CONDUCTIVE BENZOIC ACID BASED POLYMER CONTAINING BIOMATERIAL FOR REPAIRING NERVOUS SYSTEM INJURY

CROSS-REFERENCE TO RELATED APPLICATION:

[0001] This application claims the benefit of United States Provisional Application No. 63/557,264, filed February 23, 2024, the entire contents of which is hereby incorporated by reference in its entirety

FIELD:

[0002] The disclosure relates to a method of treating a neurological lesion using a conductive biocompatible biomaterial.

BACKGROUND:

[0003] Spinal cord injury (SCI) is a severe neurological disorder, leading to loss of voluntary and involuntary control of bodily functions below the injury site. Approximately 500,000 individuals are affected by SCI per year, often due to receiving physical trauma from various activities, ranging from car accidents to sports injuries [1]. This trauma, in turn, triggers various secondary pathophysiological processes, such as inflammation, ischemic-associated cell death, demyelination, protein degradation, as well as production of regeneration-inhibiting molecules, all of which contribute to the formation of cavitation and glial scar tissue within the spinal cord [2]. These processes are responsible for preventing axonal regeneration between the intact portions of the spinal cord, and thus the restoration of electrical signaling between the central (CNS) and peripheral nervous systems (PNS), which is crucial for controlling various bodily functions.

[0004] Current SCI treatments, ranging from surgery, rehabilitation protocols, and pharmaceutical agents, such as the steroid methylprednisolone, have limited effectiveness, as they focus on palliation and limiting the spread of further tissue damage, rather than restoring tissue and/or bodily functions [3, 4]. This is due to both the aforementioned secondary pathophysiological processes, as well as the mammalian CNS having a limited capacity for regeneration post-injury [5]. A variety of approaches have been developed to bypass this limitation, ranging from using enzymes to remove regeneration-inhibiting molecules, stimulating mitochondrial biogenesis via β2-adrenergic receptor agonists, and transplanting stem cells, such as human pluripotent-derived neuronal or ependymal precursors, at the injury sites [5-8]. One such approach to aid in restoring spinal cord function is biomaterials, of which a number of studies have demonstrated their effectiveness in restoring CNS signaling to the PNS post-SCI, as these biomaterials are able to serve as a bridge between the intact portions of the spinal cord across the lesion site, thereby aiding in restoring proper CNS-PNS electrical conduction [8]. Biomaterials range from biopolymer matrices, such as imidazole-poly(organophosphazene) or self-assembling peptide-based hydrogels, growth factor-conjugated scaffolds, such as PDGF-A conjugated to a hyaluronic acid-methylcellulose backbone, and those made from conductive materials, such as

poly-pyrrole (PPy) conjugated to either poly-lactic (PLA) or tannic acid [2, 9-12]. All of those were able to improve the execution of both involuntary and voluntary bodily functions, in both post-SCI rodent and human subjects, through filling in cavitations, remodelling extracellular matrix, stimulating neuronal differentiation and growth of implanted or endogenous neuronal stem cells at injured site of the spinal cord [7-12]. Restoring electrical conduction between the intact portions of the spinal cord in turn stimulates the production of neuronal growth factors from the remaining neurons, thereby activating pathways promoting axonal growth across the injury site [13, 14].

[0005] Biocompatible conductive biopolymers have been shown to restore electrical signal conduction, and synchronized contraction, within infarcted cardiac tissue in a rat model [15].

[0006] The existing biomaterials for restoring spinal cord function described above have various disadvantages. For example, it is known that acceleration of dysfunction spinal cord injury is due to regional inflammatory reaction. However, the addition of PLA or tannic acid can further increase local inflammatory cell infiltration and reaction. Furthermore, to enhance the biomaterial's conductivity, the conductive polymer has to be doped, for example, PPY has to be doped using Ions. This can be done in a controlled fashion in vitro or ex vivo. However, the use of doping agents reduces the potential in vivo applications. The conductivity of the biomaterial is also decreased over time.

[0007] There remains a need for treatments for neurological injuries such as spinal cord injury that repair or restore at least some neural conductive function.

SUMMARY:

[0008] Biocompatible conductive biopolymers have been shown to restore electrical signal conduction, and synchronized contraction, within infarcted cardiac tissue, which is a fibrotic tissue, in a rat model previously. It is demonstrated herein that unexpectedly, the conductive biopolymer PAMB conjugated to gelatin (PAMB-G) can restore electrical conductivity at an injury site of the spinal cord, which is a bundle of neural fibers and not a fibrotic tissue. It is further demonstrated herein that PAMB-G restores motive function post spinal cord injury. Post-injury inflammatory responses were also reduced. PAMB-G has self-doping capacity and provides significant advantages for in vivo applications over other conductive biomaterials.

[0009] Accordingly, in one aspect there is provided a method of treating a neurological lesion, the method comprising administering a conductive biocompatible biomaterial to a subject in need thereof, wherein the conductive biocompatible biomaterial comprises a conductive polymer and a biocompatible component, wherein the conductive polymer comprises an aminomethoxybenzoic acid (AMBA) polymer.

[0010] In another aspect, there is provided a method of administration of a conductive biocompatible biomaterial to a neurological lesion comprising i) opening one or more

administration sites proximal to the lesion; ii) administering the conductive biocompatible biomaterial disclosed herein into the one or more administration sites; and iii) closing the one or more administration sites after the conductive biocompatible biomaterial has diffused across the lesion.

[0011] In another aspect, there is provided a conductive biocompatible biomaterial for use in treating a neurological lesion.

[0012] In yet another aspect, there is provided a use of a conductive biocompatible biomaterial for treating a neurological lesion in a subject.

[0013] Other features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the disclosure are given by way of illustration only, since various changes and modifications within the spirit and scope of the disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS:

[0014] For a better understanding of the embodiments described herein and to show more clearly how they may be carried into effect, reference will now be made, by way of example only, to the accompanying drawings which show at least one exemplary embodiment, and in which:

[0015] Figs 1A-1D are illustrations and images showing delivery of PAMB-G into injured rat spinal cord. (A) Overall flow of the study. (B) Diagram indicating the 4 locations at the spinal cord injury (SCI) site, in which a total of 10 µL biomaterial (either gelatin or PAMB-G) was injected 24 hours post-SCI: 2 caudally, and 2 dorsally from the SCI epicenter. MRI images of the spinal cord at 8 weeks post-clip compression SCI from both (C) axial (line indicates grey matter) and (D) sagittal views (arrow indicates SCI site).

[0016] Figs. 2A-2F are graphs and images showing PAMB-G reduces injury-associated astrogliosis and inflammatory reactions. Real-time qPCR (RT-qPCR) measurements of mRNA expression for (A) TNF-α and (B) MCP-1, among control, gelatin, and PAMB-G rat groups at 3 days post-SCI. Individual values were normalized to GAPDH. Representative micrographs of immunofluorescence staining, along with quantifications, for (C-D) Iba-1+ and (E-F) GFAP+ cells, representing microglia and reactive astrocytes, respectively, among the 3 groups, at 7 days post-SCI. Nuclei were stained with DAPI. Data represented as mean ±SD, n=3-6/group for (A-B), n=4/group for (D, F), *$p<0.05$, **$p<0.01$.

[0017] Figs 3A-3F are graphs and images showing PAMB-G lowers apoptosis and aids in tissue preservation post-SCI. (A-B) Representative micrographs of TUNEL staining with nuclei stained by DAPI, along with quantification of TUNEL+ among control, gelatin, and PAMB-G rat

groups at 1 week post-SCI. (C) Representative H&E staining of the SCI site for the 3 groups, at 8 weeks post-SCI. Measurements of the (D) cavity from H&E staining and (E-F) percentage of white matter from MRI at 8 weeks post-SCI among the 3 groups. Data represented as mean±SD, n=4/group for (B and D), n=3/group for (F), *p<0.05, **p<0.01.

[0018] Figs. 4A-4D are graphs and images showing PAMB-G upregulates neural growth factors and stimulates axonal regeneration. (A-B) Western blot images and quantification of GAP43 protein expression, associated with neuronal growth and regeneration, among the 3 groups, at 3 days post-SCI. (C-D) Representative micrograph of immunofluorescence staining for NF160, along with quantification of NF160+ cells, among the 3 groups, at 8 weeks post-SCI. Data represented as mean±SD, n=4/group for all experiments, *p<0.05, **p<0.01.

[0019] Figs. 5A-5F are graphs and diagrams showing PAMB-G facilitates the restoration of spinal cord electrical signaling. (A) Motor evoked potentials (MEPs) traces for control, gelatin, and PAMB-G rat groups, at 8 weeks post-SCI. (B) Quantification of peak MEP amplitudes among the 3 groups, before injury, immediately after clip compression SCI (Before injection), biomaterial (gelatin or PAMB-G) injection 24 h after SCI (Week 0), as well as 2 at 8 weeks post-SCI. (C) Latency period measurements for MEPs among the 3 groups, at the same time points as (B). An inverse correlation is present between the latency period and peak MEP amplitude, in which PAMB-G has the shortest latency period and the highest peak amplitude at the 8-week mark, indicating its ability to increase post-SCI conduction capability and velocity. (D) Arrangement of the flexible multi-electrode array (MEA) around the spinal cord section to measure field potentials. (E-F) MEA traces and field potential quantifications for the 3 groups, at 8 weeks post-SCI. Data represented as mean±SD, n=5/group for (B-C), n=6/group for (F), *p<0.05, **p<0.01.

[0020] Figs. 6A-6D are graphs and illustrations showing PAMB-G improves motor functions post-SCI. (A) Average scores from the 21-point Basso, Beattie and Bresnahan (BBB) open-field locomotor scoring system among the control, gelatin, and PAMB-G groups, taken each week for 8 weeks post-SCI. *p<0.05, **p<0.01 for Control vs. PAMB-G, #p<0.05, ##p<0.01 for Gelatin vs. PAMB-G. (B) Results from the inclined plane test, showing that the angles reached for the PAMB-G group was significantly higher than for the other 2 groups at 8 weeks post SCI. (C-D) Representative images and quantification of gastrocnemius muscle weight among the 3 groups, at 8 weeks post-SCI. Data represented as mean±SD, n=6/group for all experiments, *p<0.05, **p<0.01.

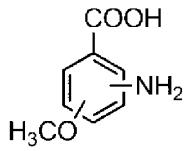
[0021] Fig. 7 is an illustration showing a conductive biomaterial poly-3-amino-4-methoxybenzoic acid-gelatin (PAMB-G) serves as a “bridge” across the injury site to restore electrical signaling conduction throughout the spinal cord, and subsequently the execution of motor functions.

DETAILED DESCRIPTION OF THE DISCLOSURE:

[0022] The following is a detailed description provided to aid those skilled in the art in practicing the present disclosure. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The terminology used in the description herein is for describing particular embodiments only and is not intended to be limiting of the disclosure. All publications, patent applications, patents, figures and other references mentioned herein are expressly incorporated by reference in their entirety.

I. Definitions

[0023] As used herein, the term "aminomethoxybenzoic acid" or "AMB" or "AMBA" means a compound represented by the formula:



(I)

as well as derivatives and mixtures thereof as well as salts of any of the foregoing. Examples of AMBA include 3-amino-4-methoxybenzoic acid (3-4-AMBA), 4-amino-2-methoxybenzoic acid (4-2-AMBA), 2-amino-4-methoxybenzoic acid (2-4-AMBA), 4-amino-3-methoxybenzoic acid (4-3-AMBA), 5-amino-2-methoxybenzoic acid (5-2-AMBA), derivatives thereof and mixtures thereof. AMBA can be synthesized using methods that are known in the art, and can be purchased for example from chemical companies such as Sigma Aldrich (MO).

[0024] The terms "PAMB", "AMBA polymer" and "AMBA based polymer" as used herein mean any polymer made using AMBA and encompass co-polymers. The polymer can be made entirely using AMBA, or it can be made using AMBA and one or more other component(s). In some embodiments the AMBA based polymer excludes co-polymers comprising aniline. In some embodiments, the AMBA base polymer is substantially comprising AMBA.

[0025] As used herein, the term "PAMB-G" refers to PAMB conjugated to gelatin. In such configuration, gelatin acts as the backbone of the biomaterial. PAMB may be covalently attached to the gelatin.

[0026] As used herein, the term "biocompatible" refers to an article that does not cause toxic or injurious effects on a biological system.

[0027] As used herein, the term "biomaterial" refers to a polymer composition, hydrogel or article that is for example for repairing, or augmenting any tissue, organ or function of the body and that can be used touching or within the body. The biomaterial can include an article in different physical forms, such as a solution, hydrogel, membrane, sponge, optionally a sheet, 3D-patch or

sponge or mesh for grafting. The biomaterial of the present disclosure can be used exclusively to form one of these articles or can be used as a component of one of these articles.

[0028] The term "conjugated" as used herein in reference to a first compound and a second compound means that the first compound is coupled to the second compound, optionally electrostatically and/or via a covalent bond. For example, the covalent bond may be through an amino group.

[0029] The term "amino group" as used herein means a —NH_2 group.

[0030] As used herein, the term "hydrogel" refers to a polymeric material, typically a network or matrix of polymer chains, capable of swelling in water or becoming swollen with water. A hydrogel can also be understood to be a material that retains water in an equilibrium state. The network or matrix may or may not be crosslinked.

[0031] As used herein, a "conductive polymer" means a polymer that is capable of electrical conductivity. For example, the conductivity of a conductive biomaterial can be about or at least 10^{-6} S/cm.

[0032] As used herein, a "biocompatible component" means or includes natural products, synthetic products or combinations thereof. In one embodiment, the biocompatible component can include a natural product, such as a linear or branched polysaccharide, protein or polypeptide. These biocompatible components can include for example chitosan, gelatin, collagen, fibronectin, elastin, alginate, and derivatives and combinations thereof. As a further example, the biocompatible component can include a synthetic product, such as a biodegradable synthetic polymer.

[0033] As used herein, the term "gelatin" also referred to as G in for example PAMB-G, refers to a polypeptide product derivative of collagen typically composed of a heterogeneous mixture of polypeptides, and includes Type A and Type B gelatin. Gelatin can for example, be obtained by acid treating collagen or heating collagen at a suitable temperature. Gelatin can be derived from mammalian collagen such as bovine, porcine or ovine collagen, as well as from marine collagen or avian collagen. Gelatin can be used, for example, as a sponge such as GELFOAM®.

[0034] The term "spinal cord injury" as used herein, includes damage to any part of the spinal cord or nerves in the spinal canal (cauda equina) and includes for example injuries resulting from damage to the vertebrae, ligaments or disks of the spinal column or to the spinal cord itself. The cause of the injury can be traumatic or non-traumatic. For example, the damage may be caused by motor vehicle accident, falls, violence, sporting or recreational activities as well as diseases such as cancer removal, osteoporosis, or inflammation of the spinal cord.

[0035] The term "subject", also referred to as patient, as used herein includes all members of the animal kingdom including mammals, and suitably refers to humans.

[0036] The terms “treat, “treatment”, “treating” and the like as used herein mean administering to a subject a therapeutically effective amount of a compound or composition, and may consist of a single administration, or alternatively comprise a series of administrations. As well understood in the art, “treatment” or "treating" is an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease or disorder, stabilized (i.e. not worsening) state of disease or disorder, preventing spread of disease or disorder, delay or slowing of disease or disorder progression, amelioration or palliation of the disease or disorder state, diminishment of the reoccurrence of disease or disorder, and remission (whether partial or total), whether detectable or undetectable. In the context of a neurological lesion, treating can include reducing post-lesion inflammation, reducing astrogliosis and/or reducing glial scar formation in a subject comprising the neurological lesion. As another example, a subject with spinal cord injury can be treated to reduce inflammation, reduce glial scar formation and/or restore (for example partially restore or improve) electrical conduction at the site of injury.

[0037] In understanding the scope of the present disclosure, the term "comprising" and its derivatives, as used herein, are intended to be open ended terms that specify the presence of the stated features, elements, components, groups, integers, and/or steps, but do not exclude the presence of other unstated features, elements, components, groups, integers and/or steps. The foregoing also applies to words having similar meanings such as the terms, "including", "having" and their derivatives.

[0038] All definitions, as defined and used herein, should be understood to control over dictionary definitions, definitions in documents incorporated by reference, and/or ordinary meanings of the defined terms.

[0039] All references, patents and patent applications disclosed herein are incorporated by reference with respect to the subject matter for which each is cited, which in some cases may encompass the entirety of the document.

[0040] All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

[0041] The term “consisting” and its derivatives, as used herein, are intended to be closed ended terms that specify the presence of stated features, elements, components, groups,

integers, and/or steps, and also exclude the presence of other unstated features, elements, components, groups, integers and/or steps.

[0042] Further, terms of degree such as "substantially", "about" and "approximately" as used herein mean a reasonable amount of deviation of the modified term such that the end result is not significantly changed. These terms of degree should be construed as including a deviation of at least ±5% of the modified term if this deviation would not negate the meaning of the word it modifies.

[0043] More specifically, the term “about” means plus or minus 0.1 to 20%, 5-20%, or 10-20%, 10%-15%, preferably 5-10%, most preferably about 5% of the number to which reference is being made.

[0044] As used in this specification and the appended claims, the singular forms “a”, “an” and “the” include plural references unless the content clearly dictates otherwise. Thus, for example, a composition containing “a compound” includes a mixture of two or more compounds. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise.

[0045] The definitions and embodiments described in particular sections are intended to be applicable to other embodiments herein described for which they are suitable as would be understood by a person skilled in the art.

[0046] The recitation of numerical ranges by endpoints herein includes all numbers and fractions subsumed within that range (e.g. 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.90, 4, and 5). It is also to be understood that all numbers and fractions thereof are presumed to be modified by the term "about."

[0047] As used herein, any values provided in a range of values include both the upper and lower bounds, and any values contained within the upper and lower bounds.

[0048] Further, the definitions and embodiments described in particular sections are intended to be applicable to other embodiments herein described for which they are suitable as would be under-stood by a person skilled in the art. For example, in the following passages, different aspects of the disclosure are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

[0049] Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, examples of methods and materials are now described.

II. Methods

[0050] Spinal cord injury (SCI) is a severe neurological disorder, leading to loss of voluntary and involuntary control of bodily functions below the injury site. SCI is currently an incurable, permanent condition, owing to the resulting inability of the patient to control bodily functions associated with regions below the injury site. This lack of control is due to the initial physical force, such as shearing, compression, and laceration, damaging the spinal cord neural tissue, as well as associated blood vessels, at the injury site [20]. This primary damage is then followed by ischemia, along with inflammatory and pro-apoptotic processes, such as inflammatory cytokine and reactive oxygen species production, as well as loss of calcium homeostasis, all of which contributes to astrocyte hypertrophy and neuronal cell death [20]. As a result of the hypertrophic astrocytes and neuron loss, glial scar tissue forms at the injury site, blocking electrical conduction between the remaining intact portions of the spinal cord and leading to the lack of bodily function control below the scar [20,21]. Current therapies include pharmacological intervention, surgical management and/or rehabilitation. These treatments enhance tissue repair, but are unable to repair or restore neural conductive function.

[0051] As demonstrated herein, injection of PAMB-G into the SCI site reduced post-SCI inflammatory reactions, in the form of lowered astrogliosis, microgliosis, and pro-inflammatory cytokine levels, such as TNF-α. This lowered inflammation was coupled with reduced neuronal apoptosis, both of which yielded increased preservation of remaining intact spinal cord tissue. Additionally, PAMB-G stimulated increased axonal and synapse regeneration. These regenerative processes most likely stem from the conductive properties of PAMB, which serve as a “bridge” across the SCI site, conducting signals throughout the organ and facilitating communication between the CNS and PNS. This restoration of signal conduction was reflected by improvements in bodily function control below the SCI site, particularly in regard to lower body locomotion.

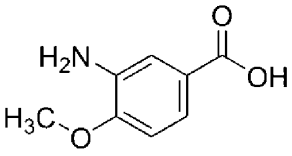
[0052] Accordingly, in one aspect, the present disclosure provides a method of treating a neurological lesion, the method comprises administering a conductive biocompatible biomaterial to a subject in need thereof, wherein the conductive biocompatible biomaterial comprises a conductive polymer and a biocompatible component, wherein the conductive polymer comprises an aminomethoxybenzoic acid (AMBA) polymer.

[0053] The conductive polymer can include benzoic acid based polymers, and mixtures or copolymers thereof. In particular, the conductive polymer can be or comprise an aminomethoxybenzoic acid (AMBA) based polymer.

[0054] In some embodiments, the aminomethoxybenzoic acid (AMBA) is 3-amino-4-methoxybenzoic acid (3-4-AMBA). In some embodiments, the aminomethoxybenzoic acid is 4-amino-2-methoxybenzoic acid (4-2-AMBA). In some embodiments, the aminomethoxybenzoic

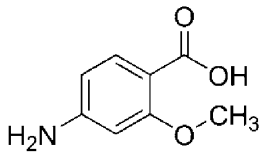
acid is 2-amino-4-methoxybenzoic acid (2-4-AMBA). In some embodiments, the aminomethoxybenzoic acid is 4-amino-3-methoxybenzoic acid (4-3-AMBA). In some embodiments, the aminomethoxybenzoic acid is 5-amino-2-methoxybenzoic acid (5-2-AMBA). AMBA can be synthesized through methodologies well known in the art from other substituted benzenes using, e.g., nucleophilic or electrophilic aromatic substitutions.

[0055] In some embodiments, the aminomethoxybenzoic acid includes:



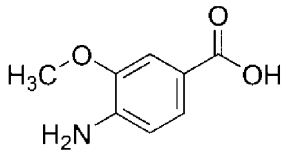
and salts thereof.

[0056] In some embodiments, the aminomethoxybenzoic acid includes:



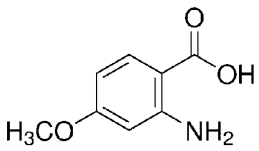
and salts thereof.

[0057] In some embodiments, the aminomethoxybenzoic acid includes:



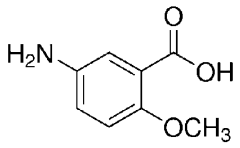
and salts thereof.

[0058] In some embodiments, the aminomethoxybenzoic acid includes:



and salts thereof.

[0059] In some embodiments, the aminomethoxybenzoic acid includes:



and salts thereof.

[0060] The conductive polymer can be linear or branched. In some embodiments, the molecular weight of the conductive polymer is greater than about 300 Daltons, or about 500 Daltons, or about 1,000 Daltons, or about 1,500 Daltons, or about 2,000 Daltons, or about 3,000 Daltons, or about 4,000 Daltons, or about 5,000 Daltons, or about 7,000 Daltons, or about 9,000 Daltons, or about 10,000 Daltons, or about 12,000 Daltons, or about 14,000 Daltons, or about 16,000 Daltons. In other embodiments, the molecular weight of the conductive polymer is less than about 200 Daltons, or about 500 Daltons, or about 1,000 Daltons, or about 1,500 Daltons, or about 2,000 Daltons, or about 3,000 Daltons, or about 4,000 Daltons, or about 5,000 Daltons, or about 7,000 Daltons, or about 9,000 Daltons, or about 10,000 Daltons, or about 12,000 Daltons, or about 14,000 Daltons, or about 16,000 Daltons, or about 18,500 Daltons. In still other embodiments, the molecular weight can be a range between any of these values (e.g., between about 200 Daltons and about 7,000 Daltons, or between about 50 Daltons and about 10,000 Daltons, etc.).

[0061] In an embodiment, the biocompatible component comprises a natural product, a synthetic product, and mixtures thereof.

[0062] In an embodiment, the biocompatible component is selected from gelatin, chitosan, collagen, fibronectin, elastin, alginate, and derivatives and mixtures thereof.

[0063] In one embodiment, the biocompatible component comprises or is gelatin. Gelatin is a derivative of collagen and is widely used in tissue engineering field for its biocompatibility and mechanical properties.

[0064] In another embodiment, the biocompatible component comprises a synthetic product, for example a biodegradable synthetic polymer.

[0065] The biocompatible component can have a molecular weight ranging from about 50,000 to about 150,000 Daltons optionally from about 50,000 Daltons to about 100, 000 Daltons. In some embodiments, the molecular weight is greater than about 50,000 Daltons, or about 60,000 Daltons, or about 70,000 Daltons, or about 80,000 Daltons, or about 90,000 Daltons or about 100,000 Daltons or about 110,000 Daltons, or about 120,000 Daltons, or about 130,000 Daltons. In other embodiments, the molecular weight of the biocompatible component is less than about 60,000 Daltons, or about 70,000 Daltons, or about 80,000 Daltons, or about 90,000 Daltons, or

about 100,000 Daltons, or about 110,000 Daltons, or about 120,000 Daltons or about 130,000 Daltons, or about 140,000 Daltons or about 150,000 Daltons.

[0066] The conductive polymer and the biocompatible component can be combined, for example by chemical conjugation, to form an electrically conductive biocompatible biomaterial. The molar ratio of the conductive polymer and biocompatible component in the biomaterial can range from 1000:1 to 1:1000, respectively. In some embodiments, the molar ratio of the conductive polymer and biocompatible component can be greater than about 1: 20, about 1: 15, about 1:10, about 1: 8, about 1:3, or about 1:2, or about 1:1, or about 2:1, or about 3:1, or about 5:1, or about 10:1, or about 25:1, or about 50:1, or about 100:1, or about 150:1, or about 200:1, or about 250:1, or about 300:1 or about 350:1 or about 400:1, or about 500:1. In other embodiments, the molar ratio of the conductive polymer and biocompatible component can be less than about 1:2, or about 1:1, or about 2:1, or about 3:1, or about 5:1, or about 10:1, or about 25:1, or about 50:1, or about 100:1, or about 150:1, or about 200:1, or about 250:1, or about 300:1 or about 350:1 or about 400:1, or about 500:1, or about 1000:1. In still other embodiments, the molar ratio of the conductive polymer and biocompatible component can be a range between any of these values (e.g., between 1:1 to 1:350, or between 1:3 to 1:150, or between 3:1 and 300:1, etc.). In one embodiment, the ratio is 2:1 to 1000:1. In one embodiment, the molar ratio is about 30:1 to about 60:1.

[0067] In some embodiments, the molecular weight of the biocompatible conductive biomaterial can range from about 50,000 to about 1,000,000 Daltons. In some embodiments, the molecular weight of the biomaterial is greater than about 50,000 Daltons, or about 60,000 Daltons or about 75,000 Daltons, or about 100,000 Daltons, or about 150,000 Daltons, or about 200,000 Daltons, or about 300,000 Daltons, or about 400,000 Daltons, or about 500,000 Daltons, or about 600,000 Daltons, or about 700,000 Daltons, or about 800,000 Daltons. In other embodiments, the molecular weight of the biocompatible conductive biomaterial is less than about or about 60,000 Daltons, or about 75,000 Daltons, or about 100,000 Daltons, or about 150,000 Daltons, or about 200,000 Daltons, or about 300,000 Daltons, or about 400,000 Daltons, or about 500,000 Daltons, or about 600,000 Daltons, or about 700,000 Daltons, or about 800,000 Daltons, or about 1,000,000 Daltons. In still other embodiments, the molecular weight of the biocompatible conductive biomaterial can be a range between any of these values (e.g., between about 50,000 Daltons and about 800,000 Daltons, or between about 150,000 Daltons and about 300,000 Daltons, etc.).

[0068] In one embodiment, the conductivity of the biocompatible conductive biomaterial is greater than, at least or equal to about 10^{-6} S/cm or greater than, at least or equal to about 10^{-5} S/cm. In some embodiments, the conductivity of the biocompatible conductive biomaterial is greater than, at least or equal to about 10^{-5} S/cm, or about 10^{-4} S/cm, or about 10^{-3} S/cm or about

10^{-2} S/cm. For example, the range may be from about 10^{-6} S/cm to about 10^{-2} S/cm, or to about 10^{-1} S/cm.

[0069] In an embodiment, the biocompatible conductive biomaterial has a conductivity of at least or greater than about 2-fold, at least or greater than about 3-fold, at least or greater than about 4-fold, at least or greater than about 5-fold, at least or greater than about 6-fold, at least or greater than about 7-fold, at least or greater than about 8-fold, at least or greater than about 9-fold, at least or greater than about 10-fold, at least or greater than about 11-fold, at least or greater than about 12-fold, at least or greater than about 13-fold, at least or greater than about 14-fold, at least or greater than about 15-fold or at least or greater than about or up to 20-fold or 25 fold greater than a control biocompatible biomaterial that does not comprise the conductive polymer.

[0070] The biocompatible conductive biomaterial can be prepared with other components. For example, an AMBA-gelatin sponge can comprise gelatin and other components such as other polypeptides. The biocompatible conductive biomaterial can for example be physically encompassed within a device such as a sponge, it can be crosslinked or covalently conjugated to the device, e.g. sponge.

[0071] In an embodiment, the biomaterial is a liquid solution, a hydrogel, a membrane, a 3D-patch or sponge, a sheet, or a mesh for grafting.

[0072] Methods for making the liquid solution or a hydrogel comprising AMBA-gelatin, are described in WO2019018942A1, the content of which is incorporated herein in its entirety. For example, the method can comprise combining AMBA (one or more different AMBAs) and gelatin, polymerizing the AMBA and gelatin to produce conjugated AMBA-gelatin (e.g. liquid solution), and optionally cross-linking the AMBA-gelatin or cooling the liquid solution to form the hydrogel.

[0073] AMBA can be conjugated to gelatin, for example, using ammonium persulfate (APS), the conjugated material being in liquid form. The conjugated material can have an even distribution of conductive polymers throughout the biomaterial.

[0074] The conjugated material in liquid form can be cross-linked, for example, using N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC) to cross-link the AMBA-gelatin solution into hydrogel. When using a gelatin sponge such as Gelfoam or other scaffold such as a mesh etc, APS can be used to conjugate AMBA to the gelatin sponge (or scaffold) and a crosslinking agent such as EDC is not necessary.

[0075] The biocompatible conductive biomaterial, for example, when a solution, can be crosslinked using a crosslinking agent to assist in hydrogel formation. For example, the AMBA-Gelatin polymers can be cross-linked to form the cross-linked hydrogel. The crosslinking agent can be a known crosslinking agent and contain electrophilic groups, nucleophilic groups, or both. The crosslinking agent can be a natural product or a synthetic product. Examples of multi-

functional crosslinking agents which may be used include, for example, EDC, N-Hydroxysuccinimide, gluteraldehyde, methylene-bis-acrylamide, diethylene glycol diacrylate, ethylene glycol diacrylate, triethylene glycol-bis-methacrylate, ethylene glycol-bis-methacrylate, ethylene glycol-dimethacrylate, bisacrylamide, triethyleneglycol-bis-acrylate, 3,3'-ethylidene-bis(N-vinyl-2-pyrrolidone), trimethylolpropate trimethacrylate, glycerol trimethacrylate, polyethylene glycol dimethacrylate, other polyacrylate and polymethacrylate esters, and mixtures thereof. In one embodiment, the crosslinking agent is EDC. In one embodiment, the crosslinking agent is genipin or tannic acid.

[0076] The ratio of crosslinking agent to biocompatible conductive biomaterial can be within the range of about 2:100,000 to about 5:1,000 by volume. The crosslinking agent can be added to the biomaterial just prior to introduction to the target location, for example, the spinal cord (e.g., 1-10 minutes prior to introduction). In some embodiments, it takes 1-10 minutes for the biomaterial to gel. During the gelling time, the biomaterial can be introduced to the target location, for example, the spinal cord.

[0077] In an embodiment, the hydrogel comprises an aminomethoxybenzoic acid (AMBA) polymer and gelatin. For example, the AMBA polymer can be conjugated to one or more amino groups of gelatin.

[0078] In an embodiment, the water content of the hydrogel is about 75 wt. % to about 95 wt. %. For example, the water content is about 80 wt. %. For example, the water content is about 82 wt. %. For example, the water content is about 85 wt. %. For example, the water content is about 90 wt. %.

[0079] In an embodiment, the conductive biocompatible biomaterial is administered into or onto a site of the injury. For example, the conductive biocompatible biomaterial can be administered by injection, for example to the injured site and/or the board-zone of the injured site.

[0080] The biocompatible conductive biomaterial (e.g.,hydrogel) can be introduced by known methods of treating biological tissue and organs with a hydrogel and similar materials. In an embodiment, the biomaterial is introduced by needle injection, optionally image guided needle injection, into or onto the site of the injury. In one embodiment, the biocompatible conductive biomaterial can be injected into or onto the spinal cord.

[0081] In one embodiment, the biocompatible conductive biomaterial is introduced (optionally needle injected) prior to solidification into or onto the affected area. The biomaterial subsequently solidifies (e.g. becomes gelled). In another embodiment, the biomaterial is introduced in a precast form, for example precast into fiber, sheet, graft 3D-patch or sponge, or mesh, and then implanted into the affected area.

[0082] The biocompatible conductive biomaterials can also be formed in sheet, or other articles such as a 3D-patch, which can be used on top of or to surround the injured tissue.

[0083] In one embodiment, the amount of the biocompatible conductive biomaterial (e.g., hydrogel) introduced to the tissue or organ can depend on a number of factors, such as the composition of the biomaterial, the location and the condition of the tissue or organ, the purpose for introducing the biomaterial, the size of the tissue or organ and/or the size of the damaged or area to be treated. In one embodiment, the volume of biomaterial can range from about 1 µl to about 10 mL, or about 2 µl to about 5 mL, or about 5 µl to about 3 mL, or about 10 µl to about 2 mL, or about 50 µl to about 1 mL, or about 100 µl to about 500 µl, or any combination of these values (e.g., about 1 mL to about 2 mL, etc).

[0084] As demonstrated herein, the conductive biocompatible biomaterial improves motor functions in a rat model of spinal cord injury, which is a severe neurological disorder. Not being bound by a theory, the conductive biocompatible biomaterial can serve as a “bridge” between the intact spinal cord sections, conducting signals throughout the organ and facilitating communication between the central nervous system and the peripheral nervous system. This restoration of signal conduction is reflected by improvements in bodily function control below the spinal cord injury site, particularly in regard to lower body locomotion. The biomaterial scaffolding can serve as “artificial axons” between the remaining living neurons on both sides of the injury site and conduct electrical signals to stimulate new axonal growth post-injury. Additionally, it is demonstrated herein that the conductive biocompatible biomaterial reduces inflammatory reactions post-spinal cord injury, in the form of lowered astrogliosis, microgliosis, and pro-inflammatory cytokine levels, such as TNF-α. The conductive biocompatible biomaterial also reduces neuronal apoptosis. Not being bound by a theory, reducing inflammation responses and neuronal apoptosis can increase preservation of remaining intact spinal cord tissue.

[0085] Accordingly, in an embodiment, the conductive biocompatible biomaterial is for restoring electrical conduction at the site of injury.

[0086] In another embodiment, the conductive biocompatible biomaterial is for increasing electrical conduction at the site of injury by at least or greater than about 2-fold, at least or greater than about 3-fold, at least or greater than about 4-fold, at least or greater than about 5-fold, at least or greater than about 6-fold, at least or greater than about 7-fold, at least or greater than about 8-fold, at least or greater than about 9-fold, or at least or greater than about 10-fold compared to an untreated control, optionally up to about 20-fold.

[0087] In an embodiment, the conductive biocompatible biomaterial is for stimulating axonal growth.

[0088] In an embodiment, the conductive biocompatible biomaterial is for reducing neuron apoptosis.

[0089] In an embodiment, the conductive biocompatible biomaterial is for, or the treating comprises, reducing inflammatory response (e.g. inflammation at or around the site of the neurological lesion).

[0090] In an embodiment, the conductive biocompatible biomaterial is for or the treating comprises reducing inflammation, reducing astrogliosis and/or reducing glial scar formation. For example, it is described herein that administration of PAMB-G post neurological lesion, reduces inflammation and astrogliosis in mice.

[0091] In an embodiment, reducing inflammatory response/inflammation comprises lowering pro-inflammatory cytokine expression, reducing reactive astrocyte number, and/or reducing microglial number.

[0092] As demonstrated herein, the conductive biocompatible biomaterial can be used to treat neurological lesions in a subject in need thereof. In an embodiment, the neurological lesion is caused by stroke. In an embodiment, the subject has a lesion causing a vision disorder. For example, echo guided local injection can be used to treat neuro-tissue lesion involved in a vision disorder or brain tissue with a lesion such as a scar.

[0093] In an embodiment, the neurological lesion is spinal cord injury.

[0094] The conductive biocompatible biomaterial can be introduced to the site of spinal cord injury by any suitable method. In an embodiment, the conductive biocompatible biomaterial is administered by injection caudally and/or dorsally from the spinal cord injury epicenter. In an embodiment, the conductive biocompatible biomaterial is administered by surgery as a membrane or a 3-D patch on the site of spinal cord injury. An example of preparing a 3-D patch is described in the Examples. The 3D patch can be similar to those used for heart repair. [39, 40]

[0095] In an embodiment, the conductive biocompatible biomaterial is administered or for use post-injury. In an embodiment, the conductive biocompatible biomaterial is administered or for use post-surgery for an injury.

[0096] Also provided is use of a composition and a composition for use with the methods disclosed herein. For example, also provided is a composition for use in treating a subject with a neurological lesion in need thereof.

[0097] While the present application has been described with reference to what are presently considered to be the preferred examples, it is to be understood that the application is not limited to the disclosed examples. To the contrary, the application is intended to cover various

modifications and equivalent arrangements included within the spirit and scope of the appended claims.

EXAMPLES

Example 1

Materials and Methods

Establishing the rat SCI model

[0098] Adult Sprague Dawley rats (Charles River) were used in the study, which were provided food and water ad libitum in a 12 h light/dark cycle. All procedures were approved by the Animal Care Committee of Toronto General Hospital, and were performed according to the Guide for the Care and Use of Laboratory Animals (NIH, 8th Edition, 2011). The surgical procedure was performed as described in previous studies, with minor modifications, in which rats were anesthetized under ventilation with 3% isoflurane [16-18]. All rats were placed on a 37°C heating pad, and laminectomies were performed at the level of T10 to expose the thoracic spinal cord segment, with the dura remaining intact. For the SCI rats, a cylinder weighted 20 g, with 0.05 cm^2 cross-sectional area, was dropped freely from 3 cm to compress the spinal cord at the T10 segment. Afterwards, all rats were randomly divided into the Control, Gelatin, and PAMB-G groups.

Synthesis and injection of the PAMB-G co-polymer

[0099] A 1:10 ratio for, respectively, 3-amino-4-methoxybenzoic acid (AMB) and gelatin, was used to generate injectable PAMB-G [15]. Two grams of gelatin powder was dissolved in 5 ml deionized (DI) water at 60ºC, followed by adding and mixing with 200 mg AMB (Alfa Aesar). Polymerization of the AMB monomers, and grafting the resulting polymer onto the gelatin backbone, was carried out by adding 273 mg ammonium persulfate ($(NH_4)_2S_2O_8$) powder, then maintaining the subsequent reaction for 24 h. This resulting mixture was placed into a dialysis bag, with 12-14 kDA molecular weight cut-off, for 10 h in DI water at 50ºC; afterwards, it was freeze-dried for 48-72 h. This freeze-dried PAMB-G was re-dissolved in 5 mL phosphate-buffered saline (PBS), adjusted for pH at physiological range (~7.4) with 10 M NaOH, which was followed by adding N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC, 22980, Thermo Fisher) cross-linker and N-hydroxysuccinimide (NHS, 130672, Sigma-Aldrich) to form a hydrogel. Injectable gelatin hydrogel was prepared by crosslinking 20% aqueous gelatin solution with EDC in the presence of NHS.

[00100] After hydrogel formation, either gelatin or PAMB-G was injected into rats immediately after SCI was induced. This injection occurred at 4 locations within the SCI site: 2 caudally, and 2 dorsally, from the epicentre of the injury site, and all 4 sites received, in total, 10 µL of gelatin or PAMB-G; control rats received saline injections instead. The injection rate was 0.5

μL/min, and at the end of injection, the needle was left in the cord for at least 1 min to allow diffusion from the injection site prior to closing the wound. Afterwards, all rats were placed in a bedding-free cage on top of a 37°C heating pad, before being returned to their regular cages. Bladders for all rats were manually extruded twice daily, until normal bladder function was restored.

MRI Imaging of the Spinal Cord

[00101] After SCI, the injured spinal cord was observed under MRI for up to 8 weeks, using a 7.0 T MRI scanner (Bruker, PharmaScan), with transmit volume and receive surface radiofrequency coils. The SCI site was scanned transversely, using T2w imaging, at 8 weeks post-injury to observe the grey-to-white matter ratio. Diffusion tensor imaging data were then processed and analyzed with MIPAV software.

Real-time qPCR (RT-qPCR) analysis

[00102] Rats from all 3 groups were sacrificed 3 days after injury, followed by removal of the spinal cord section with the SCI site. Total RNA was isolated and was used to prepare cDNA using NxGen M-MulV Reverse Transcriptase (Cat#: 30222-1, Lucigen). cDNA was analyzed for TNF-α, MCP-1, and GAPDH gene expression and normalized against GAPDH.

Western blot

[00103] Total protein was extracted from lesion site tissue by lysis buffer (50 mM Tris, 1% NP-40, 150 mM NaCl, 1 mM EDTA, 1 mM β-glycerolphosphate, pH 7.4) with protease and phosphatase inhibitors. Equal amounts of protein was loaded onto SDS-polyacrylamide gel and transferred to PVDF membranes. After blocking, membranes were incubated with the primary antibody for growth associated protein 43 (GAP43; Cat#: AB5220, Sigma) overnight at 4°C, followed by incubation with HRP-conjugated secondary antibodies, and signal detection using an enhanced ECL western blotting detection reagent. The density of the resulting bands was obtained by ImageJ software (NIH), and protein expression level was calculated relative to GAPDH (1:5000; Cat#: MAB374, Millipore) loading control.

Immunohistochemistry

[00104] Animals were perfused trans-cardially with 4% paraformaldehyde in 0.1M PBS. A 1.5 cm length of the spinal cord centered at the injury site was obtained, followed by fixation with 4% paraformaldehyde for 8 h at 4°C. The tissues were then cryo-protected in 30% sucrose, followed by embedding and snap-freezing of the spinal cord in OCT gel. A cryostat (CM3050S; Leica) was then used to cut the snap-frozen spinal cord transversely, yielding tissue sections with 10 μm thickness; these sections were then fixed with 4% paraformaldehyde in PBS for 20 min at room temperature, followed by permeabilization with 0.2% Triton X-100 in PBS, then blocked for 1 h in PBS containing 10% bovine serum albumin. They were then incubated with the following

primary antibodies overnight at 4°C: ionized calcium-binding adaptor molecule 1 (Iba-1; 1:200, Cat #: pa527436, Life Technology) for macrophages/microglia, glial fibrillary acidic protein (GFAP; 1:200, Cat #: G4546, Sigma) for astrocytes, and neuro-filament 160 (NF160; 1:400, Cat #: MAB5254, Sigma). Incubation with secondary antibody, either Alexa 488 (green) or Alexa 546 (red), was then carried out at room temperature for 1 h. Nuclei were identified with DAPI (Sigma). Images was obtained using a Nikon fluorescence microscope, and the numbers of positive nuclei were counted, and averaged from 4 or 5 field of views per slide with n=4 animals tested for each group.

TUNEL staining

[00105] Apoptotic cells within the SCI site were labelled by terminal deoxynucleotidyl-transferase dUTP nick end-labeling (TUNEL) staining, using the In Situ Cell Death Detection Kit, TMR Red (Sigma-Aldrich). Briefly, tissue sections were first incubated in permeabilization solution (0.1% Triton X-100 in 0.1% sodium citrate buffer), followed by incubation with the kit enzyme and labelling solution for 2 h at 37°C, according to the manufacturer's instructions. Afterwards, sections were incubated in DAPI (1:2000) for 5 min. The numbers of TUNEL-positive nuclei were quantified, as a percentage compared to the total number of DAPI-stained nuclei.

Motor evoked potential (MEP) and multi-electrode array (MEA) measurements

[00106] MEPs were measured immediately after compression SCI and biomaterial injection, as well as 2 and 8 weeks post-SCI. Rats were lightly anesthetized using isofluorane (<1%), and recordings were obtained from hind-limb gastrocnemius muscle, via inserting a pair of stainless steel subdermal needle electrodes, serving as the recording and stimulating electrodes, into the muscle, followed by placing a ground electrode under the skin between those 2 electrodes. Square pulse stimulation of 4 V, for 0.1 ms, at 0.2 Hz, was applied, and recordings were acquired by Powerlab (AD Instruments, Colorado Springs, Colorado). MEPs were acquired using transcranial electrical stimulation, in which 2 monopolar needle electrodes were inserted subcutaneously over the skull. The tip of the electrode serving as the cathode was placed in such a way that it touched the bone at the motor cortex area, while the electrode serving as the anode was placed at the base of the nose. The amplitude was measured as the difference between positive and negative peaks, while the latency was calculated as the time from the start of the stimulus to the appearance of the first prominent peak. MEA measurements were then carried out in vitro for all 3 groups, in which 200 mV of stimulation was provided with a stimulator (STG 4002, Multichannel Systems Reutlingen, Germany), with a recording area of 1.5 × 1.5 mm. The regional electrical field potential across the SCI scar area was then evaluated using Cardio 2D software.

Behavioural analyses using Basso-Beattie-Bresnahan (BBB) and slope test

[00107] Bodily functional recovery, in the form of locomotion, among the 3 rat groups was first assessed by 2 independent observers using the 21-point Basso, Beattie and Bresnahan (BBB) locomotor rating scale, from 0 to 8 weeks after SCI, in which 0 points represented the lack of any visible movement whatsoever, and 21 points the presence of a normal gait [19]. BBB was used to assess the extent of post-SCI hind-limb locomotor recovery, including joint movements, stepping ability, coordination and trunk stability. Testing was done every week within a 60 cm × 61.5 cm × 40 cm demarcated space, in which the rats were allowed to freely explore their surroundings within a 4 min period. BBB scores were averaged across both right and left hind-limbs to obtain a final motor recovery score for each week of testing.

[00108] Additionally, the inclined plane test was then carried out, in which the SCI rats were placed on a gridded slope, whose angle was able to be adjusted in 5° increments, to a maximum of 90°. Starting from 0°, the angle of the slope was increased every 5°, and the rats were observed after each increase to see whether they could stay on for at least 5 s before slipping off; the maximum angle of the slope the rats were able to stay on before slipping was thus measured.

Wet weight of bilateral gastrocnemius muscle

[00109] At 8 weeks, gastrocnemius muscles, as well as tibial shafts for both bilateral hind limbs were removed from rats for all 3 groups. These muscles and shafts were then measured to obtain the average wet weight of gastrocnemius muscle (g) and average tibia lengths (cm). The ratios between gastrocnemius muscle weights to tibia length were then calculated to determine the extent of atrophy and recovery in gastrocnemius muscle post-SCI.

Statistical Analyses

[00110] All data were expressed as mean ± standard deviation (SD) and analyzed by GraphPad Prism version 7.0 software (GraphPad software, San Diego, CA, USA). Comparisons between 3 or more groups were made using one-way analysis of variance (ANOVA) for single-factor variables, or two-way ANOVA for two-factor variables with repeated measurements over time, followed by Tukey's post-hoc tests. $p<0.05$ was considered statistically significant.

Example 2

PAMB-G delivery into injured rat spinal cord

[00111] PAMB-G or gelatin was injected into the injury site 1 day after compression SCI. Biochemical analyses were then conducted on days 3 and 7 after injection and examination of electrical and motor functions was performed weekly for up to 8 weeks (Figure 1A). Figure 1B depicts the injection into 4 locations: 2 caudally and 2 dorsally from the injury site epicentre, for a total volume of 10 µL. Under MRI, the injury site was found to be visible with respect to its effect on the spinal cord white matter (Figure 1C), as well as under sagittal view (Figure 1D). This

facilitated observations regarding the effects of the conductive biomaterial on spinal cord and subsequent bodily functional restoration.

Example 3

PAMB-G reduces SCI-associated astrogliosis and inflammatory reactions

[00112] Post-SCI inflammatory reactions and astrogliosis have been regarded as major contributors to glial scar formation, which is a major impediment against neuronal regeneration, and thus CNS-PNS signalling restoration. To determine whether PAMB-G had any effect on modulating astrocyte reactivity and inflammatory responses post-SCI, real-time qPCR and immunohistochemistry analyses were used to measure the expression levels of factors associated with inflammatory cells and reactive astrocytes. It was found that the expression levels for pro-inflammatory cytokines TNF-α and MCP-1 were significantly lower in PAMB-G-injected rats, compared to those controls injected with saline, at 3 days post-SCI (Figures 2A, 2B), thereby indicating a reduction in post-SCI inflammatory responses. This lowered inflammatory response was also associated with lowered inflammatory cell and reactive astrocyte numbers, as observed under immunofluorescence staining, in that the numbers of Iba-1$^+$ and GFAP$^+$ cells, associated respectively with microglia and reactive astrocytes, were significantly fewer at 7 days post-SCI for PAMB-G than for the other 2 groups (Figures 2C-2F). All of these findings suggest that PAMB-G reduced astrogliosis and inflammation occurrence, especially around the epicenter of the SCI site.

Example 4

PAMB-G reduces post-SCI neuron apoptosis and aids in neuronal tissue preservation

[00113] TUNEL staining was then used to determine short-term apoptotic occurrence at 1 week post-SCI, and significantly fewer TUNEL$^+$ cells were found in PAMB-G-injected rat spinal cords, compared to those injected with either saline control or gelatin (Figures 3A, 3B). To determine whether PAMB-G was able to maintain the remaining neuronal tissue post-injury on a macro-scale, as well as long-term, histological analysis of the spinal cord tissue around the injury site at 8 weeks post-SCI was performed. The cavity resulting from the SCI was found to be the smallest in PAMB-G-injected spinal cords, with that cavity being filled with the biomaterial and neuronal tissue. By contrast, a larger cavity, in the form of an “empty circle” within the spinal cord tissue section, was present among saline control and gelatin-injected spinal cords (Figures 3C, 3D). This increased neuronal tissue presence in the PAMB-G group was also supported by the finding of a greater percentage of white matter being present in PAMB-G-injected spinal cords, compared to the other 2 groups under MRI, indicating the presence of a greater number of both intact and possible newly-grown axons (Figures 3E, 3F). These observations thus indicate that PAMB-G reduces the onset of apoptosis, both within short (1 week) and long (8 week) term

duration, enabling neuronal tissue maintenance post-SCI to facilitate possible future regeneration and functional restoration.

Example 5

PAMB-G upregulates neural growth factors and stimulates axonal regeneration

[00114] The presence of an increased proportion of white matter among PAMB-G-injected spinal cords suggested that those rats had increased axonal growth, compared to those without PAMB-G. To further investigate this possibility, the expression levels of GAP43 protein, which is expressed by neuronal growth cones during the axonal regeneration process, as well as being associated with neuronal growth and synapse formation, was measured. Western blot analysis found that GAP43 levels at 3 days post-injury were significantly higher in the spinal cords injected with PAMB-G compared to those injected with either saline or gelatin, indicating rapid upregulation of factors favoring neuronal regeneration (Figures 4A, 4B). The presence of increased neuronal growth itself, on top of increased neuronal growth-associated markers, was also demonstrated through immunostaining for NF160, where the cell count for $NF160^+$ cells across a distal cross section was significantly higher for PAMB-G-injected spinal cords, compared to the other 2 groups (Figures 4C, 4D). Taken together, all this evidence therefore indicates that PAMB-G fostered neuronal growth and regeneration post-SCI.

Example 6

PAMB-G facilitates spinal cord electrical signaling restoration post-injury

[00115] The increased axonal regeneration observed for PAMB-G-injected rat spinal cords suggested that PAMB-G may also increase electrical signaling conduction in the aftermath of SCI. To investigate this possibility, the MEPs among all 3 groups were measured. All groups demonstrated a biphasic deflection pattern and PAMB-G-injected rats had the highest peak amplitude compared to those injected with saline control or gelatin from 2-8 weeks post-injury (Figures 5A, 5B). Therefore, the PAMB-G group had the highest conduction capability, which was coupled with those rats having the shortest latency period compared to saline control or gelatin groups during that period (Figure 5C). Latency period length has been found to be inversely correlated with conduction velocity, where shorter lengths are associated with higher velocities, meaning that PAMB-G group yielded the highest conduction capabilities and velocities post-SCI at the end of the 8 week period (Figure 5C).

[00116] The flexible MEA apparatus was used for field potential measurement across the spinal cord (Figure 5D), in which PAMB-G group also has significantly higher post-SCI field potentials compared to the other 2 groups (Figures 5E, 5F). Without wishing to be bound to theory, the evidence supports the idea that the conductive properties of PAMB-G, along with its stimulation of axonal regeneration from remaining intact neurons, facilitates the formation of a

"conductive bridge" across the SCI-caused lesion, allowing the restoration of electrical conduction throughout the spinal cord, and thus between CNS and PNS for possibly regaining bodily functional control.

Example 7

PAMB-G improves the execution of post-injury motor functions

[00117] To examine the effects of PAMB-G on rat motor functions, a number of behavioral assays were utilized. The extent of rat hind-limb locomotive behavior was judged according to the 21-point BBB open-field locomotor scoring system and average scores for the 3 rat groups taken weekly over the course of 8 weeks post-injury. Under the BBB system, the PAMB-G group had the highest degree of hind-limb locomotive behavioral recovery over the 8-week period, reaching a score of ~15 out of 21 points, compared to ~10 out of 21 for the other 2 groups (Figure 6A). Furthermore, inclined plane test results showed that at the end of the 8 week period, PAMB-G-injected rats were able to stay on the inclined plane at significantly steeper angles, compared to that of control and gelatin-injected rats (Figure 6B). This CNS-PNS connectivity restoration via PAMB-G serving as a spinal cord "bridge", through its conductive properties, was further confirmed by gastrocnemius muscle wet weight measurements. It has been previously noted that the gastrocnemius muscle loses weight after SCI, owing to atrophy associated with the loss of electrical signaling from the CNS, and subsequently, the PNS. Based on these findings, it was observed that the PAMB-G group had significantly higher gastrocnemius muscle-to-tibia length ratios, compared to the other 2 groups, indicating that PAMB-G aids in alleviating post-SCI muscle atrophy by restoring electrical signaling from the CNS to the PNS, and in turn, PNS-controlled muscles like the gastrocnemius (Figures 6C, 6D).

Example 8

Preparation of Conductive Patch

[00118] The conductive patch can be prepared by conjugating the PAMB conductive polymer onto the backbone of gelatin that is present in a commercially available Gelfoam, using an oxidative polymerization process. AMB are dissolved in 10 mL deionized water in the presence of an oxidative catalyst (ammonium persulfate; same mole ratio as AMB) at 40°C. Gelfoam are immersed in the solution and then reacted for 12 h at 40°C. The resulting PAMB-Gel patches are then thoroughly washed in phosphate buffered saline and then are used.

[00119] The conductive patch can be used for example for spinal cord injuries.

[00120] All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety. Specifically, the sequences associated with each accession numbers provided herein

including for example accession numbers and/or biomarker sequences (e.g. protein and/or nucleic acid) provided in the Tables or elsewhere, are incorporated by reference in its entirely.

[00121] 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.

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CLAIMS:

1. A method of treating a neurological lesion, the method comprising administering a conductive biocompatible biomaterial to a subject in need thereof, wherein the conductive biocompatible biomaterial comprises a conductive polymer and a biocompatible component, wherein the conductive polymer comprises an aminomethoxybenzoic acid (AMBA) polymer.

2. The method of claim 1, wherein the AMBA is selected from 3-amino-4-methoxybenzoic acid (3-4-AMBA), 4-amino-2-methoxybenzoic acid (4-2-AMBA), 4-amino-3-methoxybenzoic acid (4-3-AMBA), 2-amino-5-methoxybenzoic acid (2-5-AMBA), and 2-amino-4-methoxybenzoic acid (2-4-AMBA), and mixtures thereof.

3. The method of claim 1 or 2, wherein the biocompatible component is selected from gelatin, chitosan, collagen, fibronectin, elastin, alginate, and derivatives and mixtures thereof or wherein the biocompatible component comprises a synthetic product, optionally a biodegradable synthetic polymer.

4. The method of claim 3, wherein the biocompatible component is or comprises gelatin.

5. The method of any one of claims 1-4, wherein the conductive polymer is covalently conjugated to the biocompatible component.

6. The method of any one of claims 1-5, wherein the conductive biocompatible biomaterial is a liquid solution, a hydrogel, a membrane, a 3D-patch or sponge, a sheet, or a mesh for grafting.

7. The method of any one of claims 1-6, wherein the conductive biocompatible biomaterial is a hydrogel, optionally wherein the hydrogel is crosslinked.

8. The method of any one of claims 1-7, wherein the conductive biocompatible biomaterial has a conductivity of least or greater than about 10^{-6} or at least or greater than about 10^{-5} S/cm, or of at least or greater than about 10^{-4} S/cm or least or greater than about 10^{-3} S/cm or least or greater than about 10^{-2} S/cm.

9. The method of any one of claims 1-8, wherein the conductive biocompatible biomaterial has a conductivity of at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, or at least 10-fold greater than a control biocompatible biomaterial that does not comprise the conductive polymer.

10. The method of any one of claims 1-9, wherein the molar ratio of the conductive polymer and the biocompatible component is about 30:1 to about 60:1.

11. The method of any one of claims 1-10, wherein the conductive biocompatible biomaterial is a hydrogel comprising an aminomethoxybenzoic acid (AMBA) polymer and gelatin.

12. The method of claim 11, wherein the AMBA polymer is conjugated to one or more amino groups of the gelatin.

13. The method of claim 11 or 12, wherein the hydrogel has a water content of about 80 wt. % to about 90 wt. % of the hydrogel.

14. The method of any one of claims 1-13, wherein the conductive biocompatible biomaterial is administered into, proximal to, and/or onto a site of injury, optionally a board-zone of the injured site.

15. The method of claim 14, wherein the conductive biocompatible biomaterial is for increasing electrical conduction at the site of injury by at least or greater than about 2-fold, at least or greater than about 3-fold, at least or greater than about 4-fold, at least or greater than about 5-fold, at least or greater than about 6-fold, at least or greater than about 7-fold, at least or greater than about 8-fold, at least or greater than about 9-fold, or at least or greater than about 10-fold compared to an untreated control, optionally up to about 20-fold.

16. The method of claim 14 or 15, wherein the conductive biocompatible biomaterial is for restoring electrical conduction at the site of injury.

17. The method of any one of claims 14-16, wherein the conductive biocompatible biomaterial is for or the treating comprises reducing neuron apoptosis.

18. The method of any one of claims 14-17, wherein the conductive biocompatible biomaterial is for or the treating comprises stimulating axonal growth.

19. The method of any one of claims 14-18, wherein the conductive biocompatible biomaterial is for or the treating comprises reducing an inflammatory response, reducing astrogliosis and/or reducing glial scar formation.

20. The method of claim 19, where reducing the inflammatory response comprises lowering pro-inflammatory cytokine expression, reducing reactive astrocyte number, and/or reducing microglial number.

21. The method of any one of claims 1-20, wherein the conductive biocompatible biomaterial is a liquid solution or a hydrogel, wherein the conductive biocompatible biomaterial is administered by injection.

22. The method of any one of claims 1-21, wherein the neurological lesion is caused by stroke.

23. The method of any one of claims 1-21, wherein the subject has a lesion causing a vision disorder.

24. The method of any one of claims 1-21, wherein the neurological lesion is spinal cord injury.

25. The method of claim 24, wherein the conductive biocompatible biomaterial is a liquid solution or a hydrogel, wherein the conductive biocompatible biomaterial is administered by injection caudally and/or dorsally from the spinal cord injury epicenter.

26. The method of claim 24, wherein the conductive biocompatible biomaterial is a membrane or a patch, wherein the conductive biocompatible biomaterial is administered by surgery on the site of spinal cord injury.

27. A method of administration of a conductive biocompatible biomaterial to a neurological lesion comprising

i) opening one or more administration sites proximal to the lesion;

ii) administering the conductive biocompatible biomaterial as defined in any one of claims 1-24 into the one or more administration sites; and

iii) closing the one or more administration sites after the conductive biocompatible biomaterial has diffused across the lesion.

28. A conductive biocompatible biomaterial as defined in any one of claims 1-26 for use in treating a neurological lesion.

29. Use of a conductive biocompatible biomaterial as defined in any one of claims 1-26 for treating a neurological lesion in a subject in need thereof or for the manufacture of a preparation for treating a neurological lesion.