhibitory molecules create an environment that blocks the regrowth of neural processes and may potentially cause the exclusion of neural cells by their presence.

The physical properties of the microelectrode arrays (size, shape and surface characteristics) are other factors that may contribute to the tissue reaction to implanted microelectrodes. It has been suggested that a small prosthesis with smooth surfaces and rounded corners is less likely to damage tissue when inserted (Edell *et al.* 1992). However, Szarowski *et al.* (2003) compared the tissue response with planar silicon electrode arrays of different sizes, shapes and surface characteristics through GFAP, vimentin and ED-1 staining, and the histological evidence indicated that although these factors made a difference in the tissue reaction around the implanted devices in the first week after implantation, responses observed after four weeks were similar for all devices. Bjornsson *et al.* (2006) observed that tip geometry of silicon neuroprosthetic devices had little effect on vascular damage.

### 3.4. Strategies to minimize tissue reaction to the implanted neural electrodes

Research groups are working on different approaches to reduce the inflammatory tissue response around implanted neural electrodes. These approaches can be divided into two categories: the materials science strategies and the bioactive molecule strategies (Polikov *et al.* 2005). The materials science strategies include modifying the size and shape of the electrodes (Edell *et al.* 1992; Szarowski *et al.* 2003) or using alternative materials such as polymers (Rousche *et al.* 2001; Schneider & Stieglitz 2004) or ceramics (Singh *et al.* 2003; Moxon *et al.* 2004). To date, none of these efforts have shown any significant reduction of the inflammatory tissue reaction.

Bioactive molecule strategies have focused on administration of anti-inflammatory agents through electrode coatings (Kim & Martin 2006; Zhong & Bellamkonda 2007), direct injection through microchannels fabricated into the electrodes (Retterer *et al.* 2004) and systemic injection (Spataro *et al.* 2005). The systemic injections and local release of anti-inflammatory agents from non-functional polymers have each been shown to reduce the reactive tissue reaction to the neural implants (Shain *et al.* 2003; Spataro *et al.* 2005). Systemic injection, though effective and easy to operate, is not a viable option owing to the side effects associated with peripheral metabolism and chronic use, and the difficulty in getting the drugs across the BBB (Retterer *et al.* 2004; Kim & Martin 2006).

Several research groups are seeking to integrate microfluidic drug delivery systems into electrical devices during fabrication (Chen, J. K. *et al.* 1997; Rathnasingham *et al.* 2004; Retterer *et al.* 2004). Microfluidic channels capable of releasing biomolecules have been successfully integrated into silicon neural prosthetics. The diffusion of test biomolecules from the microfluidic channels was investigated both *in vitro* and *in vivo* (Retterer *et al.* 2004). In some designs, the drug

release rate can be controlled by pumps and valves (Paparg Georgiou *et al.* 2001). These studies represent preliminary steps towards developing a viable clinical intervention strategy to improve the biocompatibility and chronic stability of silicon-based multielectrode arrays (Retterer *et al.* 2004).

An alternative strategy to local drug delivery is electrode coatings. Designs include nitrocellulose coatings as a polymer matrix for storage and sustained release of the anti-inflammatory agent dexamethasone (Zhong & Bellamkonda 2007), alginate hydrogel matrices embedded with dexamethasone-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles (NPs; Kim & Martin 2006), and conducting polymer polypyrrole coatings using dexamethasone phosphate as the negative dopant (Wadhwa *et al.* 2006). This local delivery of dexamethasone reduces the inflammatory tissue response and prevents the increase of electrode impedance *in vivo*.

The direct effect of drug release is to manage the acute local inflammatory response, which in turn will have long-term repercussions to compatibility. Since the acute inflammatory response is closely related to long-term stability, drug release can help improve long-term stability of chronic recording electrodes. The experience from drug-eluting stents that also aim to manage the acute injury response, albeit in the blood vessels, suggests that the release of anti-inflammatory agents in the early stage of implantation inhibits the long-term tissue reaction (De Scheerder *et al.* 1996; Huang *et al.* 2002). In the CNS, administration of anti-inflammatory agents in the early stage of brain injury might be able to inhibit the expression of proinflammatory molecules that leads to progression of astrogliosis and has a long-term effect (Zhong & Bellamkonda 2007).

### 3.5. Summary

Recording-based CNPs hold great promise for the treatment of a wide variety of movement disorders. However, the long-term performance of the implanted CNSs is compromised by the formation of glial scar around these devices. Local administration of anti-inflammatory drugs from microfluidic channels or bioactive coatings of the neural prosthetics have the capacity to manage the cellular and tissue responses around the implanted devices, and therefore holds great promise to improve the long-term stability of chronically implanted neural electrodes.

## 4. DRUG DELIVERY IN THE CNS

### 4.1. Strategies for CNS drug delivery

The principal obstacle to deliver drugs into the CNS is the presence of the BBB, which forms a physiological and pharmacological barrier to the entry of therapeutic agents from the blood stream (Wang *et al.* 2002; Misra *et al.* 2003; Garcia-Garcia *et al.* 2005). To circumvent the BBB, various drug carrier systems have been developed. These strategies can be categorized as either systemic or local delivery.

## 4.2. Systemic drug delivery systems

The promising drug carriers that have been investigated in systemic delivery systems include liposomes, polymeric NPs, polymeric micelles, ceramic NPs and dendrimers (Cherian *et al.* 2000; Lian & Ho 2001; Adams *et al.* 2003; Na *et al.* 2006; Kaur *et al.* 2008). However, only liposomes and polymeric NPs have been widely exploited in brain drug delivery (Garcia-Garcia *et al.* 2005). Systemic drug delivery is achieved by intravenous or intraperipheral injection and therefore is non-invasive. The drugs can be administered repeatedly as needed. However, systemic administration requires large dosages to achieve therapeutic concentrations at the target site, which can affect non-target tissues and organs. Active targeting may provide a promising solution to this problem. In the design of adequate brain delivery systems, two important requirements must be taken into account: long circulating properties of the carrier and appropriate surface characteristics to permit interactions with endothelial cells (Misra *et al.* 2003).

**4.2.1. Liposomes.** Liposomes are small vesicles in which an aqueous inner core is entirely enclosed by unilamellar or multilamellar phospholipid bilayers (Schnyder & Huwyler 2005; Ishida *et al.* 2006). Liposomes are divided into three types based on their size and number of bilayers: small unilamellar vesicles with a single lipid layer and 25–50 nm in diameter; large unilamellar vesicles with a single lipid layer and 100–2000 nm in diameter; and multilamellar vesicles with several lipid layers separated from one another by a layer of aqueous solution and 200–5000 nm in diameter (Sahoo & Labhasetwar 2003; Yoshida & Mizuno 2003).

Liposomes are biocompatible and biodegradable drug carriers that have the potential to enhance the potency and reduce the toxicity of therapeutic agents (Lian & Ho 2001). However, conventional liposomes do not undergo significant transport through the BBB in the absence of vector-mediated drug delivery (Misra *et al.* 2003; Ishida *et al.* 2006). Furthermore, these liposomes are coated with serum proteins immediately after intravenous administration and are rapidly removed from the bloodstream and cleared by the cells of the reticuloendothelial system (RES; Siwak *et al.* 2002; Sadzuka *et al.* 2006). The RES is a group of mononuclear cells originating from bone marrow that phagocytize small foreign particles in the vascular space (Lockman *et al.* 2002). Plasma clearance of liposomes can be solved by modification of liposome surfaces with hydrophilic polymers, which reduce liposome aggregation and avoid liposome recognition by RES (Lian & Ho 2001; Misra *et al.* 2003). Poly(ethyleneglycol) (PEG) is commonly used to provide an additional surface hydration layer, which prevents binding of opsonins from physiological fluids such as plasma and CSF, and in turn avoids recognition by phagocytic cells (Huwyler *et al.* 1996; Sahoo & Labhasetwar 2003; Garcia-Garcia *et al.* 2005; Schnyder & Huwyler 2005). The PEGylated liposomes demonstrate longer blood circulation time and reduced clearance by the RES, allowing for selective

extravasation of liposomes into the pathology sites with a leaky endothelium (Siegal *et al.* 1995).

Liposome penetration through the BBB can be enhanced by active targeting. Active targeting modifies the organ and tissue distribution of liposomes by conjugating them to an antibody or a ligand that will be recognized by cell surface receptors in the targeted tissue (Garcia-Garcia *et al.* 2005; Schnyder & Huwyler 2005). Examples of compounds or proteins that traverse the BBB by receptor- or absorptive-mediated transcytosis include cationized albumin, the OX26 monoclonal antibody to the rat transferrin receptor and monoclonal antibodies to the insulin receptor (Pardridge *et al.* 1992; Schnyder & Huwyler 2005). Thus, conjugation of liposomes with both hydrophilic polymers such as PEG and targeting vectors is an efficient strategy to prolong blood circulation time and improve transport through the BBB to reach the target site. In addition to facilitating liposome transport through the BBB, active targeting is also widely used to promote selective binding of liposomes to specific cells using ligands or receptors that are unique to the target tissue or cells (Eavarone *et al.* 2000; Lian & Ho 2001; Saul *et al.* 2003; Yoshida & Mizuno 2003). Selective delivery of liposomes through active targeting enhances drug distribution and cell uptake of the liposomes in the target tissue and reduces or prevents drug uptake in other tissue or organs. Liposomes have been used to treat CNS diseases including brain tumour, ischaemia, infection and experimental autoimmune encephalitis. As the newly formed blood vessels in tumour tissue have leaky vasculature with discontinuous basement membranes and wide inter-endothelial junctions, the BBB at the tumour site is compromised, permitting the diffusion of liposome into the target tissue; therefore, most of the studies have focused on tumour therapies.

**4.2.2. Polymeric nanoparticles.** Polymeric NPs are particles ranging in size from 10 to 1000 nm, made of natural or artificial polymers in which therapeutic drugs can be adsorbed, dissolved, entrapped, encapsulated or covalently attached (Lockman *et al.* 2002; Sahoo & Labhasetwar 2003; Roney *et al.* 2005). NPs can be classified as nanospheres and nanocapsules according to the preparation process (Brigger *et al.* 2002). Nanospheres are matrix systems in which drug is either dispersed throughout or adsorbed onto the surface of the polymeric matrix, while nanocapsules consist of a liquid core surrounded by a polymeric shell, and may be considered as reservoir systems (Brigger *et al.* 2002; Roney *et al.* 2005). Compared with liposomes, polymeric NPs are more stable when in contact with the biological fluids. Also, their polymeric nature permits the attainment of desired properties such as controlled and sustained drug release, allowing drug release at the targeted site over a period of days or even weeks after injection (Garcia-Garcia *et al.* 2005; Roney *et al.* 2005; Nahar *et al.* 2006). Drug release from NPs is mediated by drug desorption, diffusion through the NP matrix, polymer wall degradation of NPs or some combination of these mechanisms (Lockman *et al.* 2002;



Misra *et al.* 2003). The polymers used for NP synthesis include poly(alkylcyanoacrylates) (PACAs), polyacetates, polysaccharides and copolymers (Garcia-Garcia *et al.* 2005).

The transport of NPs across the BBB has been hypothesized to be mediated by receptor-mediated endocytosis and/or passive diffusion (Lockman *et al.* 2002; Misra *et al.* 2003). Polybutylcyanoacrylate (PBCA) NPs coated with polysorbate 80 have been used to successfully transport drugs through the BBB (Range *et al.* 2000; Kreuter 2001). Current research areas are focused on anaesthetic and chemotherapeutic agents (Lockman *et al.* 2002). Drugs that have been successfully delivered to the CNS using PBCA NPs include dalargin, loperamide, tubocurarine and doxorubicin (Alyautdin *et al.* 1997; Gulyaev *et al.* 1999; Range *et al.* 2000; Kreuter *et al.* 2003).

NP uptake by the RES plays an important role in the failure of NPs to reach the CNS in appreciable quantity (Lockman *et al.* 2002). As in the case of liposomes, a promising solution is coating NPs with hydrophilic polymer that can reduce uptake by the RES and prolong circulation time. The hydrophilic polymers include PEG, poloxamines, poloxamers and polysaccharides (Brigger *et al.* 2002). These coatings repel plasma proteins by providing a dynamic 'cloud' of hydrophilic and neutral chains at the particle surface (Brigger *et al.* 2002). While the long circulating NPs increase the exposure of target tissue to the drug, they also prolong the exposure of other tissues and organs, which may cause systemic side effects and toxicity.

#### 4.3. Local delivery systems

To reduce systemic side effects and increase the therapeutic effectiveness, selective delivery of drugs for the treatment of diseases localized in a specific organ or tissue is desired. Local administration of the therapeutic agents from a biocompatible polymeric delivery system implanted at the target site provides a promising strategy (Jain *et al.* 2006). This approach is particularly appropriate for recurrent malignant gliomas, since 89–90% recur within 2 cm of the original site of resection (Wang *et al.* 2002). Local drug delivery using polymeric implants in the CNS avoids the difficulty of penetration through the BBB, systemic side effects and toxicity, peripheral drug inactivation and necessity for modification of the carrier surface (Domb 1995; Begley 2004). The disadvantages of local delivery are that the dosage cannot be adjusted after implantation, the rate of drug release typically decreases with time, repeated implantation may be required for long-term release and the implantation surgery is invasive (Meilander *et al.* 2001; Saltzman & Olbricht 2002). Care must be taken in choosing the proper drug delivery system for treatment of a specific disease.

The biocompatible polymers used for local, controlled drug delivery can be categorized as biodegradable and non-biodegradable. Biodegradable polymers release their loaded agents as they breakdown to non-toxic products and are eliminated by the body, while the matrix of non-biodegradable polymers remains

intact even after all of the therapeutic agent has been released. The non-degradable polymers that are commonly used for drug delivery include ethylene-vinyl acetate copolymers, various acrylate-based hydrogels and segmented polyurethane (Domb 1995; Sawyer *et al.* 2006). The primary limitation of non-degradable polymers is that the polymer matrix remains permanently as a foreign body, continuously stimulating an inflammatory response. The common degradable polymer carriers include poly(lactic acid) (PLA), PLGA, poly(glycolic acid) (PGA), poly(caprolactone), poly(hydroxybutyrate), poly(orthoester), poly(phosphazene), polyanhydrides, gelatin, collagen and oxidized cellulose (Domb 1995; Fournier *et al.* 2003). In the CNS, the most widely used biodegradable polymers are PLGA and polyanhydride poly[bis(*p*-carboxyphenoxy)] propane-sebacic acid (PCPP-SA).

Studies have shown that the CNS tissue response to PLGA drug carriers is a moderate and non-specific inflammatory reaction due to the mechanical trauma by implantation, irrespective of the drug carrier shape or the implantation site (Menei *et al.* 1993; Lillehei *et al.* 1996; Kou *et al.* 1997; Emerich *et al.* 1999; Fournier *et al.* 2003). Local injection of PLGA microspheres has been used to deliver anti-tumour agents such as mitoxantrone, hemopexin, platelet factor 4 fragment, 5-fluoro-uracil and carboplatin (Menei *et al.* 1996; Chen, W. *et al.* 1997; Benny *et al.* 2005; Yemisci *et al.* 2006) for treatment of brain tumours. This method is also used for treatment of neurodegenerative disease. For example, PLGA microspheres were used to locally deliver neurotransmitters such as dopamine and noradrenaline for treatment of Parkinson's disease (McRae & Dahlstrom 1994). In addition, local administration of PLGA microparticles loaded with nerve growth factor (NGF) was shown to protect neurons from excitotoxin-induced lesions and may be a promising strategy for treatment of Huntington's disease (Benoit *et al.* 2000).

While local delivery of drug with PLGA polymers has been shown to be effective for treatment of brain tumour and neurodegenerative diseases, the drug release is mediated by bulk erosion, which can result in sporadic dumping of drug and potential toxicity (Wang *et al.* 2002). To circumvent this problem, biocompatible polyanhydride polymer PCPP-SA, whose degradation is mediated by surface erosion, was developed. Local implantation of 3.85% carmustine (beta-chloro-nitrosourea; BCNU)-loaded PCPP-SA polymer (Gliadel) has been shown to be safe and effective in the treatment of recurrent malignant gliomas and was approved by the Food and Drug Administration in 1996 (Wang *et al.* 2002). Taxol-loaded PCPP-SA disc was shown to improve the median survival in a rat model of malignant glioma (Walter *et al.* 1994). Compared with a Gliadel-treated group, 50% camptothecin-loaded PCPP-SA greatly improved rat survival in a glioma model (Storm *et al.* 2002). A recent study reported local delivery of doxorubicin via PCPP-SA for the treatment of intracranial glioma in rats, and the median survival was significantly extended (Lesniak *et al.* 2005).



It is noteworthy that local drug delivery through biocompatible polymers is mediated by passive diffusion. Thus, local drug distribution and penetration in target tissue depend on rates of drug diffusion and elimination (Saltzman & Radomsky 1991). Drug penetration distance is limited by a slow diffusion coefficient coupled with a high rate of elimination (Haller & Saltzman 1998). In many instances, tissue exposed to therapeutic levels of drug concentration is limited at millimetres of the implant (Haller & Saltzman 1998; Mahoney & Saltzman 1999; Neeves *et al.* 2006). Convection-enhanced delivery (CED) offers an alternative approach that uses pumps and catheters to create an external pressure gradient to infuse drug-containing fluid into the tissue, so that the transport is dominated by convection (Hall & Sherr 2006; Sawyer *et al.* 2006; Ferguson *et al.* 2007). CED increases drug distribution volume and exposes the tissue to a consistent drug concentration over a long infusion time (Sawyer *et al.* 2006). However, this method has several disadvantages including invasiveness, potential high intracranial pressure associated with fluid infusion into small ventricular volumes and unpredictable drug distribution (Misra *et al.* 2003; Sawyer *et al.* 2006).

#### 4.4. Summary

Drug delivery in the CNS is challenging due to the presence of the BBB. One strategy to overcome the BBB is local delivery of drug via biocompatible polymers. This approach offers the advantage of local exposure to drugs at therapeutic levels while eliminating systemic drug exposure. This method has been successfully used for treatment of recurrent malignant brain tumour. However, the surgery for polymer implantation is invasive, and drug delivery at therapeutic levels over the long term is difficult to achieve, which limits the application of local drug delivery. Systemic drug delivery, in which drug can be repeatedly administered as required, provides an alternative strategy. Penetration through the BBB and reduced systemic side effects can be managed by active targeting. However, systemic exposure to the drug is not avoidable at this stage. Since both drug delivery systems have advantages and disadvantages, the selection of appropriate drug delivery carrier is dependent on the nature and location of the disease.

## 5. HYDROGEL SCAFFOLDS FOR CNS REPAIR

### 5.1. Hydrogel in spinal cord repair

Traumatic spinal cord injury (SCI) results in immediate cell death in the vicinity of the injury site, including neurons, glial cells and endothelial cells. The loss of neurons and axon degeneration can cause functional impairment, paraplegia or tetraplegia. The primary injury is followed by a secondary injury cascade including inflammation, Wallerian degeneration and formation of astroglial scar. The scar mainly consists of reactive astrocytes and invading meningeal fibroblasts, which express various inhibitory molecules such as CSPGs. In addition, the injured spinal cord contains

inhibitory molecules from myelin debris, such as Nogo and myelin-associated proteoglycan. The glial scar presents an inhibitory cellular and molecular micro-environment for axon regeneration and tissue repair (Fawcett & Asher 1999; Woerly *et al.* 2005; Hagg & Oudega 2006; Sykova *et al.* 2006).

Currently there is no effective treatment for SCI (Woerly *et al.* 2005; Bradbury & McMahon 2006). Systemic delivery of methylprednisolone is the only clinically used therapy (Gupta *et al.* 2006). While this method has been demonstrated to reduce SCI and improve functional recovery, it can cause adverse systemic side effects such as immunosuppression, gastrointestinal bleeding and myopathy (Amar & Levy 1999; Qian *et al.* 2005; Bernards & Akers 2006). The common problems for systemic delivery of therapeutic agents to the spinal cord include difficulty of crossing the blood–spinal cord barrier and degradation of therapeutic proteins (Gupta *et al.* 2006). Local delivery of therapeutic molecules at the site of injury presents an alternative strategy that can overcome these problems. In addition, implantation of biomaterial scaffold at the injury site not only provides a matrix for local drug delivery, but also provides a physical substrate for axon attachment and growth (Geller & Fawcett 2002; Tsai *et al.* 2004; Piantino *et al.* 2006; Chvatal *et al.* 2008).

Hydrogels are cross-linked networks of insoluble hydrophilic polymers that swell with water (Tsang & Bhatia 2004). The high water content and tissue-like mechanical properties of hydrogels make them highly attractive scaffolds for implantation in soft tissue (Woerly *et al.* 1999; Balgude *et al.* 2001; Tsang & Bhatia 2004; Tan *et al.* 2005). The water held within swollen hydrogels allows for the exchange of ions and metabolites with tissue fluids to maintain chemical balance with surrounding tissue (Woerly *et al.* 1999). The porous structure of hydrogels allows cell attachment and growth into the scaffold. In addition, hydrogels have the potential to attach growth-promoting ECM or adhesion peptides to promote cell attachment and tissue growth, as well as release biological agents to the injury site (Meilander *et al.* 2003; Tan *et al.* 2005; Jain *et al.* 2006). Therefore, hydrogel scaffolds provide an attractive strategy for improving regeneration in the CNS.

Ideal properties of a hydrogel scaffold for spinal cord regeneration include the following: (i) it is biocompatible, to minimize adverse tissue reaction *in vivo*, (ii) it can be shaped *in situ* by either *in situ* gelation or direct injection, (iii) it permits cell migration and axon outgrowth, and (iv) it is biodegradable or bioresorbable to obviate the need for removal after drug release and tissue regeneration (Gutowska *et al.* 2001; Gupta *et al.* 2006; Jain *et al.* 2006). *In situ* gelation can be mediated by temperature change (Tate *et al.* 2001; Jain *et al.* 2006), ionic cross linking (Lin *et al.* 2004) and photo-activation (Piantino *et al.* 2006). Below, examples of hydrogels that fulfil these requirements and have been used for spinal cord regeneration are discussed.

Collagen, methylcellulose (MC) and agarose are biodegradable temperature-responsive polymers. Both collagen and MC can gel at physiological temperature.

The gelation temperature of agarose is lower than physiological temperature; therefore, a cooling system is needed for rapid *in situ* gelation (Jain *et al.* 2006).

Collagen gels have been commonly used for building a scaffold to promote axon regeneration after SCI in rodents (Nomura *et al.* 2006). *In vitro* studies demonstrate that collagen promotes neural cell attachment and neurite outgrowth (Thompson & Pelto 1982; Carbonetto *et al.* 1983; Zhong *et al.* 2001). However, collagen gel implanted in injured spinal cord showed little or no axon regeneration (Joosten *et al.* 1995; Houweling *et al.* 1998a,b; Nomura *et al.* 2006). Thus, combination therapy of collagen gels with neurotrophic factors was explored by a number of research groups. Implantation of collagen gel containing NT-3 into lesioned rat spinal cord induced a significant number of corticospinal tract fibres into the graft and function recovery was observed, although the fibres were not able to cross the lesion and grow into host tissue caudal to the lesion site (Houweling *et al.* 1998a). Collagen gel containing brain-derived neurotrophic factors (BDNF) attenuated the loss of function in the partially transected rat spinal cord (Houweling *et al.* 1998b). Localized delivery of EGF and FGF-2 to injured spinal cord via collagen gels resulted in less cavitation (Jimenez Hamann *et al.* 2005).

MC is a thermoreversible polymer that gels at 37°C, but it gels too slowly. Blending MC with shear-thinning hyaluronan (HA) creates a fast gelling hydrogel (hyaluronan and methylcellulose, HAMC; Gupta *et al.* 2006). HAMC gels at room temperature prior to injection, and the gel strength increased after injection into the spinal cord due to the temperature increase. Studies *in vivo* demonstrated decreased inflammatory response and limited improved functional recovery in rats injured by clip compression. Studies exploring localized, sustained release of bioactive molecules from the HAMC hydrogel are ongoing.

Agarose gel scaffolds elicited minimal inflammatory response in rat spinal cord, but did not support neurite growth into the scaffold. When agarose gel was embedded with BDNF containing lipid microtubules for sustained release, the new construct enhanced axonal infiltration of the scaffold and further reduced the inflammatory response (Jain *et al.* 2006). However, no regenerating fibres could cross into the distal cord (distal to the lesion site). The authors suggest that this might be solved by delivery of BDNF both at and distal to the lesion site.

A recent study reported a degradable PEG-based hydrogel in which gelation is mediated by photopolymerization under visible light (Piantino *et al.* 2006). The macromer is acrylated poly(lactic acid)-b-poly(ethylene glycol)-b-(poly lactic acid) (PLA-b-PEG-b-PLA). In this study, macromers dissolved in PBS containing photoinitiator was mixed with NT-3, injected into the lesioned spinal cord cavity and exposed to blue light for 60 s for rapid *in situ* gelation. Hydrogel/NT-3-treated rats with spinal cord hemisection showed improved axon growth and functional recovery.

Alginate is a biodegradable polysaccharide that gels by ionic cross linking, when aqueous alginate solution is mixed with divalent cations such as calcium salts

(Gutowska *et al.* 2001). Freeze-dried alginate sponge or gel has been used as a scaffold to fill the cavity of injured spinal cord (Suzuki *et al.* 1999, 2002; Nomura *et al.* 2006). Alginate gel scaffold was also used to encapsulate BDNF-producing fibroblasts for spinal cord regeneration (Tobias *et al.* 2005). While all these studies showed promising results, the scaffolds were fabricated before application to the spinal cord instead of gelling *in situ*, which requires intrusive implantation surgery techniques. In addition, the shape of the scaffolds may not conform to the spinal cord cavity.

## 5.2. Hydrogel in brain repair

Similar to spinal cord, traumatic brain injury (TBI) evokes a cascade of secondary biochemical and molecular changes that result in delayed tissue damage and cell death, and ultimately leads to the formation of an irregularly shaped lesion cavity encapsulated by glial scar (Yakovlev *et al.* 1997; Duconseille *et al.* 1998; Fitch *et al.* 1999; Loh *et al.* 2001; Stabenfeldt *et al.* 2006). It is suggested that the inflammatory processes initiate the cascade of secondary tissue damage, progressive cavitation and glial scarring in the CNS (Fitch *et al.* 1999). In addition to TBI, surgical removal of damaged tissue or tumours also creates cavities in the brain (Woerly 2000). The lack of regeneration in the CNS might be attributed to the complex cellular and molecular environment in the lesion area, which contains both inhibitory and permissive molecules, as well as the parenchymal discontinuity that makes the growth cone progression by cellular adhesion impossible (Duconseille *et al.* 1998; Woerly 2000; Stabenfeldt *et al.* 2006). Implanting a scaffold into the brain cavity offers the opportunity to provide supporting substrates that are conducive to cell infiltration and axon outgrowth and may be used for delivery of biologically active molecules to promote axon regeneration. As discussed in the previous subsection, hydrogels are attractive scaffold biomaterials in the CNS.

A number of hydrogels have been used for brain lesion repair, such as poly[N-2-(hydroxypropyl) methacrylamide] (pHPMA), hyaluronan (also called hyaluronic acid; HA), poly(hydroxyethyl-methacrylate) (pHEMA) and MC-based hydrogels (Woerly *et al.* 1999; Tate *et al.* 2001; Lesny *et al.* 2002; Tian *et al.* 2005). It is noteworthy that pHPMA and pHEMA are non-degradable polymers, while HA and MC are biodegradable. Unmodified pHPMA hydrogel or pHPMA hydrogel containing glucosamine or *N*-acetylglucosamine groups was implanted between the septum and the hippocampus in a fimbria-fornix lesion cavity. All three hydrogels showed cellular infiltration and axonal ingrowth (Duconseille *et al.* 1998). However, the hippocampus failed to show any increase of acetylcholinesterase staining when compared with that seen in lesion-only rats. When pHPMA and pHEMA hydrogels were implanted into cortical lesion cavities, astrocyte and axon ingrowth were observed in both hydrogel scaffolds. It is interesting to note that pHEMA hydrogel showed markedly less infiltration of connective tissue than pHPMA (Lesny *et al.* 2002). pHPMA and pHEMA cannot gel *in situ* and therefore must be preformed before implantation, which

makes the implantation surgery invasive. *In situ* gelation is especially important for treating the CNS injury, as the irregularly shaped lesion cavity poses structural and integration problems for preformed scaffold implants (Stabenfeldt *et al.* 2006). Thus, *in situ* gel-forming polymers are highly attractive candidates for minimally invasive delivery of scaffold implants to the lesion cavity.

MC exhibits low viscosity at 23°C and forms a soft gel at 37°C (Tate *et al.* 2001). This property allows for microinjection of liquid MC into brain lesion cavities with varying size and shape without significant compromise of the dura membrane and brain tissue, and forming hydrogel scaffolds that fill the irregular shape of the lesion cavity. A study *in vivo* showed that MC exhibited minimal inflammatory tissue reaction following implantation into a TBI lesion cavity (Tate *et al.* 2001). MC was further conjugated with laminin-1 (LN) to promote neuronal cell adhesion and survival (Stabenfeldt *et al.* 2006).

HA gels can form *in situ* upon injection of a viscous (but still injectable) gel formulation due to its viscoelastic and shear-thinning properties (Gutowska *et al.* 2001). Recent studies report that HA hydrogels conjugated with laminin or arginine–glycine–aspartic acid (RGD) peptides (Hou *et al.* 2005; Cui *et al.* 2006) showed cell infiltration and angiogenesis in the scaffolds implanted into lesioned brain. In addition, these hydrogel scaffolds could promote neurite extension and inhibit formation of glial scar. However, HA hydrogel scaffolds used in these studies were preformed before implantation. It is interesting to investigate the possibility of using *in situ* gelling HA as a scaffold for brain lesion cavities.

*In situ*-gelling agarose hydrogels loaded with BDNF were used as scaffolds for repair of spinal cord defects and showed promising results (Jain *et al.* 2006). However, no study has been reported using agarose hydrogel in brain injury repair. Nonetheless, agarose hydrogel possesses the following appealing properties as a scaffold candidate for treatment of brain injury. First, it is biocompatible and elicits only minimal inflammatory response when implanted *in vivo* (Jain *et al.* 2006). Second, it can be conjugated with ECM molecules or peptides and still maintain its thermoreversible gelling property (Bellamkonda *et al.* 1995; Yu *et al.* 1999; Gilbert *et al.* 2005; Dodla & Bellamkonda 2006). Third, it can be loaded with drug or gene delivery carriers for sustained release (Yu *et al.* 1999; Meilander *et al.* 2003). Thus, agarose hydrogel is a promising scaffold candidate for brain defect repair.

### 5.3. Summary

Hydrogels are attractive scaffolds for improving tissue regeneration and CNS repair, owing to their tissue-like mechanical abilities conformable to the soft CNS tissue; porous structure allowing cell infiltration, transplantation and axon outgrowth; potential to attach adhesion and/or growth-promoting molecules for promoting cell attachment and tissue growth; and capacity for drug/gene incorporation and delivery. It is noteworthy that the ability to gel *in situ* is a very important property for hydrogel scaffold so that the scaffold is able to conformally fill the irregularly

shaped lesion cavities and avoid intrusive implantation surgery techniques.

## 6. NEURAL STEM CELL ENCAPSULATION FOR NEUROTRAUMA

TBI and SCI are two severe neurotraumas that cause disability and even death of victims. Current clinical treatments focus on prevention of the secondary injury after the initial trauma and partial function recovery with drug therapy, physical rehabilitation, psychotherapy, etc. (Bracken *et al.* 1990; Dopperberg & Bullock 1997; Geisler *et al.* 2001; Maas 2001; Maas *et al.* 2004). However, the results are far from ideal and new therapy methods must be established for better treatment.

Recently, stem cell-based tissue replacement strategies have been widely investigated for SCI and TBI therapy (Shear *et al.* 2004). These strategies basically consist of harvesting, culturing and transplanting exogenous neural stem/progenitor cells to the injury site in the CNS for tissue replacement, or simulating endogenous stem cells to migrate to the desired site, and proliferate and differentiate into functional tissues.

The reasons for stem cells being an appealing candidate for the treatment of neurotrauma include the following: (i) mature neurons in the damaged CNS tissue are highly differentiated and difficult to be replaced by local cell proliferation, thus a cell substitute has to be supplied for large tissue damage, (ii) neural stem cells, either endogenous or exogenous, are multipotent (can differentiate into both neurons and glia) and can produce large numbers of progeny, (iii) they can differentiate into functional cells and integrate into the damaged neural circuits to restore lost function, and (iv) neural stem cells can secrete neurotrophic factors, either naturally or through genetic modification, to help brain and spinal cord regeneration (Kulbatski *et al.* 2005).

Compared with implantation of exogenous neural stem cells, augmenting endogenous neural stem/progenitor cells to respond to the tissue injury is a more difficult task, not only because the population of endogenous stem cells is low and their distribution is region specific, but also because of the difficulties in finding the necessary combination of molecular signals *in vivo* to induce the proliferation and differentiation of these stem cells for appropriate tissue replacement. Therefore, implantation of exogenous stem cells into the injury site is a better strategy for CNS regeneration.

However, implantation of exogenous neural stem cells also faces some problems. One severe problem is the host immune response, which not only requires the patient to continue taking medicines for sustained immunosuppression, but also reduces the viability of implanted cells. In addition, when vast amounts of tissues are lost and a cystic cavity is formed, the ability of the implanted cells to reconstitute the tissue and reform the connections is limited (Park *et al.* 2002). The survival of the cells is also affected due to a large distance (if more than a few hundred micrometres) to the nearest capillary (Langer & Vacanti 1993; Colton 1995). A three-dimensional biomaterial scaffold seeded with neural stem cells is an



alternative strategy to improve the cell replacement therapy, by increasing the cell viability and reducing the acute host immune response.

The research for encapsulating neural stem cells in three-dimensional scaffold for CNS regeneration is still in the preliminary stage. Studies in this area are classified into two categories: *in vitro* studies for evaluating stem cell proliferation and differentiation on the biomaterial scaffold and *in vivo* studies for evaluating the interaction of scaffold seeded with stem cell with the host tissue and the function recovery of the host.

### 6.1. In vitro studies

Among the *in vitro* studies, various materials were tested for optimizing stem cell culture conditions. Willerth *et al.* tested fibrin as scaffolds for two-dimensional (dissociated cells) and three-dimensional cultures of murine embryonic stem cells, and fibrinogen, thrombin and aprotinin were added to augment cell proliferation. It was found that three-dimensional culture in fibrin scaffold exhibited more favourable conditions for cell proliferation and differentiation, and after 14 days in three-dimensional culture, stem cells differentiated into neurons and astrocytes (Willerth *et al.* 2006). A three-dimensional network of nanofibres, formed by self-assembly of peptide amphiphile molecules, was used to encapsulate the neural progenitor cells. Interestingly, this artificial nanofibre scaffold induced very rapid cell differentiation into neurons, but inhibited the development of astrocytes. This rapid selective differentiation is believed to be caused by the amplification of bioactive epitope presentation to cells by the nanofibres (Silva *et al.* 2004). Thonhoff *et al.* examined the toxicity and ability to support stem cell differentiation of several hydrogels including pluronic F127 (PF127), Matrigel and PuraMatrix. The results demonstrated that PF127 (30%) was toxic to foetal human neural stem cells (hNSCs) and Matrigel prevented neuronal differentiation. PuraMatrix showed low toxicity and supported cell migration and neuronal differentiation (Thonhoff *et al.* 2008). Brännvall *et al.* (2007) observed enhanced neuronal differentiation in a three-dimensional collagen–HA matrix hydrogel.

The biocompatibility of PLGA, poly(L-lactide-co-epsilon-caprolactone) and poly(L-lactic acid) was compared in hippocampal progenitor cell (HiB5) culture. Among the tested polymers, PLGA showed the best performance regarding cell viability, mitochondrial metabolic activity and apoptotic activity. In addition, PLGA also showed favourable results for neurite outgrowth of HiB5 cells (Bhang *et al.* 2007). Gelatin scaffolds were found to support the adhesion and growth of hNSCs, and better cell proliferation was achieved by coating the scaffolds with basic fibroblast growth factor (bFGF; Chen *et al.* 2006). To investigate the effect of substrate chemical composition on neural stem cell adhesion and differentiation, hydrophobic polymers poly(ethyl acrylate) (PEA) and poly(methyl acrylate) (PMA), hydrophilic polymers poly(hydroxyethyl acrylate) (PHEA), polyacrylamide (PAAm) and chitosan (CHT), and copolymers of EA with HEA and with methacrylic acid have been studied. Some of these

materials have comparable hydrophilicity but different chemical nature (PEA and PMA on one hand, PHEA, CHT and PAAm on the other hand), and some have similar chemical composition but different intermediate degrees of hydrophilicity (the EA–HEA copolymer series). The results showed that CHT, PMA and the P(EA-co-HEA) 50/50 copolymer were the most suitable substrates to promote embryonic neural explant cell attachment and differentiation, suggesting that the biological performance of the materials is modulated more by material's parameters rather than directly correlating with surface wettability (Soria *et al.* 2006).

Hunt *et al.* showed that neural stem cells could behave differently under single-cell or neurosphere conditions. The study found that in the absence of serum, CHT and poly(vinylidene fluoride) (PVDF) substrates both inhibited the proliferation and differentiation of single neural stem cells. However, neurospheres responded differently to the two substrates. PVDF had an inhibitory effect on neural stem cells differentiating into neurons but more cell differentiation was observed on CHT. In the presence of serum, both CHT and PVDF induced the differentiation of neural stem cells from neurospheres (Hung *et al.* 2006). The same group also compared the effect of polyvinyl alcohol (PVA) and poly(ethylene-co-vinyl alcohol) (EVAL) substrates on the proliferation and differentiation of embryonic rat cerebral cortical stem cells. It was found that EVAL inhibited cell activity at the single-cell level even in the presence of bFGF in serum-free medium. However, when grown as neurospheres, the cells could continue to proliferate under high-density conditions, but differentiate into neurons and astrocytes when cell density was low (Young & Hung 2005). In addition, polymer surface morphology affected the proliferation and differentiation of neural stem cells (Recknor *et al.* 2006). Micropatterned polystyrene substrates chemically modified with laminin supported adult rat hippocampal progenitor cells to extend along the groove direction. This indicates that the three-dimensional topography of the substrate, combined with chemical and biological guidance cues, enhances neuronal differentiation and neurite alignment.

In summary, the selection of biomaterials, the surface morphology of the substrates, neurotrophic factors, cell density, the effect of serum and many other factors can all affect the proliferation and differentiation of cultured neural stem cells. When designing the cell culture environment, as many factors as possible should be considered and optimized to achieve the best result.

### 6.2. In vivo studies

In addition to *in vitro* experiments, several *in vivo* tests have been performed to evaluate the interaction of the neural stem cell transplantation system with the host tissue. Teng *et al.* designed a polymer scaffold, which was composed of 50:50 PLGA (75%) and a block copolymer of PLGA–polylysine (25%), seeded with murine neural stem cells and implanted into an adult rat hemisection model of SCI. The scaffold's inner portion emulated the grey matter via a porous polymer

layer designed to be seeded with NSCs for cellular replacement as well as trophic support; the outer portion emulated the white matter with long axially oriented pores for axonal guidance and radial porosity to allow fluid transport while inhibiting ingrowth of scar tissue. Implantation of the scaffold promoted long-term improvement in function (persistent for 1 year in some animals). The animals implanted with cell-seeded scaffolds also exhibited coordinated, weight-bearing hindlimb stepping 70 days after injury, which is believed to link to the reduction in tissue loss from secondary injury processes as well as diminished glial scarring. The reason for absence of scar formation is not clear, but may be correlated with inhibition of cellular ingrowth by the outer scaffold (Teng *et al.* 2002).

Ford *et al.* synthesized a polylysine–PEG hydrogel with a macroporous network structure by casting the hydrogel solution around a salt-leached polylactic-co-glycolic acid scaffold that was degraded in a sodium hydroxide solution after the composite was cured. The hydrogel was seeded with brain endothelial cells and neural progenitor cells and implanted subcutaneously into mice. Functional microvascular network was formed in the hydrogel, which is critical to support engineered tissue replacement (Ford *et al.* 2006).

Park *et al.* designed a PGA–neural stem cell scaffold to fill the infarction cavities of mouse brains injured by hypoxia–ischaemia. As the PGA fibres degraded, new parenchyma was regenerated and vascularized within two weeks. Therefore, the scaffold not only reduced further tissue loss in the second injury but also supported new tissue regeneration. Furthermore, neurological function seemed to be improved and the animals appeared to evince normal behaviour (Park *et al.* 2002).

Instead of encapsulating the stem cells inside the scaffold, Mahoney and Saltzman attached PLGA microparticles, which contained NGF for controlled release and were coated with polylysine, to stem cell surface to mimic the extracellular controllable synthetic microenvironments. Animal transplantation showed significant elevation of NGF level and ChAT activity near the implantation site for up to 21 days (Mahoney & Saltzman 2001).

All these studies provide a promising strategy to combine biocompatible polymer, neurotrophic factors and neural stem cells to form an effective cell transplantation system for the treatment of SCI and TBI. Future study should focus on optimizing the conditions for augmenting the neural stem cell proliferation, differentiation and integration into the host tissue.

## 7. CONCLUSIONS

This article reviews the applications of biomaterials in the CNS including (i) shunting systems for hydrocephalus, (ii) CNPs, (iii) drug delivery systems in the CNS, (iv) hydrogel scaffolds for CNS repair, and (v) neural stem cell encapsulation for neurotrauma. Each of the strategies has multiple applications in CNS repair. For example, delivery of drugs and/or bioactive molecules can be used to treat tumour and neurodegenerative diseases, reduce inflammatory tissue

response and promote tissue regeneration. Stem cell therapy can be used to treat neurodegenerative diseases and promote tissue regeneration. Hydrogel scaffolds are mostly used for supporting tissue regeneration in the CNS; however, its potential for tumour therapy was also explored (Tauro & Gemeinhart 2005). As each strategy has its own advantages and limitations, several strategies can be combined for treatment of neurological diseases or injuries. For example, so far the treatments for tumours in the CNS mostly focus on delivery of chemotherapy either locally or systemically to the tumour site. Combined drug delivery, gene therapy and stem cell encapsulation into *in situ* gelling hydrogel scaffolds can be used not only to prevent recurrence of surgically removed malignant tumours but also to promote neural tissue regeneration into the cavity at the same time to achieve functional recovery. Combination of sustained release of anti-inflammatory agents and neurotrophic factors from CNPs may improve neuron–electrode communication, and lead to long-term functional stability of these implanted devices. Thus, while each strategy shows promising results, combinations of multiple strategies may lead to more successful recovery in the CNS repair.

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