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(54) **Titre : METHODES ET COMPOSITIONS POUR LE TRAITEMENT DE BLESSURES OUVERTES ET FERMEES DE LA MOELLE EPINIERE**

(54) **Title: METHODS AND COMPOSITIONS FOR THE TREATMENT OF OPEN AND CLOSED WOUND SPINAL CORD INJURIES**

(57) **Abrégé/Abstract:**
Devices and methods for the treatment of open and closed wound spinal cord injuries are disclosed. For example, described herein are devices and methods for mitigating secondary injury to, and promoting recovery of, spinal cord primary injuries. More particularly, certain embodiments of the present invention are directed to polymeric mini-tubes that may be used for the treatment of spinal cord injuries. In addition, other embodiments are directed to polymeric "fill-in" bandages that may be used for the treatment of spinal cord injuries. For example, an erodible, or biodegradable, form of biocompatible polymer of the present invention is fabricated for surgical implantation into the site of the spinal cord injury.

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(54) Title: METHODS AND COMPOSITIONS FOR THE TREATMENT OF OPEN AND CLOSED WOUND SPINAL CORD INJURIES

(57) Abstract: Devices and methods for the treatment of open and closed wound spinal cord injuries are disclosed. For example, described herein are devices and methods for mitigating secondary injury to, and promoting recovery of, spinal cord primary injuries. More particularly, certain embodiments of the present invention are directed to polymeric mini-tubes that may be used for the treatment of spinal cord injuries. In addition, other embodiments are directed to polymeric "fill-in" bandages that may be used for the treatment of spinal cord injuries. For example, an erodible, or biodegradable, form of biocompatible polymer of the present invention is fabricated for surgical implantation into the site of the spinal cord injury.

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METHODS AND COMPOSITIONS FOR THE TREATMENT OF OPEN AND CLOSED WOUND SPINAL CORD INJURIES

BACKGROUND OF THE INVENTION

Many spinal cord injuries (SCIs) are a result of the spinal cord being compressed, not cut. Insult to the spinal cord often results in vertebrae, nerve and blood vessel damage. Bleeding, fluid accumulation, and swelling can occur inside the spinal cord or outside the spinal cord but within the vertebral canal. The pressure from the surrounding bone and meninges structure can further damage the spinal cord. Moreover, edema of the cord itself can additionally accelerate secondary tissue loss. There is considerable evidence that the primary mechanical injury initiates a cascade of secondary injury mechanisms including excessive excitatory neurotransmitter accumulation; edema formation; electrolyte shifts, including increased intracellular calcium; free radical production, especially oxidant-free radicals; and eicosanoid production. Therefore, SCIs can be viewed as a two-step process. The primary injury is mechanical, resulting from impact, compression or some other insult to the spinal column. The secondary injury is cellular and biochemical, wherein cellular/molecular reactions cause tissue destruction. By interrupting this second process and diffusing any compression resulting from the primary mechanical lesion, as well as any cord edema, healing is expedited.

As discussed above, spinal cord injury involves not only initial tissue injury, but also devastating secondary injuries. These pathological events, caused by excitotoxicity, free-radical formation and lack of neurotrophic support, include glial scarring, myelin-related axonal growth inhibition, demyelination, secondary cell death such as apoptosis. For example, oligodendrocyte death continues for weeks after many SCIs. An environment antagonistic to axonal regeneration is subsequently formed. In addition to damaged regeneration pathways, reflexia hyperexcitability and muscle spasticity, there are further complications of respiratory and bladder dysfunction, for example. Over time, muscle mass is lost as a result of loss of

innervations and non-use. The end result of these spinal cord insults invariably is lost function, the extent of which is determined by the severity of the spinal cord primary lesion as well as by secondary injuries. Even in the case of incomplete motor function loss, common problems include posture, reduced walking speed, abnormal balance and gait, and lack of sufficient weight-bearing.

Surgical decompression of the spinal cord is often used to relieve any pressure from surrounding bone (by removing fractured or dislocated vertebrae or disks). However, the timing of surgical decompression has been a controversial topic. While rat studies have shown early decompression to reduce secondary injury, the results in human clinical trials have been less than consistent. It has been difficult to determine a time window for the effective application of surgical decompression intervention in the clinical setting. Furthermore, there are no technologies which can be used to effectively control the increase in intra-parenchyma pressure resulting from the primary SCI. The absence of such a technology renders surgical decompression surgery, in many cases, ineffective. The removal of bone and soft tissue structures do not address the underlying problem of secondary intrinsic pressure at the SCI site. Therefore, there exists a need to provide alternative devices and methods to impede the process that drive secondary injury at the primary spinal cord injury site. These alternative methods can be used to complement decompression surgical protocols.

There has been scant, if any, therapeutic attention given to the intrinsic nature of the injured/compressed spinal cord (i.e. the injured/compressed cord itself). As mentioned above, decompression surgery is directed to the extrinsic nature of the injury (i.e. removal of bone or fluid surrounding, and causing, the injury) in hopes of alleviating consequences of intra-tissue pressure build-up. Secondary injury will often impede the nerve regeneration and/or nerve regrowth process. Consequently, there exists a need for devices and methods that alleviate the primary spinal cord injury from, for example, secondary tissue destruction, edema formation, and an influx of inflammatory factors.

Furthermore, it is well known that penetrating spinal cord injuries (SCIs) are the most deadly neurotrauma encountered by people. Reports on combat related open wound SCIs during the Vietnam war indicate that this type of injury leads to close to 100% lethality. While there have been advances in the protective ability of bullet-proof vests, the neck region of persons wearing many of today's vests is often vulnerable to many high velocity weapons. More than 90% of SCIs are initially

diagnosed as "incomplete," wherein the injury does not result in complete severing of the spinal cord. Technology which can protect the spared tissue and promote endogenous healing and repair will mitigate functional deficits resulting from both penetrating and contusion traumatic SCIs.

BRIEF SUMMARY OF THE INVENTION

Certain embodiments of the present invention are directed to biocompatible polymeric materials which can be fabricated into "mini-tubes," or "tubular articles." These mini-tubes can be used to treat any localized SCI. In one embodiment, the mini-tube is inserted into the epicenter of the injury, wherein the hollow tube runs through the injury site. *See Figure 1.* The mini-tube can be inserted through a surgical incision made rostral or caudal to the lesion to be treated. The mini-tube creates a new interface within the compressed spinal cord parenchyma. This new interface relieves the site of pressure and protects tissue that has been spared from injury. Pressure resulting from the compression force exerted on the cord is alleviated by (1) diffusing or redirecting the force down the surface of the mini-tube and away from the initial compressed site, and (2) absorbing the compression energy into the biocompatible material of the mini-tube. *See Figure 1.* Furthermore, by providing a structure between the injured site and surrounding tissue (the new interface), inflammation may be mitigated in the adjacent area where functionally relevant residual cord tissue can be spared.

In another embodiment, the present invention relates to biocompatible polymers fabricated into hollow mini-tubes, or tubular articles, having an inner surface, an outer surface and two opposing ends. The mini-tubes may be fabricated into any geometrical shape and size. For example, the size and the shape of the mini-tube may be varied in order to deliver more effective relief. A thin, elongated cylinder is one possible configuration, but other shapes, such as elongated rectangular tubes, spheres, helical structures, and others are possible. Additional alterations in configuration, such as the number, orientation, and shape of the mini-tubes may be varied in order to deliver more effective relief. For instance, the mini-tubes may be rectangular, or any other useful shape, and may be distributed along and/or around epicenter of the spinal cord injury. The size will vary accordingly with the spinal cord lesion to be treated. The mini-tube can be smaller than, the same size as, or longer than the lesion to be treated. In preferred embodiment, the mini-tube will be longer

than the length of the injured site. In another preferred embodiment, the length of the mini-tube to be surgically implanted will be approximately between 1.2 and 3 times the length of the injured site or lesion running lengthwise along the spinal cord. In yet another preferred embodiment, the mini-tube will extend beyond the caudal and rostral sides of the injured site at a distance of approximately 1/4 the length of the injured site. In a preferred embodiment the mini-tube will extend equally beyond the caudal and rostral sides of the injured site.

The diameter of the mini-tube (outer surface to outer surface; or "outside diameter") can range from 0.1 microns to 10 millimeters. In a preferred embodiment, the overall diameter of the mini-tube (outer surface to outer surface) is between about 5 and 200 microns. In other embodiments the diameter of the mini-tube (outer surface to outer surface) is between about 20 and 200 microns, between about 50 and 175 microns, between about 100 and 200 microns, and between about 150 and 300 microns. In another embodiment, the diameter of the mini-tube (outer surface to outer surface) is between about 0.5 millimeters and 20 millimeters. In other embodiments, the diameter of the mini-tube (outer surface to outer surface) is between about 1 millimeter and 10 millimeters, between about 1 millimeter and 5 millimeters, and between about 1 millimeter and 3 millimeters.

The diameter of the mini-tube (inner surface to inner surface; or the "lumen diameter") can also range from microns to millimeters. In a preferred embodiment, the diameter of the mini-tube (lumen diameter) is between about 5 and 200 microns. In other embodiments the diameter of the mini-tube (lumen) is between about 20 and 200 microns, between about 50 and 175 microns, between about 100 and 200 microns, and between about 150 and 300 microns. In another embodiment, the diameter of the mini-tube (lumen) is between about 0.5 millimeters and 15 millimeters. In other embodiments, the diameter of the mini-tube (lumen) is between about 1 millimeter and 10 millimeters, between about 1 millimeter and 5 millimeters, and between about 1 millimeter and 3 millimeters.

In another embodiment of the present invention, formable, moldable, biocompatible polymeric materials are disclosed herein. Advantageously, the polymeric material may be fabricated as a putty. By "putty" it is meant that the material has a dough-like consistency that is formable or moldable. These materials are sufficiently and readily moldable and can be formed into flexible three-dimensional structures or shapes complementary to a target site to be treated.

In yet another embodiment, the biocompatible polymeric materials of the present invention can be fabricated into readily formable or moldable bandages, or neuropatches. In one embodiment, a SCI is localized and the bandage or neuropatch is hand-formed to complement the injured site (for example, a hemi-sected spinal cord). The hand formed bandage is then implanted into the epicenter of the injury, wherein the bandage fills in the injury site. The implanted bandage bridges any gap formed by the spinal cord lesion and functions as an artificial pathway, nurturing regrowing neurons, reorganizing neurites and helping to form functional synapses. This new bandage interface allows for interactions between endogenous neural cells (including neural stem cells, if incorporated onto the bandage) and the inhibitory molecule-free polymer implant environment to promote cell survival. Furthermore, by providing a structure between the injured site and surrounding tissue (the new interface), inflammation may be mitigated in the adjacent area where functionally relevant residual cord tissue can be spared.

In another embodiment, the present invention relates to biocompatible polymeric bandages, which can be readily fabricated/formed into any shape and size, comprising a single polymeric scaffold having an inner surface and an outer surface. See example 15. The formed bandages may be fabricated into any geometrical shape and size. For example, the size and the shape of the bandage may be varied in order to deliver more effective relief. A thin, elongated bandage is one possible configuration, but other shapes, such as elongated rectangular bandages, spheres, helical structures, and others are possible. Additional alterations in configuration, such as the number, orientation, and shape of the bandages may be varied in order to deliver more effective relief. For instance, the bandages may be rectangular, or any other useful shape, and may be distributed within and/or around epicenter of the spinal cord injury. In addition, the bandage may have a textured surface including a plurality of pores and/or microgrooves on its inner and/or outer surface. In one embodiment, the pores have diameters between about 0.5μm to 4μm and depths of at least 0.5μm. The microgrooves may have widths of between about 0.5μm and 4μm and depths of at least 0.5μm. The sizes of the bandage, and the sizes and diameters of its pores and microgrooves, will vary accordingly with the spinal cord lesion to be treated. The pores and/or microgrooves on the inner and/or outer surface may be seeded with one or more medicinal agents, for example human neuronal stem cells to provide cellular replacement and trophic support. In preferred embodiment, the

bandage will act as a filler (i.e. fill the lesion) after implantation of the bandage within the lesioned area of the spinal cord, for example. In one embodiment, the bandage inner surface is flush with the lesioned spinal cord, i.e. contacts the lesion, when it is implanted.

Biocompatible polymers for the fabrication of the herein described mini-tubes and formable bandage or neuropatch articles are well-known in the art. In a preferred embodiment, the biocompatible polymers are biodegradable (for example, PLGA). As used herein, biodegradable and erodible are used interchangeably. Examples of biocompatible polymers that are biodegradable include, but are not limited to, biodegradable hydrophilic polymers such as polysaccharides, proteinaceous polymers, soluble derivatives of polysaccharides, soluble derivatives of proteinaceous polymers, polypeptides, polyesters, polyorthoesters, and the like. The polysaccharides may be poly-1,4-glucans, e.g., starch glycogen, amylose and amylopectin, and the like. Preferably, biodegradable hydrophilic polymers are water-soluble derivatives of poly-1,4-glucan, including hydrolyzed amylopectin, hydroxyalkyl derivatives of hydrolyzed amylopectin such as hydroxyethyl starch (HES), hydroxyethyl amylase, dialdehyde starch, and the like. Proteinaceous polymers and their soluble derivatives include gelation biodegradable synthetic polypeptides, elastin, alkylated collagen, alkylated elastin, and the like. Biodegradable synthetic polypeptides include poly-(N-hydroxyalkyl)-L-asparagine, poly-(N-hydroxyalkyl)-L-glutamine, copolymers of N-hydroxyalkyl-L-asparagine and N-hydroxyalkyl-L-glutamine with other amino acids. Suggested amino acids include L-alanine, L-lysine, L-phenylalanine, L-leucine, L-valine, L-tyrosine, and the like.

Definitions or further description of any of the foregoing terminology are well known in the art and may be found by referring to any standard biochemistry reference text such as "Biochemistry" by Albert L. Lehninger, Worth Publishers, Inc. and "Biochemistry" by Lubert Stryer, W. H. Freeman and Company, both of which are hereby incorporated by reference.

The aforementioned biodegradable hydrophilic polymers are particularly suited for the methods and compositions of the present invention by reason of their characteristically low human toxicity and virtually complete biodegradability. Of course, it will be understood that the particular polymer utilized is not critical and a variety of biodegradable hydrophilic polymers may be utilized as a consequence of the novel processing methods of the invention.

Electrical signals in the form of action potentials are the means of signaling for billions of cells in the central nervous system. Numerous studies have shown that this electrical activity is not only a means of communication, but also necessary for the normal development of the nervous system and refinement of functional neural circuits. In the case of spinal cord injury, cell-to-cell communication may be interrupted and the mechanisms of normal neurological development imply that electrical activity should be part of the restoration of functional connections. Such activity is important for the survival of existing cells and the incorporation of any transplanted cells (such as neural stem cells) into working circuits. In an embodiment of the present invention, single and double layer scaffolds and minitubes are fabricated from synthetic biomaterials and are capable of conducting electricity and naturally eroding inside the body. In an exemplary embodiment, the single scaffold, double scaffold, or minitube comprises a biocompatible polymer capable of conducting electricity is a polypyrrole polymer. Polyaniline, polyacetyline, poly-p-phenylene, poly-p-phenylene-vinylene, polythiophene, and hemosin are examples of other biocompatible polymers that are capable of conducting electricity and may be used in conjunction with the present invention. Other erodible, conducting polymers are well known (for example, see Zelikin et al., Erodible Conducting Polymers for Potential Biomedical Applications, Angew. Chem. Int. Ed. Engl., 2002, 41(1):141-144). Any of the foregoing electrical conducting polymers can be applied or coated onto a malleable or moldable article. The coated article can be also be used as a bandage, or neuropatch, as described herein.

In a preferred embodiment the biodegradable and/or bioabsorbable polymer contains a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine. By the terminology "contains a monomer" is intended a polymer which is produced from the specified monomer(s) or contains the specified monomeric unit(s). The polymer can be a homopolymer, random or block co-polymer or hetero-polymer containing any combination of these monomers. The material can be a random copolymer, block copolymer or blend of homopolymers, copolymers, and/or heteropolymers that contains these monomers.

In one embodiment, the biodegradable and/or bioabsorbable polymer contains bioabsorbable and biodegradable linear aliphatic polyesters such as polyglycolide (PGA) and its random copolymer poly(glycolide-co-lactide) (PGA-co-PLA). The

FDA has approved these polymers for use in surgical applications, including medical sutures. An advantage of these synthetic absorbable materials is their degradability by simple hydrolysis of the ester backbone in aqueous environments, such as body fluids. The degradation products are ultimately metabolized to carbon dioxide and water or can be excreted via the kidney. These polymers are different from cellulose based materials, which cannot be absorbed by the body.

The molecular weight (MW) of the polymers used in the formable articles of the presently described invention can vary according to the polymers used and the degradation rate desired to be achieved. In one embodiment, the average MW of the polymers in the fabricated bandage is between about 1,000 and about 50,000. In another embodiment, the average MW of the polymers in the fabricated bandage is between about 2,000 and 30,000. In yet another embodiment, the average MW is between about 20,000 and 50,000 for PLGA and between about 1,000 and 3,000 for polylysine.

The herein described mini-tubes and formable articles may be incorporated with any number of medically useful substances. In a preferred embodiment, the inner and/or outer surfaces of the mini-tube is seeded with stem cells; for example, mesenchymal and/or neuronal stem cells, wherein the cells are deposited onto the inner (lumen in the case of the mini-tubes) and/or outer surface(s). See figure 3. The incorporation of stem cells provide for trophic support and/or cellular replacement at the site of injury.

In another embodiment, the foregoing described polymeric articles are used in methods for providing controlled tissue healing. These methods comprise, for example, implanting into a target compression injury site in an animal, a system for controlled tissue healing, the system comprising a biodegradable and/or bioabsorbable polymeric hollow tube. The target injury site may be any injury that is susceptible to secondary tissue injury, including but not limited to: glial scarring, myelin inhibition, demyelination, cell death, lack of neurotrophic support, ischemia, free-radical formation, and excitotoxicity. In one embodiment, the injury to be treated is a spinal cord injury, wherein the spinal cord is compressed. The herein described methods may be used in conjunction with decompression surgery; for example, concomitant with decompression surgery, prior to decompression surgery, or subsequent to decompression surgery.

In another embodiment, the foregoing described polymeric articles are used in methods for treating a compression spinal cord injury comprising implanting into a target compression injury site in an animal a biodegradable and/or bioabsorbable polymeric hollow tube. The spinal cord injury may be susceptible to secondary tissue injury, including but not limited to: glial scarring, myelin inhibition, demyelination, cell death, lack of neurotrophic support, ischemia, free-radical formation, and excitotoxicity. The herein described methods may be used in conjunction with decompression surgery; for example, concomitant with decompression surgery, prior to decompression surgery, or subsequent to decompression surgery.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Two schematic representations (A and B) of the polypyrrole scaffold inserted around the center of the lesion area in order to protect surrounding tissues.

Figure 2. Electrodeposition of erodible PPy to form mini-tube scaffolds.

Figure 3. SEM images of microfabricated PPy tubes. A. Murine neural stem cells seeded inside of a 600μm inner diameter tube (150X). B. High-magnification (350X) view of 25μm inner diameter tube. Rough surface texture is a result of low electrodeposition temperature (4°C). C. Lower magnification (150X) view of a 25μm inner diameter tube created with a smooth surface texture by electrodeposition at 24°C. D. Higher magnification (500X) view of same tube as in C.

Figure 4. MRI shows reduced fluid filled cyst (appears bright white in the T2 weighted MR image) formation in rodents treated with a PPy scaffold (shown on right) relative to untreated control (shown at left).

Figure 5. Open-field locomotor scores for polypyrrole minitube-implanted rats (n=8) and lesion-control rats (n=11).

Figure 6. BBB open-field walking scores for the four groups on the ipsilateral, lesioned side treated with double scaffold bandage (two-compartment). Hindlimbs were assessed independently to determine the degree of asymmetry. The rate of improvement for the scaffold-treated group was significantly greater than the rate for the stem cells-alone ($P<0.001$) and lesion-control groups ($P<0.004$; two-way repeated measures of ANOVA; N = 12 each group).

Figure 7. Spinal cord tissue protection resulting from application of PLGA polymer scaffold into the penetrating lesion site.

Figure 8. Functional recovery analysis summary for bandage-scaffold. a, Montages of

still images of animal open-field walking in "lesion only" (top row) and "scaffold with high dose hNSCs" (bottom row). **b**, Lesion side BBB open-field walking scores. The absolute scores of groups treated with hNSCs seeded in single-scaffolds (i.e., 16 - 17 in average) are significantly higher than "hNSCs only" group (BBB score of 9 in average; P=0.004 for regular dose, P<0.001 for high dose), "scaffold only" group (P=0.004 for regular dose, P=0.001 for high dose; the scaffold alone group received PLGA polymer in a single porous layer design, and "lesion only" group (P<0.001 for regular dose, P=0.001 for high dose, ANOVA, Bonferroni *post hoc* analysis). The *rate* of improvement also shows a significantly greater value in hNSC seeded in scaffold groups than the "hNSCs only" group (P=0.004 for regular dose, P<0.001 for high dose, two-way repeated measures of ANOVA), scaffold group (P=0.004 for regular dose, P<0.001 for high dose), and "lesion only" group (P=0.004 for regular dose, P<0.001 for high dose). **c**, Inclined plane tests. When facing downward, the hNSC+scaffold treated rats could stabilize their bodies on inclined boards angled at significantly higher degrees (Kruskal-Wallis test, P<0.001). Parametric and non-parametric analysis both reveal similar results. **d**, Pain withdrawal reflex scores. The left curve panel is the percentage of animals in each group scoring 2, corresponding to normal response. The right panel is the percentage of animals in each group scoring 3, indicating hyperactive response. The two panels consistently indicate that the groups receiving hNSCs seeded in single-scaffolds showed significantly improved hind limb reflex which was correlated with hNSC doses (Pearson χ^2 test of independence). **e**, Percentage of animals in each group demonstrating normal righting reflex. Groups receiving hNSCs seeded in single-scaffolds had significantly higher percentage of rats that recovered their righting reflex comparing to other groups (Pearson χ^2 test).
Figure 9. Functional recovery in rats with penetrating injury to the T9-10 spinal cord after double-scaffold PLGA implant treatment.

Glossary of terms

By the term biodegradable is intended a material which is broken down (usually gradually) by the body of an animal, e.g. a mammal, after implantation.

By the term bioabsorbable is intended a material which is absorbed or resorbed by the body of an animal, e.g. a mammal, after implantation, such that the material eventually becomes essentially non-detectable at the site of implantation.

By the terminology "biodegradable and/or bioabsorbable article or minitube" is intended any material which is biocompatible, as well as biodegradable and/or bioabsorbable, and capable of being formed into tubes, as described more fully herein. The material is also capable of being formed into articles which is suitable for implantation into an animal and capable of being biodegraded and/or bioabsorbed by the animal.

The biodegradable and/or bioabsorbable articles of the present invention are preferably biodegradable and bioabsorbable polymers. Examples of suitable polymers can be found in Bezwada, Rao S. et al. (1997) Poly(p-Dioxanone) and its copolymers, in Handbook of Biodegradable Polymers, A. J. Domb, J. Kost and D. M. Wiseman, editors, Hardwood Academic Publishers, The Netherlands, pp. 29-61, the disclosure of which is incorporated herein by reference in its entirety.

"Mini-tubes" and "tubular articles" are used interchangeably in the present description.

"Moldable" and "formable" are used interchangeably in the present description.

DETAILED DESCRIPTION OF THE INVENTION

Described herein are devices and methods for mitigating secondary injury to, and promoting recovery of, spinal cord primary injuries. More particularly, certain embodiments of the present invention are directed to polymeric mini-tubes that may be used for the treatment of spinal cord injuries. In addition, other embodiments are directed to polymeric "fill-in" bandages that may be used for the treatment of spinal cord injuries. For example, an erodible, or biodegradable, form of biocompatible polymer of the present invention is fabricated for surgical implantation into the site of the spinal cord injury.

Certain embodiments of the present invention are directed to biocompatible polymeric materials which can be fabricated into "mini-tubes." These mini-tubes can be used to treat the SCI once it has been localized. In one embodiment, the mini-tube is inserted into the epicenter of the injury, wherein the hollow tube runs through the injury site. *See Figure 1.* The mini-tube creates a new interface within the compressed spinal cord parenchyma. This new interface relieves the site of pressure and protects tissue that has been spared from injury. Pressure resulting from the compression force exerted on the cord is alleviated by (1) diffusing or redirecting the

force down the surface of the mini-tube and away from the initial compressed site, and (2) absorbing the compression energy into the biocompatible material of the mini-tube. *See Figure 1.* Furthermore, by providing a structure between the injured site and surrounding tissue (the new interface), inflammation may be mitigated in the adjacent area where functionally relevant residual cord tissue can be spared.

An erodible, or biodegradable, form of biocompatible polymer of the present invention is fabricated into a mini-tube for surgical implantation into the site of the spinal cord injury. Surgical implantation results in a target area, for example a necrotic section of the spinal cord, that is encapsulated by the polymer. In one embodiment, the surgery results in complete encapsulation of the target area or only the central necrotic area. See figure 1. Encapsulation of the central necrotic area minimizes secondary injury by inhibiting cell-cell signaling with inflammatory cytokines. Shunting the fluid-filled cyst reduces pressure buildup within the cord and decreases injury to neurons. Bridging the gap formed by the cyst allows a pathway for regrowing neurons to reach the caudal side and form functional synapses.

In a preferred embodiment of the present invention, the biocompatible polymer is an electrically conductive material. This material allows conduction of endogenous electrical activity from surviving neurons, thereby promoting cell survival. Any such material should be bioresorbable *in situ*, such that it naturally erodes once its function has been performed. Finally, a three-dimensional scaffold creates a substrate by which cells can be grown *in vitro* and then implanted in vivo. A hollow cylindrical scaffold (mini-tube) made of polypyrrole (PPy), for example, meets all of these design requirements. A schematic of the design *in situ* is shown in Figure 1. In an exemplary embodiment, the biocompatible polymer capable of conducting electricity is a polypyrrole polymer. Polyaniline, polyacetyline, poly-p-phenylene, poly-p-phenylene-vinylene, polythiophene, and hemosin are examples of other biocompatible polymers that are capable of conducting electricity and may be used in conjunction with the present invention. Other erodible, conducting polymers are well known (for example, see Zelikin et al., Erodible Conducting Polymers for Potential Biomedical Applications, Angew. Chem. Int. Ed. Engl., 2002, 41(1):141-144).

The polymeric mini-tubes of the present invention are not limited to electrical conducting polymers, such as PPy. Polymeric minitubes of the present invention may comprise one or more monomers selected from the group consisting of a glycolide,

lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine, for example. Furthermore, it is possible for the polymeric bandages to comprise one or more biodegradable and/or bioabsorbable linear aliphatic polyesters, copolymer poly(glycolide-co-lactide), and/or material derived from biological tissue. Material derived from biological tissue can be, but is not limited to, neuronal and/or mesenchymal stem cells which can be used as medicinal agents.

As described in further detail below, a biodegradable and/or bioabsorbable polymeric tubular article of the present invention can be formed by electrodeposition of an electrical conducting polymer onto a template conductive wire, wherein the polymer is released from the wire by applying a reverse potential to the template conductive wire in a saline solution. The polymeric minitubes of the present invention are not limited to electrical conducting polymers, such as PPy. Polymeric minitubes of the present invention may comprise one or more monomers selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine, for example. Furthermore, it is possible for the polymeric minitubes to comprise one or more biodegradable and/or bioabsorbable linear aliphatic polyesters, copolymer poly(glycolide-co-lactide), and/or material derived from biological tissue. Material derived from biological tissue can be, but is not limited to, neuronal and/or mesenchymal stem cells which can be used as medicinal agents. See figure 3, for example.

An example of a type of method used to fabricate the mini-tube polymers described herein is shown in Figure 2. The pattern of the conductive template for electrodeposition of polypyrrole (PPy), for example, controls the shape of the PPy scaffold that is created. By controlling the template, the polymer scaffold can be manufactured in different shapes and sizes, ranging from thin lines to rectangular planar implants, for example. See Example 5. Tube-like PPy scaffolds can be produced by plating the PPy onto a conductive wire. For scaffold removal from the template, a reverse potential is applied to the template in a saline solution. When applied for sufficient time and strength, the scaffold slides off of the wire mold with a slight pull. See Example 1. This method relieves the manufacturer of having to use harsh organics to etch the inner wire template, thereby resulting in polymeric devices that are ill-suited for use in vivo.

As described above, the mini-tubes may be fabricated into any geometrical shape and size. For example, the size and the shape of the mini-tube may be varied in

order to deliver more effective relief. A thin, elongated cylinder is one possible configuration, but other shapes, such as elongated rectangular tubes, spheres, helical structures, and others are possible. Additional alterations in configuration, such as the number, orientation, and shape of the mini-tubes may be varied in order to deliver more effective relief. For instance, the mini-tubes may be rectangular, or any other useful shape, and may be distributed along and/or around epicenter of the spinal cord injury. The size (length and diameter) will vary accordingly with the spinal cord lesion to be treated. For example a cord lesion that is 10 microns in length (running along the length of the spinal cord) and 3 microns deep, may require a polymeric mini-tube of 15 microns in length and having an overall diameter of 2.5 microns. The polymeric mini-tube is surgically inserted through the lesion such that the central section of the lesion is encapsulated by the tube. In this example, the tube will extend approximately 2.5 microns beyond each of the caudal and rostral ends of the target lesioned area. The polymeric tubular articles of the present invention are preferred to have overall diameters of between about 0.1 microns and 10 millimeters. More preferred are articles having overall diameters of between about 50 and 175 microns. However, any size, diameter, length can be fabricated according the herein described methods in order to accommodate any lesion of the spinal cord.

The biocompatible and biodegradable polymeric mini-tubes of the present invention can contain pharmaceutically or biologically active substances such as, for example, anti-inflammatories, growth factors, and stem cells.

In another embodiment, the present invention is directed to polymeric "fill-in" bandages that may be used for the treatment of spinal cord injuries. For example, an erodible, or biodegradable, form of biocompatible polymer of the present invention is fabricated for surgical implantation into the site of the spinal cord injury. The implantation can be accomplished immediately after molding the bandage to conform to the injured site. The target area, for example a necrotic section of the spinal cord, may be encapsulated by the polymer, or alternatively, filled in with the formed polymer. The implantation may result in complete encapsulation of the target area or only the central necrotic area; or may result in a previously open lesioned area being filled in with the formed polymer. Encapsulation of the central necrotic area minimizes secondary injury by inhibiting cell-cell signaling with inflammatory cytokines. Bridging the gap formed by the lesion allows a pathway for regrowing neurons to reach the caudal side and the formation of functional synapses.

Optionally, an electrically conductive formable and biocompatable polymeric material may be used to allow conduction of endogenous electrical activity from surviving neurons, thereby promoting cell survival. Any such material should be bioresorbable *in situ*, such that it naturally erodes once its function has been performed. Finally, a three-dimensional scaffold creates a substrate by which cells can be grown in vitro and then transplanted in vivo. A bandage scaffold made of polypyrrole (PPy), for example, meets all of these design requirements. A schematic of the design *in situ* is shown in Figure 1.

The polymeric bandages of the present invention are not limited to electrical conducting polymers, such as PPy. Polymeric bandages of the present invention may comprise one or more monomers selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine, for example. Furthermore, it is possible for the polymeric bandages to comprise one or more biodegradable and/or bioabsorbable linear aliphatic polyesters, copolymer poly(glycolide-co-lactide), and/or material derived from biological tissue. Material derived from biological tissue can be, but is not limited to, neuronal and/or mesenchymal stem cells which can be used as medicinal agents.

The biocompatible and biodegradable polymeric bandages of the present invention may contain pharmaceutically or biologically active substances such as, for example, anti-inflammatories, growth factors, and stem cells. As described above, the polymer bandages may be fabricated into structures wherein the outer surface is an outer scaffold having long, axially oriented pores for axonal guidance and/or radial pores to allow fluid transport and inhibit ingrowth of scar tissue. See Example 7, below. The inner surface, or inner scaffold, may be porous and seeded with one or more medicinal agents, for example human neuronal stem cells for cellular replacement and trophic support. Therefore, in this particular embodiment, the fabricated and formed bandage comprises two scaffolds (a double scaffold) and simulates the architecture of a healthy spinal cord through an implant consisting of a polymer scaffold, perhaps seeded with neuronal stem cells. The inner scaffold emulates the gray matter; the outer portion emulates the white matter. The bandage can be readily designed to be tailored to fit into a variety of cavities.

In another embodiment, the present invention relates to biocompatible polymeric bandages, which can be readily fabricated/formed into any shape and size, comprising a single polymeric scaffold having an inner surface and an outer surface,

wherein the formed bandages may be fabricated into any geometrical shape and size. This single polymeric scaffold may comprise pores (for example, on the surface making contact with the lesion) for incorporating medicinal agents and/or depositing neural stem cells. This porous single scaffold is fabricated as described in Example 15.

In another embodiment, the present invention relates to a medical article suitable for implanting within a patient's spinal cord. The article comprises a moldable biocompatible material comprising a 50:50 blend of (1) poly(lactic-co-glycolic acid) and (2) a block copolymer of poly(lactic-co-glycolic acid)-polylysine. The (1) poly(lactic-co-glycolic acid) is 75% poly(lactic-co-glycolic acid) and wherein the average molecular weight is Mn ~40,000. The (2) block copolymer of poly(lactic-co-glycolic acid)-polylysine is 25% poly(lactic-co-glycolic acid)-polylysine copolymer and wherein the average molecular weight of the poly(lactic-co-glycolic acid) block is Mn ~30,000 and the average molecular weight of the polylysine block is Mn ~2,000. In an alternative embodiment, the article comprises a single block of poly(lactic-co-glycolic acid). It is preferred that any of the foregoing articles have a degradation rate of about between about 30 and 60 days; however, the rate can be altered to provide a desired level of efficacy of treatment. The article may further comprise stem cells in association with any of the polymeric material. For example, the stem cells may be seeded onto the polymer or, more specifically, seeded within pores on the surface of the polymer. Any stem cell type may be used. It is preferable, for the treatment of spinal cord injury, that the stem cells be selected from neuronal stem cells and/or mesenchymal stem cells.

In yet another embodiment, the article comprises a single scaffold of an electrically conducting polymer, such as polypyrrole. It is preferred that any of the foregoing articles have a degradation rate of about between about 30 and 60 days; however, the rate can be altered to provide a desired level of efficacy of treatment. The article may further comprise stem cells in association with any of the polymeric material. For example, the stem cells may be seeded onto the polymer or, more specifically, seeded within pores on the surface of the polymer. Any stem cell type may be used. It is preferable, for the treatment of spinal cord injury, that the stem cells be selected from neuronal stem cells and/or mesenchymal stem cells.

In another embodiment of the present invention, a method is disclosed for treating an open wound spinal cord injury, comprising (a) molding a biocompatible

material comprising a 50:50 blend of (1) poly(lactic-co-glycolic acid) and (2) a block copolymer of poly(lactic-co-glycolic acid)-polylysine to conform to a lesioned area of the spinal cord injury; and (b) filling in the lesioned area with the biocompatible material. The (1) poly(lactic-co-glycolic acid) is 75% poly(lactic-co-glycolic acid) and wherein the average molecular weight is Mn ~40,000. The (2) block copolymer of poly(lactic-co-glycolic acid)-polylysine is 25% poly(lactic-co-glycolic acid)-polylysine copolymer and wherein the average molecular weight of the poly(lactic-co-glycolic acid) block is Mn ~30,000 and the average molecular weight of the polylysine block is Mn ~2,000. It is preferred that the material has a degradation rate of about between about 30 and 60 days; however, the rate can be altered to provide a desired level of efficacy of treatment. The material may further comprise stem cells in association with any of the polymeric material. For example, the stem cells may be seeded onto the polymer or, more specifically, seeded within pores on the surface of the polymer. Any stem cell type may be used. It is preferable, for the treatment of spinal cord injury, that the stem cells be selected from neuronal stem cells and/or mesenchymal stem cells.

In yet another embodiment of the present invention, a method is disclosed for treating an open wound spinal cord injury, comprising double scaffold of polypyrrole to conform to a lesioned area of the spinal cord injury; and (b) filling in the lesioned area with the biocompatible polypyrrole material. The inner surface, or inner scaffold, may be porous and seeded with one or more medicinal agents, for example human neuronal stem cells for cellular replacement and/or trophic support. Therefore, in this particular embodiment, the fabricated and formed bandage comprises two scaffolds and simulates the architecture of a healthy spinal cord through an implant consisting of a polymer scaffold, perhaps seeded with neuronal stem cells. The inner scaffold emulates the gray matter; the outer scaffold (the second scaffold) emulates the white matter by having, for example, long, axially oriented pores for axonal guidance and radial porosity to allow fluid transport and inhibiting ingrowth of scar tissue. The bandage can be readily designed to be tailored to fit into a variety of cavities.

It is preferred that the polypyrrole has a degradation rate of about between about 30 and 60 days; however, the rate can be altered to provide a desired level of efficacy of treatment. The material may further comprise stem cells in association with any of the polymeric material. For example, the stem cells may be seeded onto

the polymer or, more specifically, seeded within pores on the surface of the polymer. Any stem cell type may be used. It is preferable, for the treatment of spinal cord injury, that the stem cells be selected from neuronal stem cells and/or mesenchymal stem cells.

In another embodiment of the present invention, a kit for surgically treating spinal cord injuries is described. The kit may include any combination of the components, devices, and polymeric articles, discussed above, in one or more containers, including but not limited to: one or more pre-cut polymeric bandage scaffolds and/or mini-tube scaffolds, one or more artificial dura, a trimming tool, an alignment tool, drapes, and instructions for using the kit and components therein. The components of the kit may be packaged in a sterile manner as known in the relevant art.

Examples

The following non-limiting examples have been carried out to illustrate preferred embodiments of the invention.

Example 1: Polypyrrole mini-tube fabrication (I).

Polypyrrole tube scaffolds are created by electrodeposition of erodible PPy at 100μA for 30 minutes onto 250 μm diameter platinum wire. See figure 2. This is followed by reverse plating at 3 V for 5 minutes, allowing for the removal of the scaffold. See Figure 3 (C and D).

Example 2: PPy mini-tubes prevent post-primary injury cavity formation in the lesioned spinal cord (n=13, SCI and control rats, respectively).

MRI images of post-injury cavity development, studied two months post injury, show large cavity formation in the control spinal cord (wherein injured cord was not treated with surgically implanted mini-tube), as compared to the PPy-treated spinal cord. See Figure 4.

Example 3: Open-field locomotor scores for polypyrrole-implanted rats and lesion control rats.

Results from the polypyrrole mini-tube scaffold showed functional locomotor improvement as early as 2 weeks post injury. The amount of functional recovery

relative to non-treated controls continues to increase for up to 6 weeks. See figure 5. Treated animals are capable of weight-bearing and functional stepping, where non-treated animals show greatly diminished hindlimb function. Magnetic resonance images show that the fluid filled cyst is reduced with a herein described implant. As shown in figure 4, the spinal cord is more intact and the cyst is barely visible when treated with polypyrrole. Biodegradable and/or biocompatible polymers are well known in the art and can be used in the present invention.

Example 4: Polypyrrole mini-tube polymer treated SCIs.

Biocompatible polypyrrole polymer mini-tubes demonstrated high affinity to human neuronal stem cells. See figure 3A and 3B, for example. In an *in vivo* study, a 25mm contusion injury was delivered via the NYU Impactor on Sprague-Dawley rats. Immediately following injury in the two treatment groups, the cord meninges were incised with a short (approximately 1-3mm) cut, allowing for neurosurgical decompression and creating a space for insertion of the tube. In scaffold treatment groups, the implants were inserted into the cord, targeting the central canal and surrounding parenchyma. After implantation, the dura was covered and sealed using the Duragen collagen matrix and overlying tissues sutured closed.

Example 5: Fabrication of PPy mini-tubes (II).

Tube-like PPy scaffolds were produced by plating the PPy onto a conductive wire mold. This technique can be scaled to produce scaffolds of any length, inner diameter, and outer diameter. Furthermore, surface roughness can be controlled with electroplating temperature (figure 2). Scaffold extraction from the template by application of a negative potential in a saline solution. The negative potential causes electrochemical reduction and slightly increases the size of the scaffold. It can then be mechanically dissociated from the platinum wire mold with minimal applied force, resulting in no damage to the material. This technique is an improvement on the prior method of etching the inner wire with harsh organics, making any resulting devices unsuitable for implantation. For in vivo tests in rodents, PPy tube scaffolds were created by electrodeposition of erodible PPy at 100μA for 40min onto 250μm diameter platinum wire. This was followed by reverse plating at 3V for 20 seconds, allowing removal of the scaffold. The resulting tubes of 10-15mm length were sectioned into 3mm long pieces for implantation.

Example 6: Cell Maintenance and Seeding on Polymer mini-tubes.

Murine NSCs (neuronal stem cells) were maintained in serum-containing medium. Scaffolds were soaked in 70% ethanol for 24 hrs, rinsed three times in PBS, and seeded on an orbital shaker with 5 X 10^5 cells/ml at 37°C in a humidified 5% CO_2/air incubator. The medium was changed the next day, and the implants were incubated for 4 more days before implantation.

Example 7: Double Scaffold Fabrication.

Both the inner and outer scaffolds were fabricated from a blend of 50:50 poly(lactic-co-glycolic acid) (PLGA) (75%, number average molecular weight, Mn, ~ 40,000) and a block copolymer of poly(lactic-co-glycolic acid)-polylysine (25%, PLGA block Mn ~ 30,000, polylysine block Mn ~ 2000). The PLGA was chosen to achieve a degradation rate of about 30–60 days, and the functionalized polymer was incorporated to provide sites for possible surface modification. The inner scaffold was made using a salt-leaching process: a 5% (wt/vol) solution of the polymer blend in chloroform was cast over salt with a diameter range of 250–500 μm, and the solvent was allowed to evaporate. The salt was then leached in water. The oriented outer scaffold was fabricated using a solid–liquid phase separation technique in the following way: A 5% (wt/vol) solution of the polymers was filtered and injected into silicone tubes which were lowered at a rate of 2.6 x 10^4 m/s into an ethanol/dry ice bath. Once frozen, the dioxane was sublimated using a shelf temperature-controlled freeze drier (VirTis). The scaffolds were then removed, trimmed, assembled, and stored in a vacuum desiccator until use. The resulting product is one wherein the inner scaffold emulates gray matter via a porous polymer layer which can be seeded with stem cells, for example; and the outer scaffold emulates the white matter with long, axially oriented pores for axonal guidance and radial porosity to allow fluid transport while inhibiting ingrowth of scar tissue.

Example 8: Dramatic spinal cord parenchyma protection is observed at both gross pathology (Fig. 7A) and microscopic (Fig. 7B) levels in the penetrating lesion epicenter tissue collected 8 weeks after the lesion (n = 8) or the implantation of PLGA polymer patch (n = 8). Upper panels of 7A and 7B show the penetrating lesion

epicenter morphologies presented in gross pathology (7A upper panel) and microscopic images (7B upper panel). Eight weeks after initial open wound lesion (i.e., T9-T10 segmental removal of half spinal cord from the midline), only little amount of scarring tissue was left to link the spinal cord. In contrast, polymer patched spinal cord (inserted immediately after lesion) demonstrated significant parenchyma protection for the initially intact side of the cord; the spared tissue was clearly discernable at 8 weeks after penetrating lesion insult at levels of both gross pathology (7A lower panel) and microscopic examination (7B lower panel).

Example 9: Open-field locomotor scores for polypyrrole-implanted rats and lesion control rats.

Results from the polypyrrole scaffold showed functional locomotor improvement as early as 2 weeks post injury. The amount of functional recovery relative to non-treated controls continues to increase for up to 6 weeks. See figure 5. Treated animals are capable of weight-bearing and functional stepping, where non-treated animals show greatly diminished hindlimb function. Magnetic resonance images in figure 4 show that the fluid filled cyst is reduced with a herein described implant. As shown in the figure, the spinal cord is more intact and the cyst is barely visible when treated with polypyrrole mini-tube scaffold. Biodegradable and/or biocompatible polymers are well known in the art and can be used in the present invention.

Example 10: Functional recovery from implantation of PLGA scaffolds configured to treat SCIs.

Basso-Beattie-Bresnahan (BBB) scoring, the standard quantitative metric in the spinal cord injury research field, was used to evaluate open-field locomotion at one day postsurgery and at weekly time points over the course of 6 weeks post-injury. Results from the PLGA double-scaffold configured to treat SCI showed functional locomotor improvement as early as 2 weeks post injury. See figure 6. The amount of functional recovery relative to non-treated controls continued to increase for up to 8-10 weeks. The study was ended at the end of week 8 or 10. In additional studies, rodents were kept for over one year and demonstrated sustainable functional recovery as well as no pathology in reaction to the product. Because the average lifespan of a

rat is 2 years, the "one year plus" study demonstrates effectiveness of the herein described scaffolds.

Example 11: BBB open-field walking scores.

BBB open-field walking scores for the four groups on the ipsilateral, lesioned side. See Figure 9. Hindlimbs were assessed independently to determine the degree of asymmetry. The rate of improvement for the scaffold plus cells group was significantly greater than the rate for the cells-alone ($P < 0.001$) and lesion-control groups ($P<0.004$; two-way repeated measures of ANOVA). Additionally, the scaffold alone treated group showed significant improvement in open-field locomotion compared with the lesion-control group ($P < 0.05$) ($P < 0.05$) for all time points from 14 days after SCI on, and the cells-alone group ($P < 0.05$) at 21, 35 and 42 days post injury (ANOVA, Bonferroni post hoc analysis).

Example 12: Cell Maintenance and Seeding.

Murine and human NSCs (neuronal stem cells) were maintained in serum-containing medium. Saffoleds were soaked in 70% ethanol for 24 hrs, rinsed three times in PBS, and seeded on an orbital shaker with 5×10^5 cells/ml at 37°C in a humidified 5% CO_2/air incubator. The medium was changed the next day, and the implants were incubated for 4 more days before implantation.

Example 13: Histopathology.

Conventional histopathologic analysis was performed on the spinal cord tissue to determine changes of lesion scale, secondary injury events and healing processes. Microscopic images proved that the injury area was significantly reduced with our implant treatment. The spinal cord also demonstrated mitigated scarring as indicated by the reduced astrogliosis, a pathology which was impeded by both polymer plus stem cells and by polymer alone as well. is more intact and the cyst is barely visible when treated with polypyrrole.

Example 14:

The level of functional recovery after the same model of injury is further lifted by treatment of human NSCs seeded PLGA polymer as demonstrated in figure 9.

100% of treated animals were capable of weight-bearing and functional stepping. As shown in the figure (figure 9), 50% of treated animals met the rigorous criteria of Consistent plantar stepping and Consistent FL-HL coordination during gait; and Toe clearance occurs frequently during forward limb advancement; Predominant paw position is parallel at initial contact and rotated at lift off, corresponding to a BBB score of 16 or higher. None of the non-treated control animals reached this high standard of recovery, but rather exhibited greatly diminished hind limb function.

Example 15: Single scaffold fabrication.

The single scaffold was fabricated from a blend of 50:50 poly(lactic-co-glycolic acid) (PLGA) (75%, number average molecular weight, Mn, ~ 40,000) and a block copolymer of poly(lactic-co-glycolic acid)-polylysine (25%, PLGA block Mn ~ 30,000, polylysine block Mn ~ 2000). The PLGA was chosen to achieve a degradation rate of about 30–60 days, and the functionalized polymer was incorporated to provide sites for possible surface modification. The single scaffold was made using a salt-leaching process: a 5% (wt/vol) solution of the polymer blend in chloroform was cast over salt with a diameter range of 250–500 μm, and the solvent was allowed to evaporate. The salt was then leached in water. The product is a single porous polymer layer which can be seeded with stem cells, for example.

Example 16: Spinal cord tissue analysis.

Pathology, histology, and immunocytochemistry analysis of spinal cord tissue (via GFAP and DAPI staining of glial cells at 2mm rostral to the lesion epicenter) revealed that PLGA scaffold alone and especially PLGA scaffold seeded with human neural stem cells markedly reduced scarring formation in the injured area. Wright's staining of infiltrated polymorphonucleic leukocytes (PNLs) in spinal cord tissues 2mm rostral to the lesion epicenter show that PLGA scaffold alone and especially PLGA scaffold seeded with human neural stem cells markedly impeded infiltration of PNLs, a major iNOs (inducible nitric oxide synthase) carrier, into the spinal cord.

Example 17: Spinal cord injury (SCI) surgical procedures and animal care.

Surgical Procedures and Animal Care. Fifty adult female Sprague–Dawley rats were used. Animals were anesthetized with a 4% chloral hydrate solution (360 mg/kg

i.p.). Using a dissecting microscope, a laminectomy was made at the 9th-to-10th thoracic (T9-T10) spinal vertebrae, followed by a lateral hemi-section at the T9-T10 level by creating a 4-mm-long longitudinal cut along the midline of the cord with a No. 11 surgical blade, followed by lateral cuts at the rostral and caudal ends and removal of the tissue by aspiration. The surgical blade was repeatedly scraped along the ventral surface of the vertebral canal, followed by aspiration to remove any residual fibers at the lesion site. After gelfoam-triggered hemostasis occurred, an independent blinded observer confirmed the adequacy of the length and breadth of the lesion. Only at that time was the surgeon informed of the treatment (previously prepared) to be administered to the lesion. The lesion was affirmed a priori to be similar across all experimental groups and animals. Either the full treatment, consisting of insertion of the NSC seeded scaffold (''scaffold plus cells,'' n = 13), or one of three control treatments was performed: (a) polymer implant without NSCs (''scaffold alone,'' n = 11; (b) NSCs suspended in medium (''cells alone,'' n = 12); or (c) hemi-section alone (''lesion control,'' n = 12). Surgeries were performed in a randomized block design. The surgeries for the implant plus controls were performed on the same day to minimize differences between groups arising from any refinement in surgical technique during the study, and the order was varied each day to reduce surgical bias. Hemi-sections were alternated between the right and left sides to further reduce bias. Following either the full or control treatment, the musculature was sutured, skin closed, and the animal recovered in a clean cage on a heating pad. Ringer's lactate solution (10 ml) was given daily for 7 days post-op and bladders were evacuated twice daily until reflex bladder function was established.

Because immunosuppressive agents such as cyclosporin A have been shown to be neuroprotective on their own, these experiments were performed without such neuroimmunophilins to avoid this confounding variable. Donor cells were nevertheless present at the end of the study. A separate group of scaffold plus cells animals underwent the same procedures as above and were maintained for one year.

All procedures were reviewed and approved by the Animal Care and Use Committee of our institutions.

Example 18: Functional recovery analysis summary for bandage-scaffold.

See Figure 8, wherein a, Montages of still images of animal open-field walking in "lesion only" (top row) and "scaffold with high dose hNSCs" (bottom

row). **b**, Lesion side BBB open-field walking scores. The absolute scores of groups treated with hNSCs seeded in single-scaffolds (i.e., 16 - 17 in average) are significantly higher than "hNSCs only" group (BBB score of 9 in average; P=0.004 for regular dose, P<0.001 for high dose), "scaffold only" group (P=0.004 for regular dose, P=0.001 for high dose, and "lesion only" group (P<0.001 for regular dose, P=0.001 for high dose, ANOVA, Bonferroni *post hoc* analysis). The scaffold alone group received PLGA polymer in a single porous layer design. The *rate* of improvement also shows a significantly greater value in hNSC seeded in scaffold groups than the "hNSCs only" group (P=0.004 for regular dose, P<0.001 for high dose, two-way repeated measures of ANOVA), scaffold group (P=0.004 for regular dose, P<0.001 for high dose), and "lesion only" group (P=0.004 for regular dose, P<0.001 for high dose). **c**, Inclined plane tests. When facing downward, the hNSC+scaffold treated rats could stabilize their bodies on inclined boards angled at significantly higher degrees (Kruskal-Wallis test, P<0.001). Parametric and non-parametric analysis both reveal similar results. **d**, Pain withdrawal reflex scores. The left curve panel is the percentage of animals in each group scoring 2, corresponding to normal response. The right panel is the percentage of animals in each group scoring 3, indicating hyperactive response. The two panels consistently indicate that the groups receiving hNSCs seeded in single-scaffolds showed significantly improved hind limb reflex which was correlated with hNSC doses (Pearson χ^2 test of independence). **e**, Percentage of animals in each group demonstrating normal righting reflex. Groups receiving hNSCs seeded in single-scaffolds had significantly higher percentage of rats that recovered their righting reflex comparing to other groups (Pearson χ^2 test).

The scope of the claims should not be limited by the preferred embodiments and examples, but should be given the broadest interpretation consistent with the description as a whole.

What is claimed is:

1. A device for implanting within a patient's spinal cord comprising a single layer polymer scaffold comprising (1) poly(lactic-co-glycolic acid) and (2) a block copolymer of poly(lactic-co-glycolic acid)-polylysine.

2. The device of claim 1, wherein the (1) poly(lactic-co-glycolic acid) has an average molecular weight of between about Mn 20,000 and 50,000.

3. The device of claim 2, wherein the (1) poly(lactic-co-glycolic acid) has an average molecular weight of about Mn 40,000.

4. The device of claim 1, wherein the scaffold comprises a (l) 50:50 blend of poly(lactic-co-glycolic acid) and a (2) block copolymer of poly(lactic-co-glycolic acid)-polylysine.

5. The device of claim 4, wherein the (2) block copolymer of poly(lactic-co-glycolic acid)-polylysine comprises a poly(lactic-co-glycolic acid) block having an average molecular weight of between about Mn 20,000 and 50,000; and a polylysine block having an average molecular weight of between about Mn 1,000 and about 3,000.

6. The device of claim 5, wherein the (2) block copolymer of poly(lactic-co-glycolic acid)-polylysine comprises a poly(lactic-co-glycolic acid) block having an average molecular weight of about Mn 40,000 and a polylysine block having an average molecular weight of about Mn 2,000.

7. The device of claim 2, wherein the scaffold degrades *in vivo* in about 30 to about 60 days.

8. The device of claim 1, wherein the scaffold is a cylinder.

9. The device of claim 8, wherein the cylinder is hollow.

10. The device of claim 1, wherein the scaffold is moldable.

11. The device of claim 1, wherein the scaffold has an overall diameter of between about 0.1 microns and 10 millimeters.

12. The device of claim 11, wherein scaffold has an overall diameter of between about 1 millimeter and 6 millimeters.

13. The device of claim 1, further comprising one or more medicinal agents deposited onto the scaffold.

14. The device of claim 13, wherein the one or more medicinal agents are selected from the group consisting of anti-inflammatory agents, growth factors and stem cells.

15. The device of claim 14, wherein the stem cells are selected from the group consisting of neuronal stem cells and mesenchymal stem cells.

16. The device of claim 1, wherein the scaffold is biodegradable and/or bioabsorbable.

17. The device of claim 1, wherein the scaffold is longer than the length of a lesioned area of a spinal cord injury.

18. The device of claim 17, wherein the scaffold is approximately 1.5 times longer than the length of the lesioned area of the spinal cord injury.

19. The device of claim 1 or claim 4, further comprising a biocompatible polymer capable of conducting electricity.

20. A device for implanting within a patient's spinal cord comprising a single layer polymer scaffold of (l) poly(lactic-co-glycolic acid) and (2) a block copolymer of poly(lactic-co-glycolic acid)-polylysine.

21. A kit comprising for treating a spinal cord injury comprising in one or more containers a device for implanting within a patient's spinal cord comprising a single layer polymer scaffold comprising (1) poly(lactic-co-glycolic acid) and (2) a block copolymer ofpoly(lactic-co-glycolic acid)-polylysine.

22. The device of claim 1 or 9, wherein the scaffold is a minitube.

Figure 1 A.

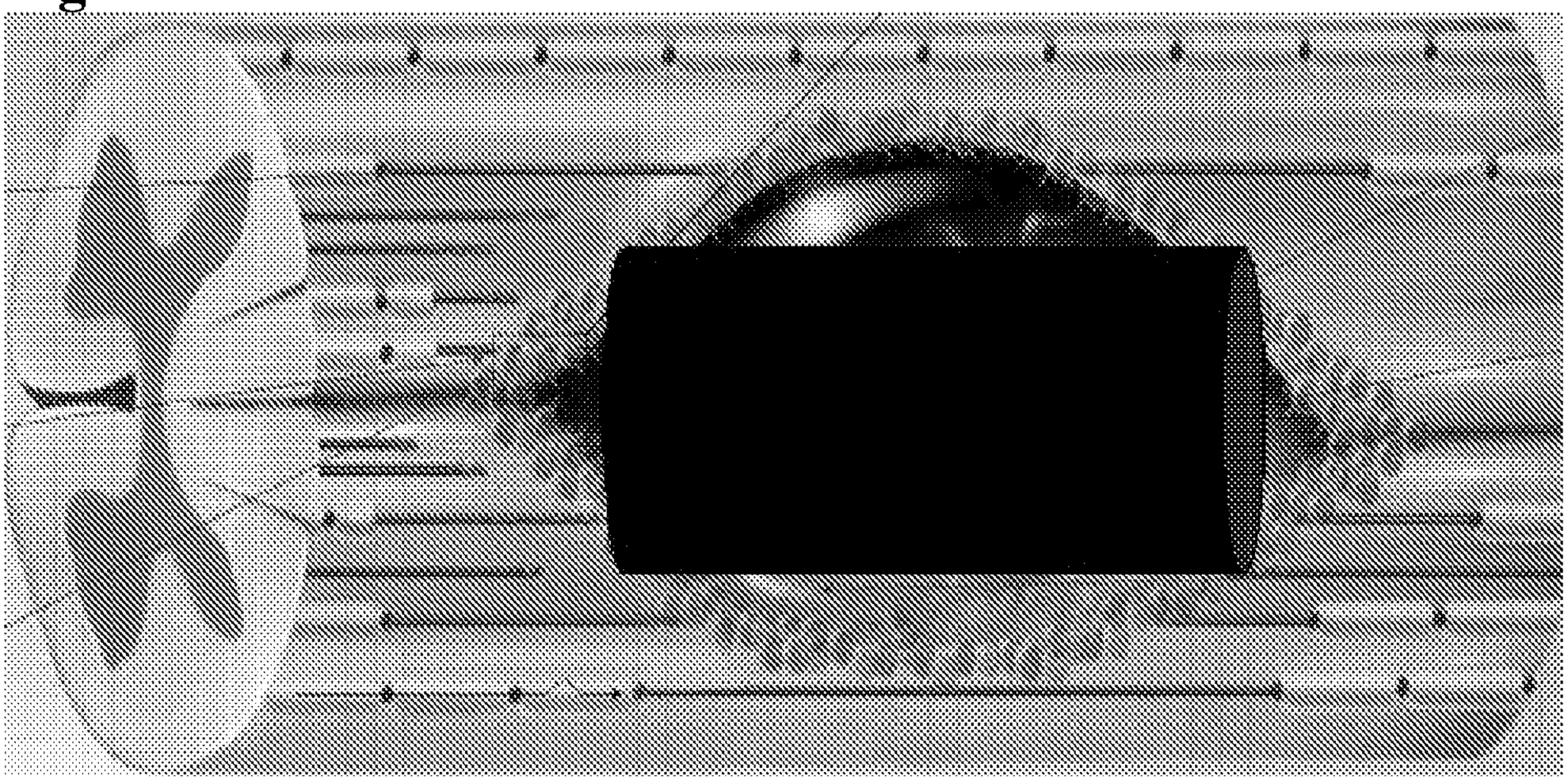


Figure 1 B.

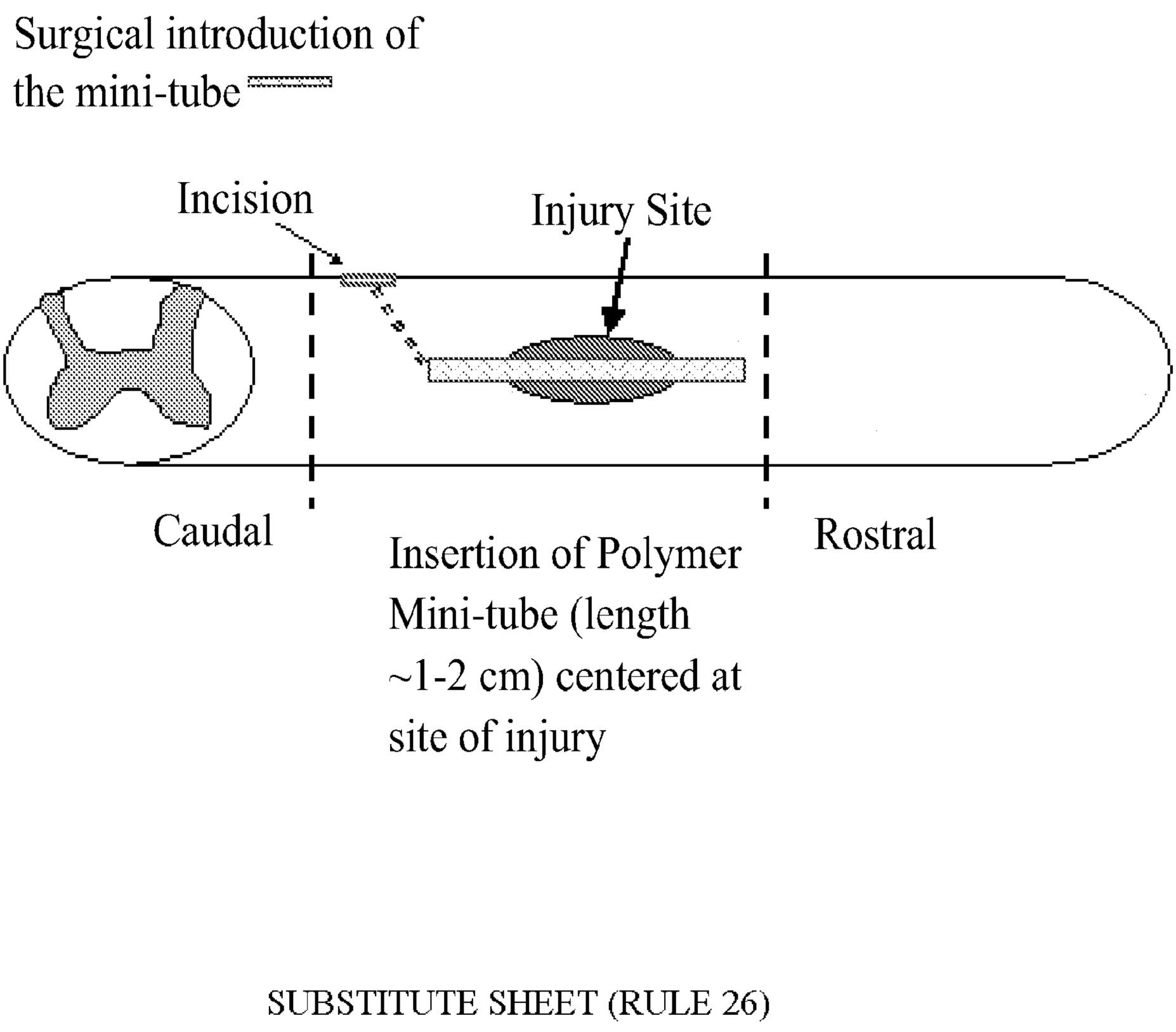


Figure 2.

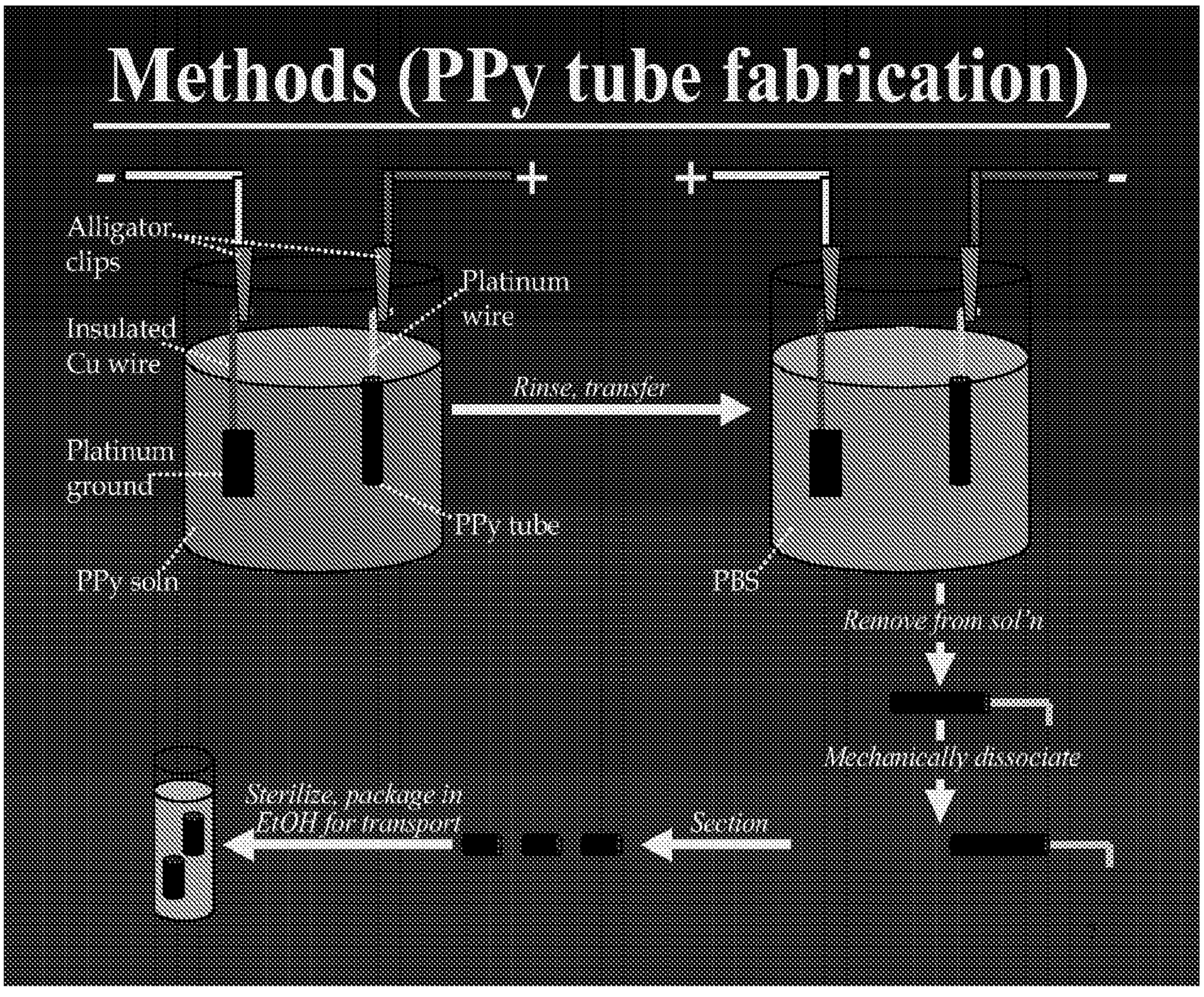
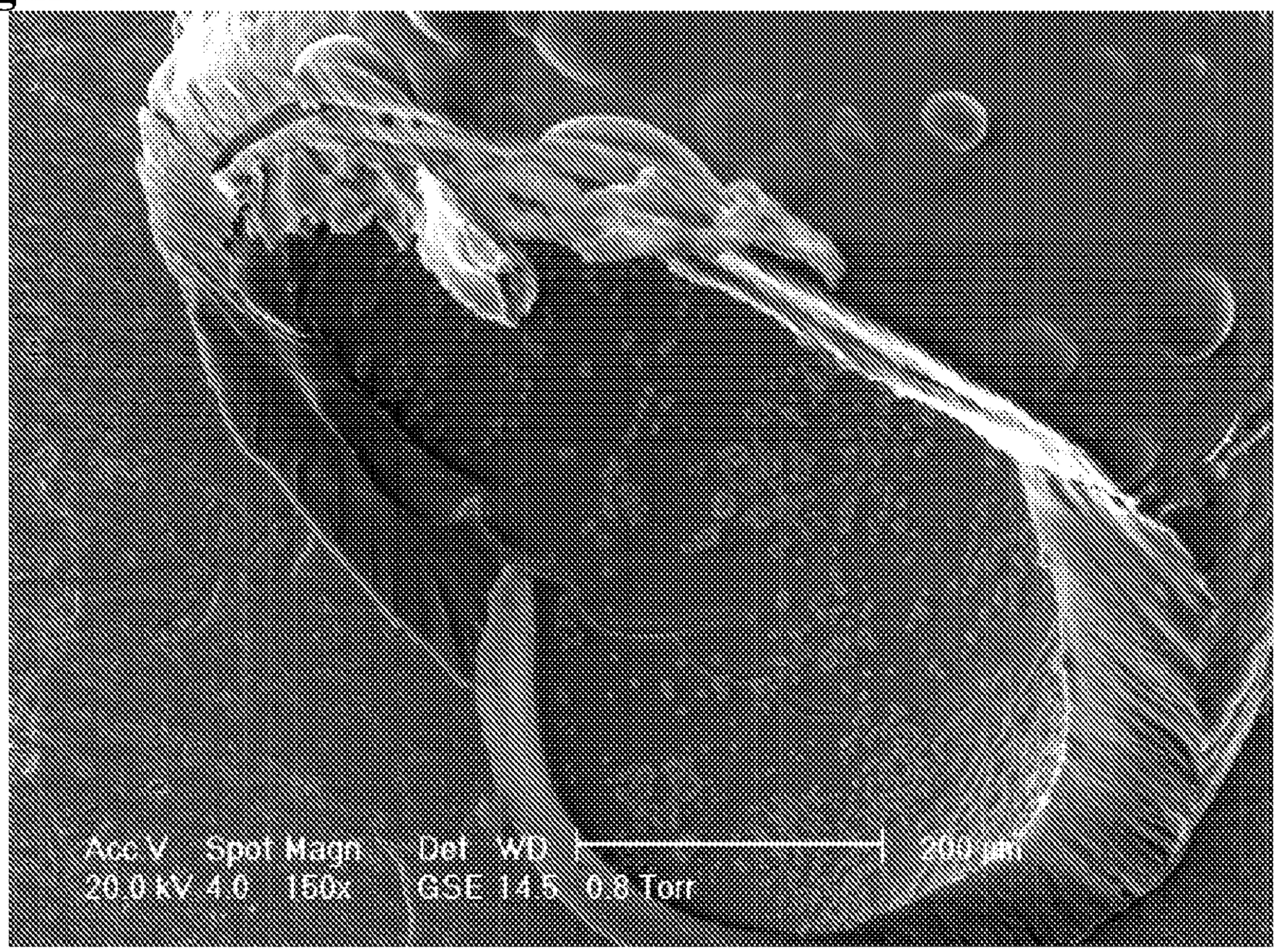
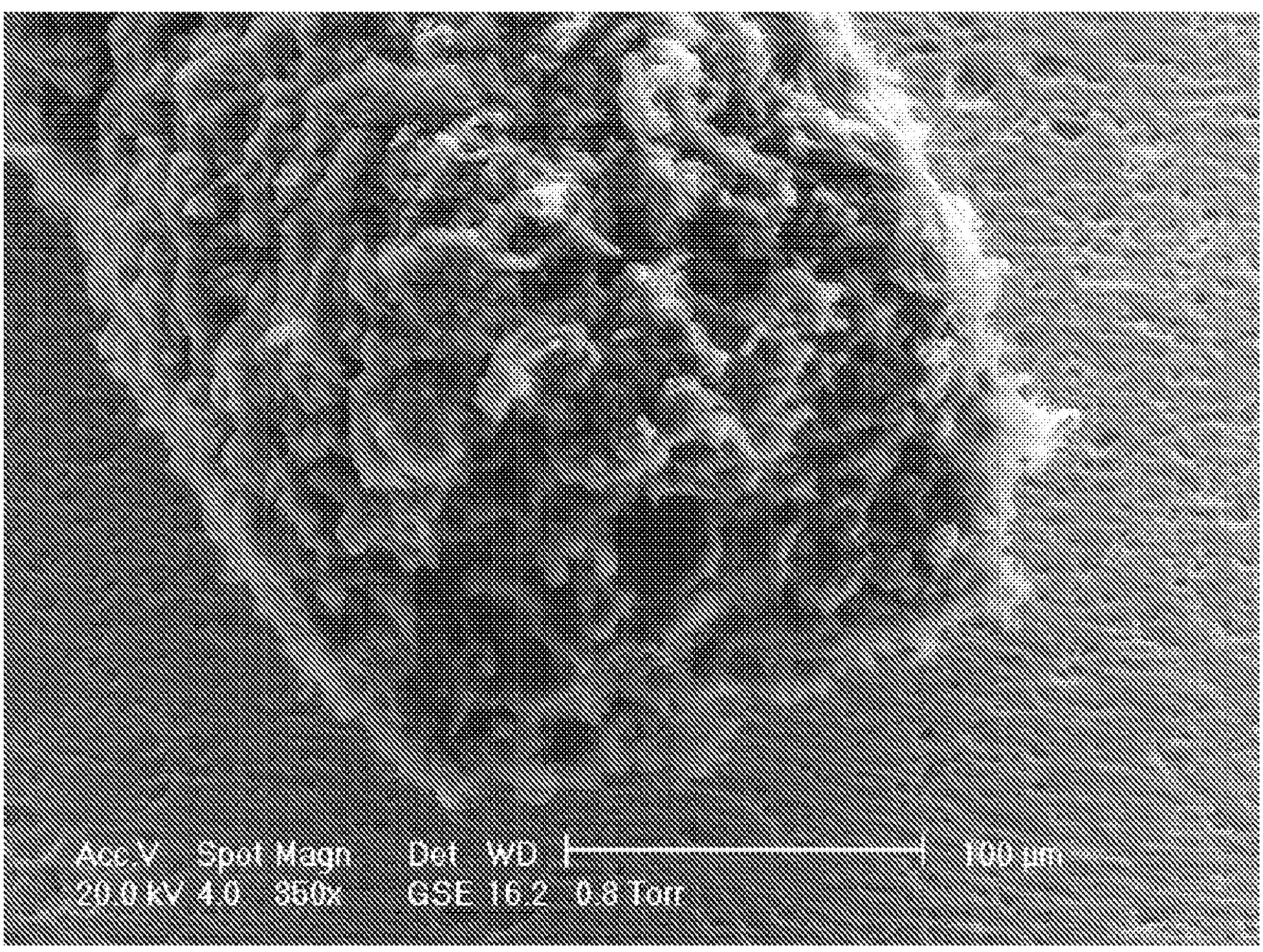

Methods (PPy tube fabrication)
Alligator clips
Insulated Cu wire
Platinum ground
PPy soln
Platinum wire
PPy tube
Rinse, transfer
PBS
Remove from sol'n
Mechanically dissociate
Section
Sterilize, package in EtOH for transport

Figure 3.


Acc.V Spot Magn Det WD 200 µm
20.0 kV 4.0 150x GSE 14.5 0.8 Torr

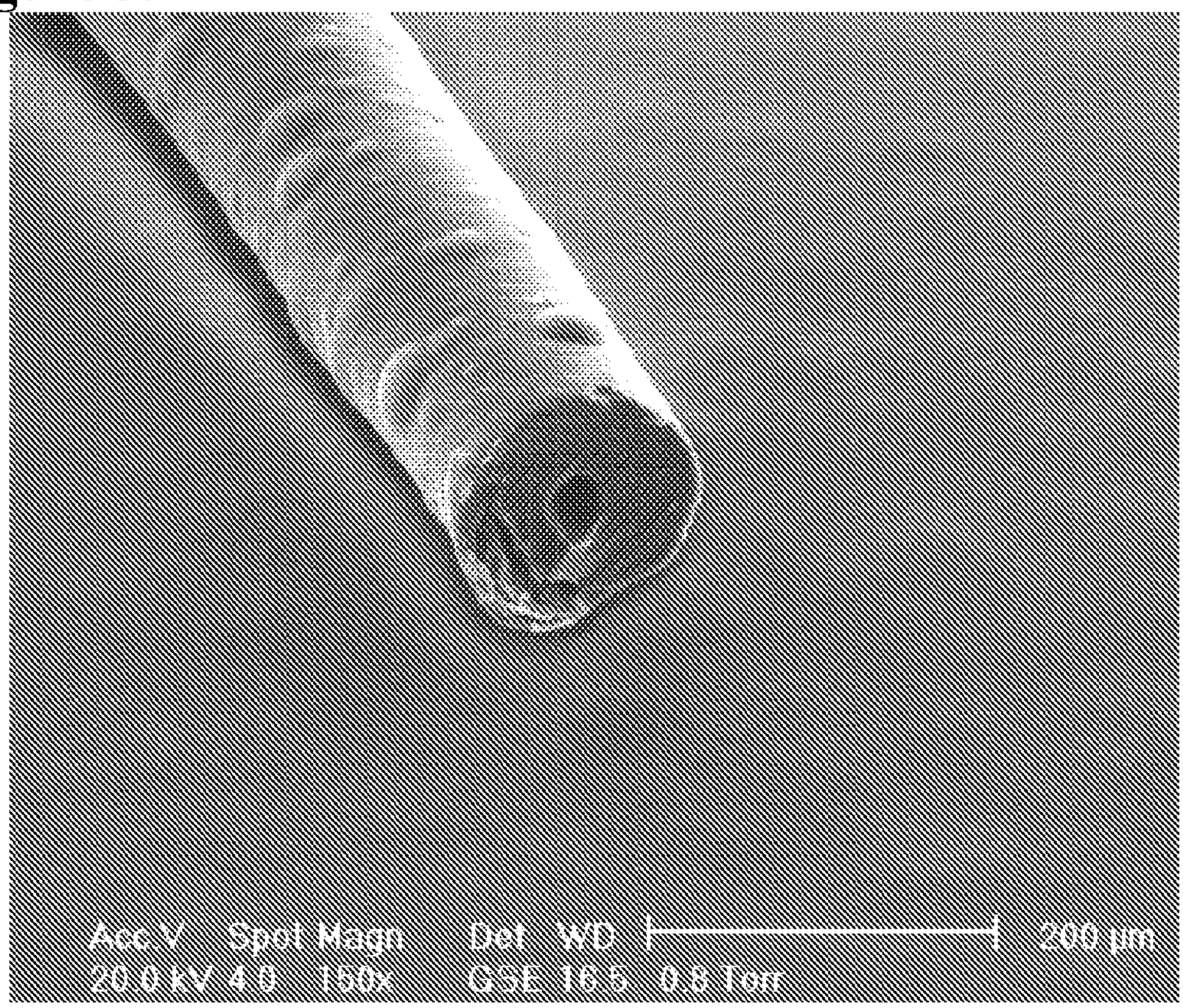
A.


Acc.V Spot Magn Det WD 100 µm
20.0 kV 4.0 350x GSE 16.2 0.8 Torr

B.

Figure 3.

C.


Acc.V Spot Magn Det WD 200 µm
20.0 kV 4.0 150x GSE 16.5 0.8 Torr

D.

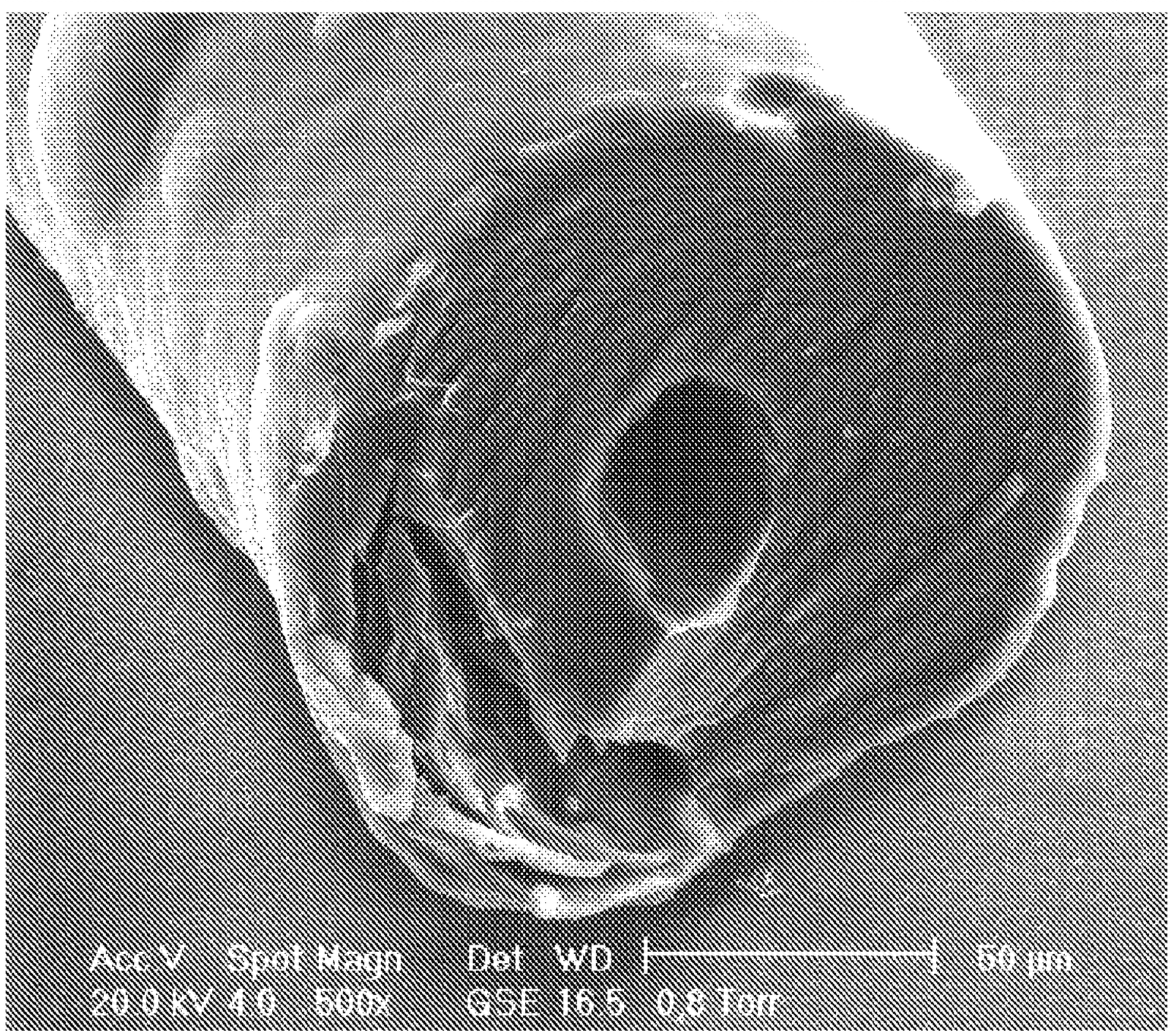

Acc.V Spot Magn Det WD 50 µm
20.0 kV 4.0 500x GSE 16.5 0.8 Torr

Figure 4.

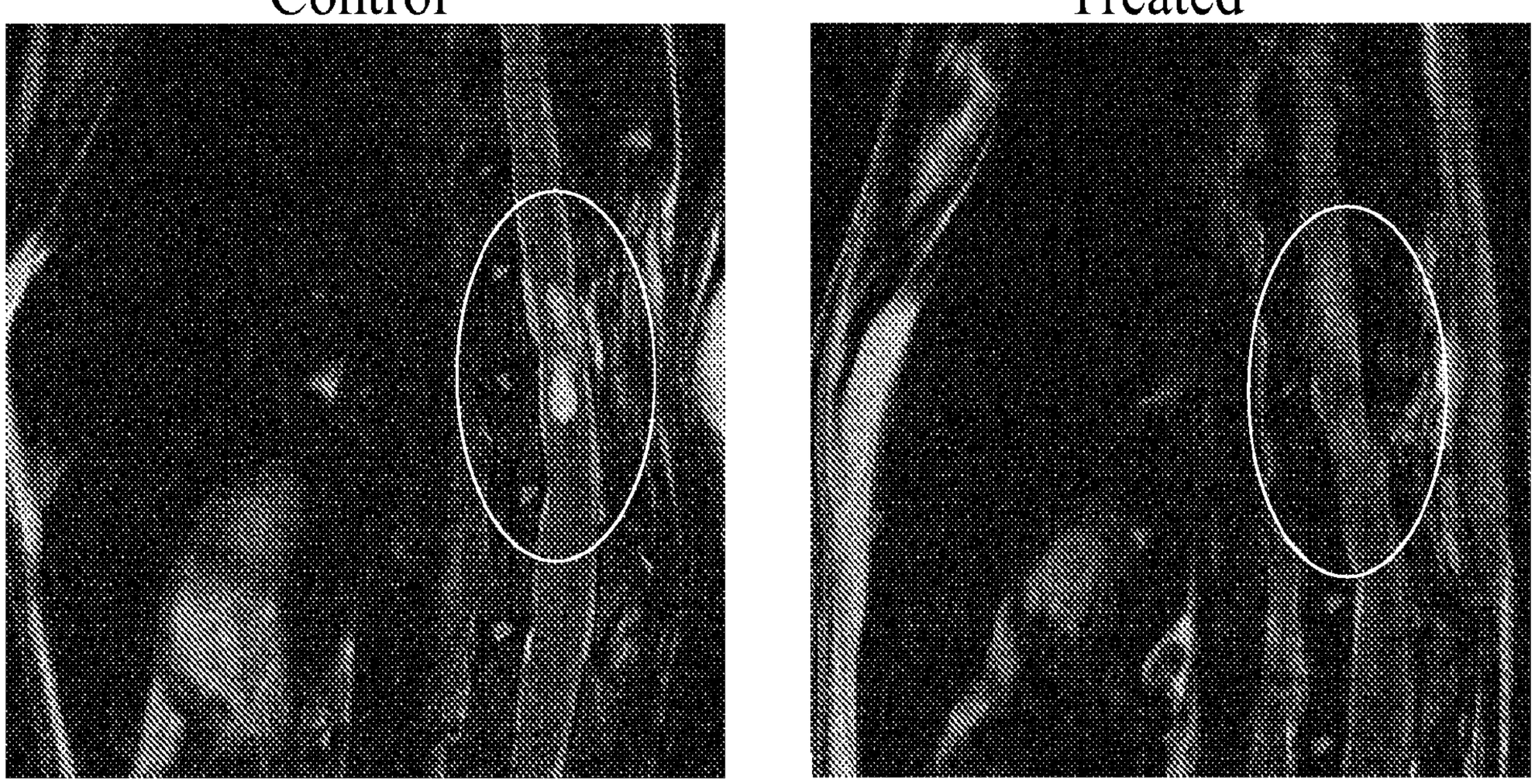


Figure 5.

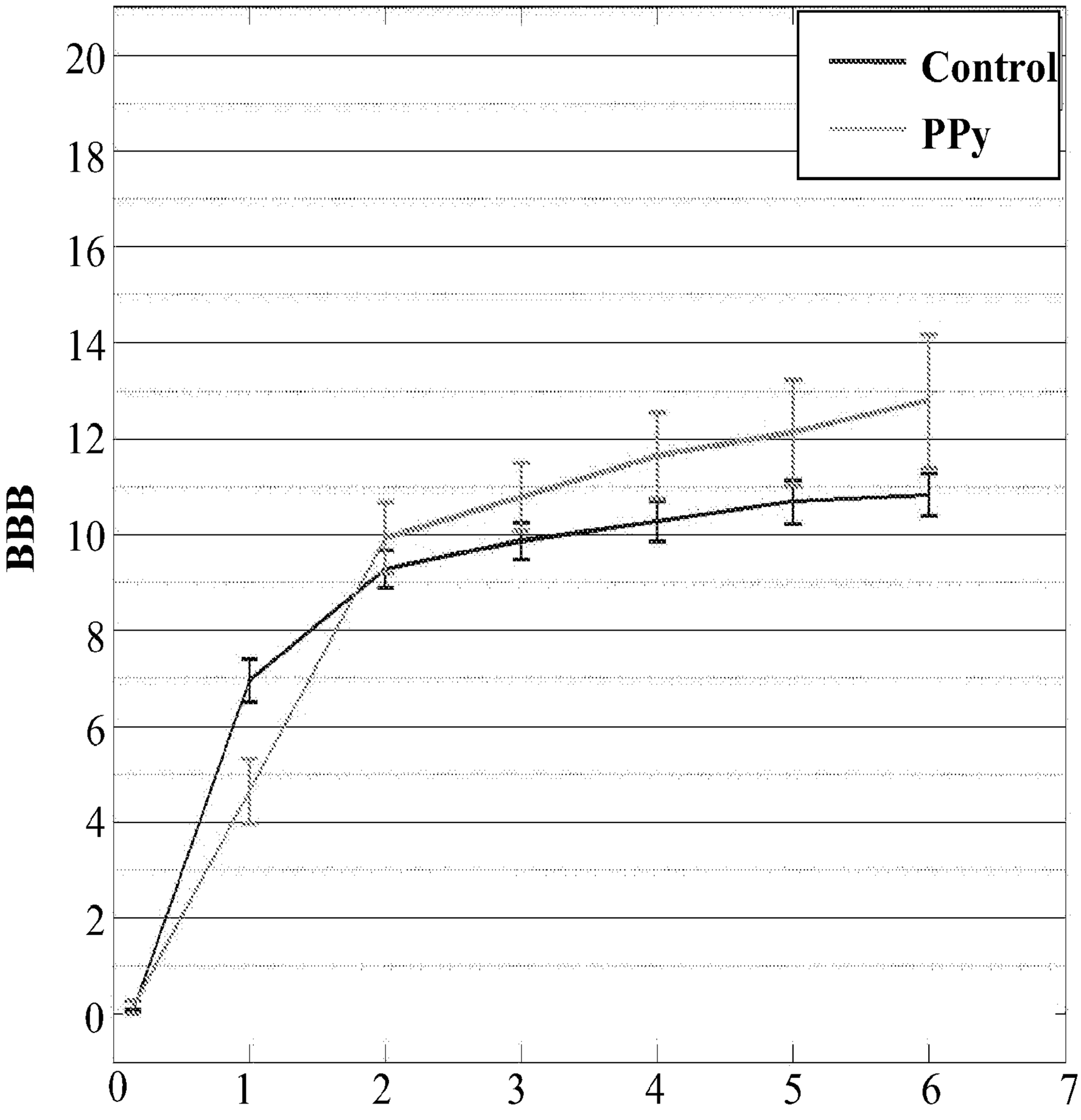

Control
PPy
BBB
Weeks Post Injury
0
2
4
6
8
10
12
14
16
18
20
0
1
2
3
4
5
6
7

Figure 6.

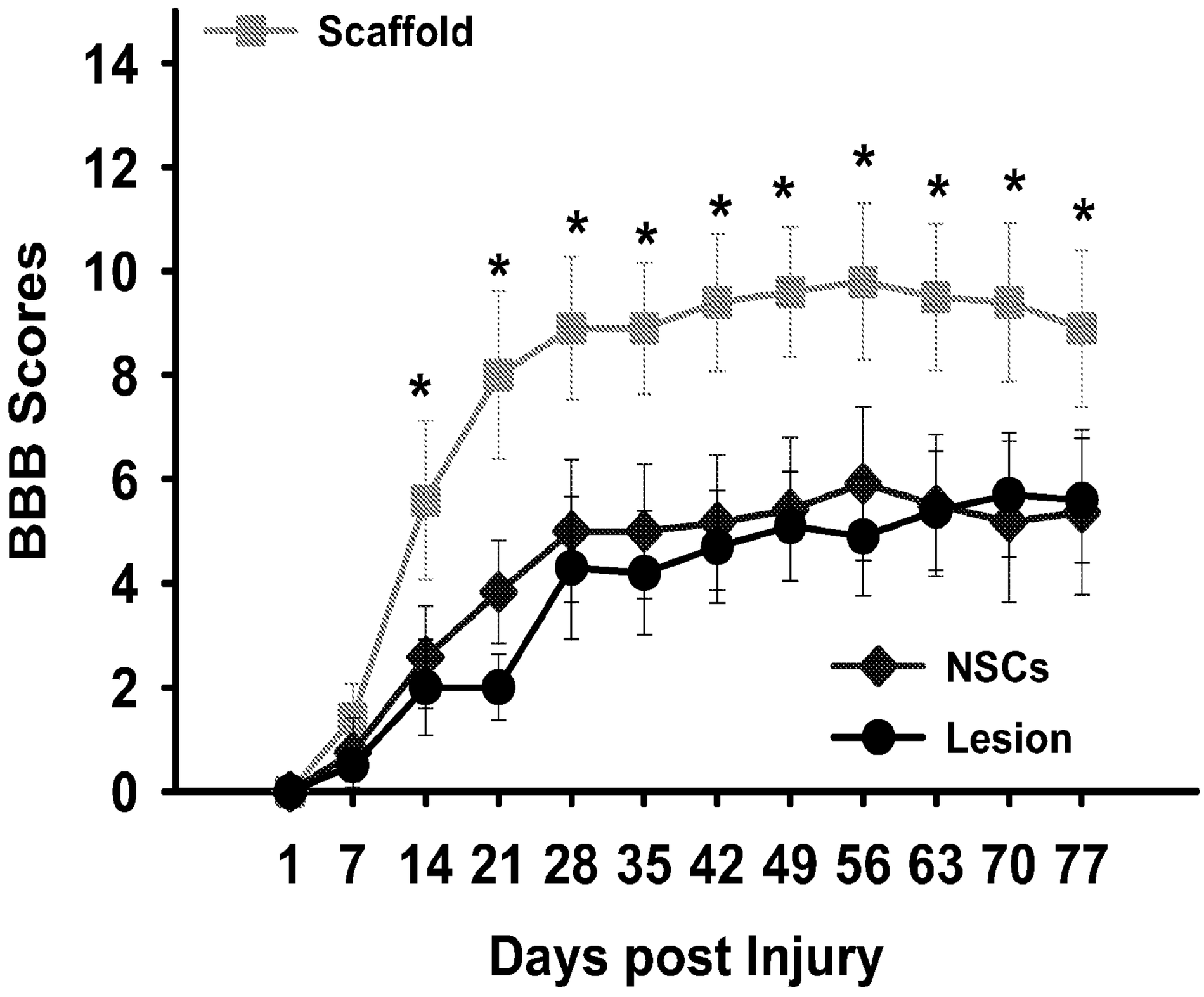

Scaffold
NSCs
Lesion
BBB Scores
0
2
4
6
8
10
12
14
1 7 14 21 28 35 42 49 56 63 70 77
Days post Injury

Figure 7.

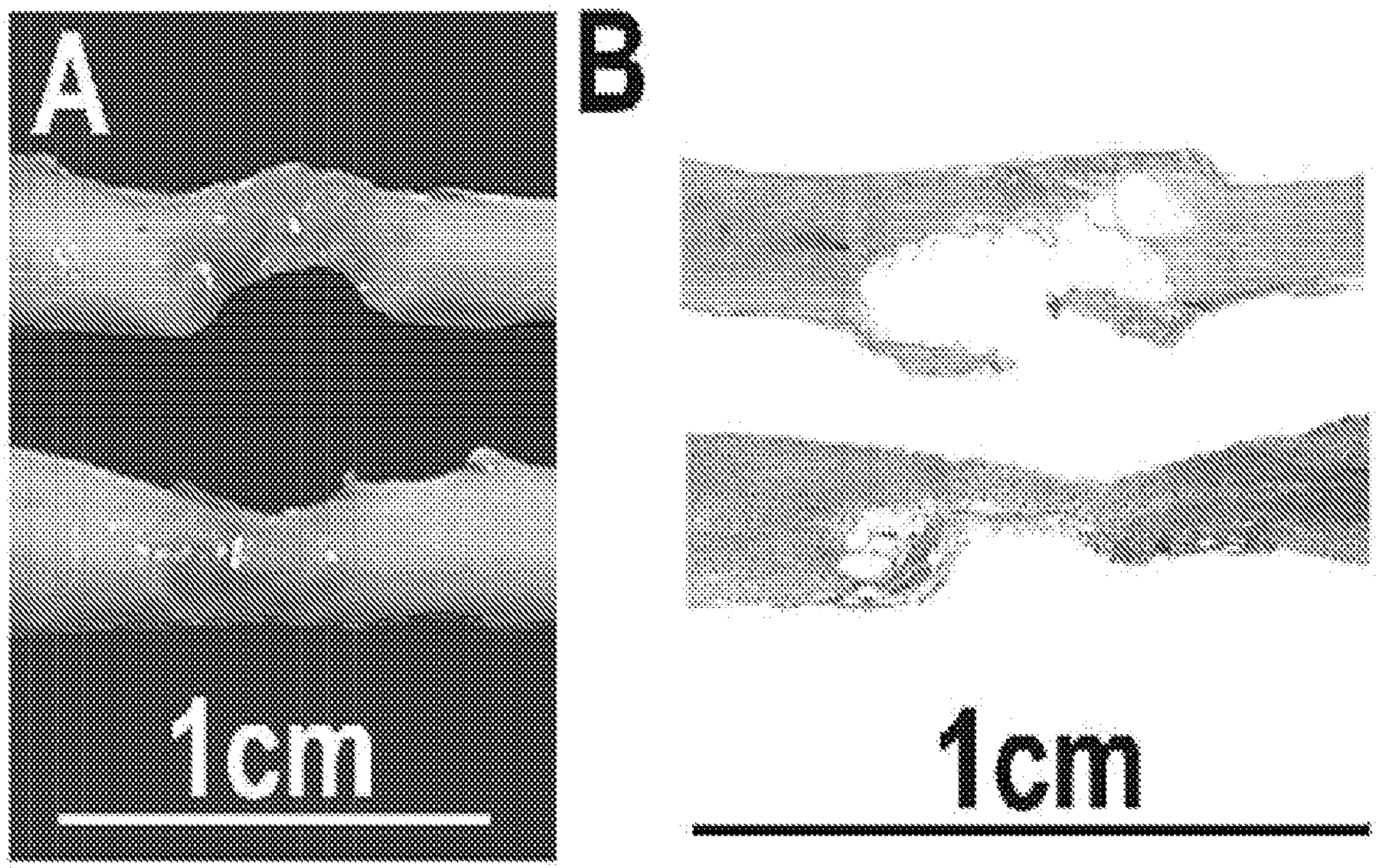


Figure 8.

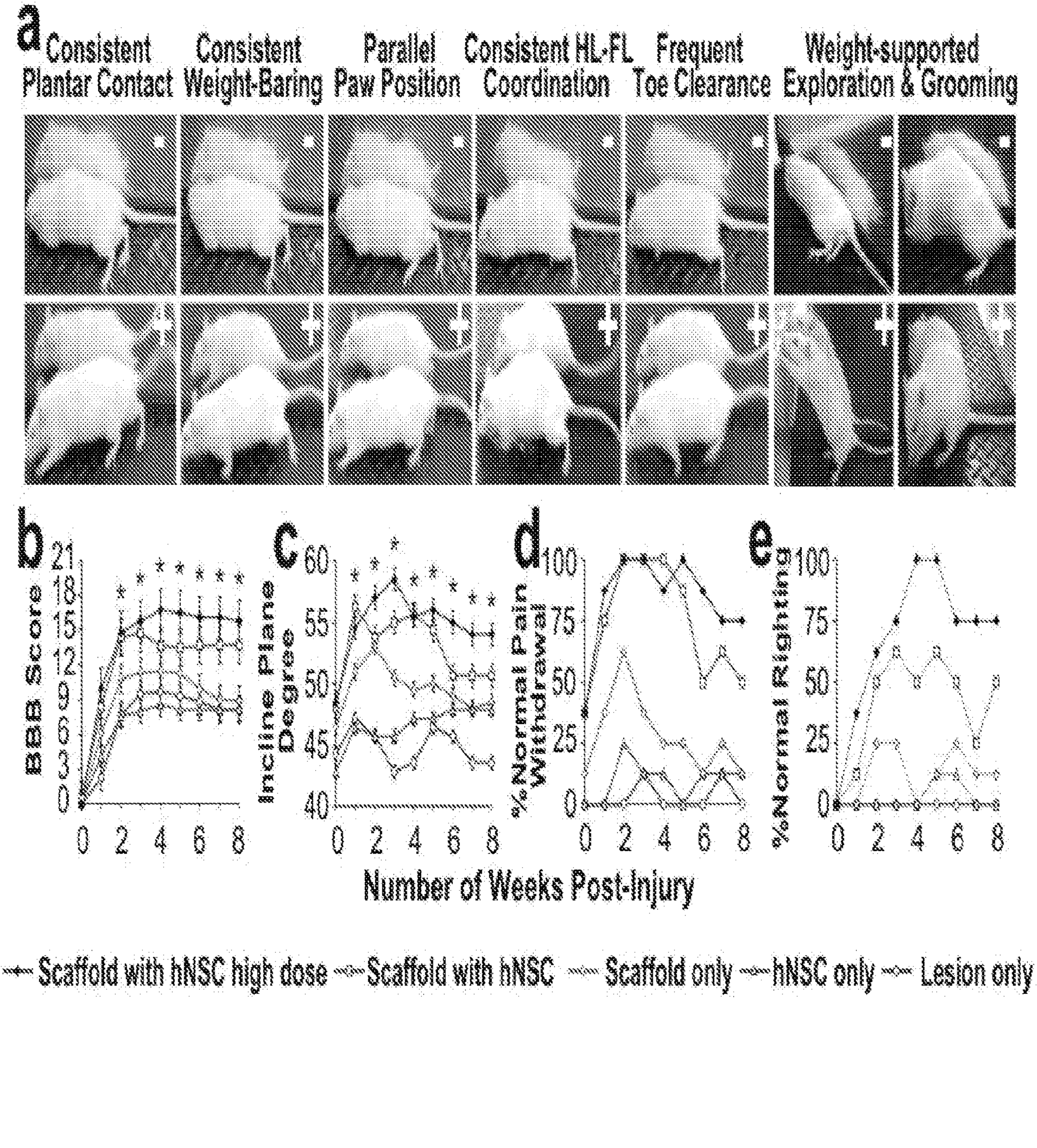
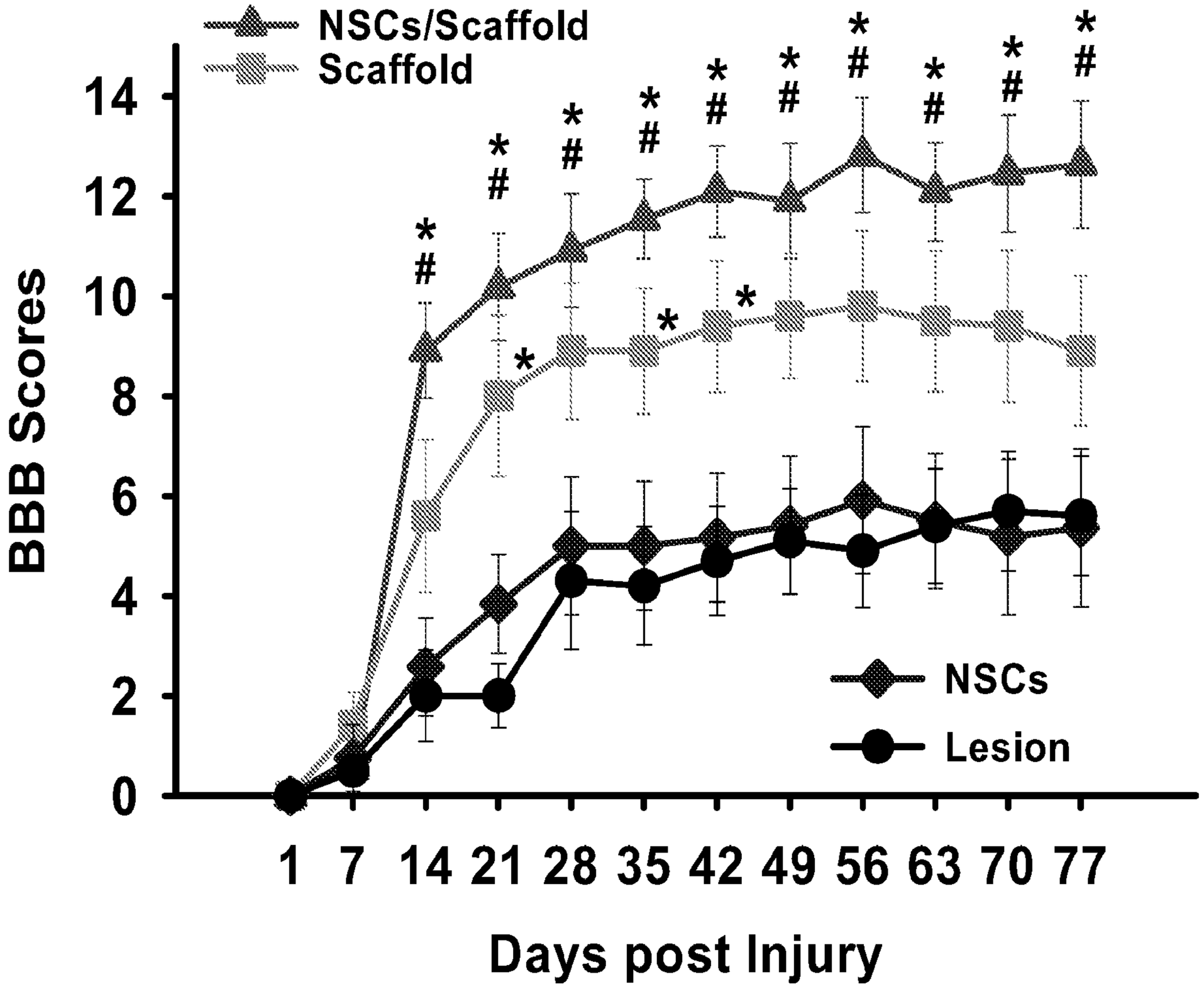

a
Consistent Plantar Contact
Consistent Weight-Baring
Parallel Paw Position
Consistent HL-FL Coordination
Frequent Toe Clearance
Weight-supported Exploration & Grooming
b
BBB Score
c
Incline Plane Degree
d
% Normal Pain Withdrawal
e
% Normal Righting
Number of Weeks Post-Injury
Scaffold with hNSC high dose
Scaffold with hNSC
Scaffold only
hNSC only
Lesion only

Figure 9.


NSCs/Scaffold
Scaffold
NSCs
Lesion
BBB Scores
0
2
4
6
8
10
12
14
1 7 14 21 28 35 42 49 56 63 70 77
Days post Injury