(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 October 2010 (21.10.2010)

PCT

(10) International Publication Number
WO 2010/121023 A2

(51) International Patent Classification:
A61K 38/10 (2006.01) *G01N 33/52* (2006.01)
C07K 7/08 (2006.01) *G01N 33/68* (2006.01)
C12N 15/115 (2010.01) *A61P 25/00* (2006.01)

(21) International Application Number:
PCT/US2010/031231

(22) International Filing Date:
15 April 2010 (15.04.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/169,626 15 April 2009 (15.04.2009) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

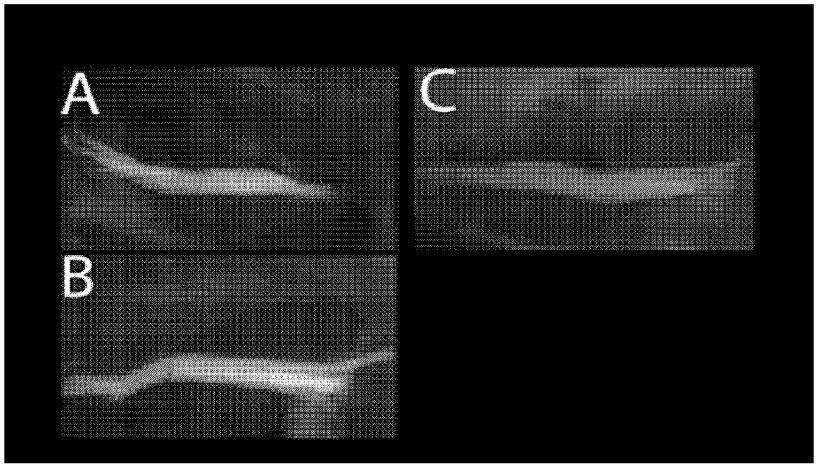
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) **Title**: PEPTIDES AND APTAMERS FOR TARGETING OF NEURON OR NERVES

Figure 1



(57) **Abstract**: The present invention provides methods for guiding preservation of neurons or nerves during surgery by administering a fluorescently-labeled peptide or aptamer that specifically binds to the neurons or nerves. The invention further provides targeting molecules of fluorescently-labeled peptides or aptamers that specifically bind to neurons or nerves and for compositions thereof.

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PEPTIDES AND APTAMERS FOR TARGETING OF NEURON OR NERVES

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Serial No. 61/169,626, filed April 15, 2009, the disclosure of which is incorporated herein by reference in its entirety for all purposes.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with Government Support under NIH Grant Nos. NS27177 and K08 EB008122-01. The Government has certain rights in the invention.

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

[0003] NOT APPLICABLE

BACKGROUND OF THE INVENTION

[0004] The central nervous system (CNS) consists of the brain and the spinal cord, as well as the retina.

[0005] The peripheral nervous system (PNS) extends outside the CNS. The PNS is divided into the somatic nervous system and the autonomic nervous system.

[0006] A neuron is an electrically excitable cell that processes and transmits information by electrical and chemical signaling. A typical neuron possesses a cell body (often called the soma), dendrites, and an axon.

[0007] A nerve is an enclosed, cable-like bundle of neural axons. Each nerve is a cordlike structure that contains many axons.

[0008] Each axon is surrounded by a layer of tissue called the endoneurium. The axons are bundled together into groups called fascicles, and each fascicle is wrapped in a layer of tissue called the perineurium. The neuron or nerve is wrapped in a layer of tissue called the epineurium.

BRIEF SUMMARY OF THE INVENTION

[0009] Disclosed herein, in certain embodiments, are targeting molecules comprising a peptide or aptamer that specifically binds to a neuron, nerve, or component of either. In some embodiments, the peptide is selected from: AHHNSWKAKHHS (SEQ ID NO:1), TYTDWLNFWAWP (SEQ ID NO:2), KSLSRHDHIHHH (SEQ ID NO:3), NTQTLAKAPEHT (SEQ ID NO:4), DFTKTSPLGIH (SEQ ID NO:5), LTPIPLPTPKPP (SEQ ID NO:6), VSTMPMSNMNGP (SEQ ID NO:7), GIFERNFGAMLH(SEQ ID NO:8), ACLREYHNWC (SEQ ID NO:9), MHRQPIAPVSSL(SEQ ID NO:10), SFADPLLFLAPP (SEQ ID NO:11), ASAHHMFTPGFD (SEQ ID NO:12), VAPTKAPLHSPS (SEQ ID NO:13), NNLKTGTSAPTG (SEQ ID NO:14), HKTAQWPFIAFR (SEQ ID NO:15), RLTNAPAYQAPA (SEQ ID NO:16), MQNPLNGKPGR (SEQ ID NO:17), THYSRSLTDGTR(SEQ ID NO:18), FSTSNNQSSPAI (SEQ ID NO:19), YPSPNRPPNLTN(SEQ ID NO:20), DIANPPPPPLYV (SEQ ID NO:21), ALQTDGPFAESA (SEQ ID NO:22), DNAQHSERFPVP (SEQ ID NO:23), and IPPTFPDRIRAPG (SEQ ID NO:24). In some embodiments, the targeting molecule further comprises a drug. In some embodiments, the targeting molecule further comprises a drug selected from: an antihistamine, a GABA receptor modulator, a neurotransmitter reuptake inhibitor, a local anesthetic, an anticholinergic, a sodium channel blocker, a calcium channel blocker, a thyrotropin-releasing hormone, a γ-secretase inhibitor, an AMPA receptor agonist or antagonist, an NMDA receptor agonist or antagonist, an mGlu receptor agonist or antagonist, a growth factor, an antiemetic agent, a corticosteroid; a cytotoxic agent; an antioxidant, an iron chelator, a mitochondrial modulator, a sirtuin modulator, a nitric oxide (NO) and/or nitric oxide synthase (NOS) modulator, a potassium channel agonist or antagonist, a purigenic receptor agonist or antagonist, or a combination thereof. In some embodiments, the targeting molecule further comprises a drug selected from: benzocaine; carticaine; cinchocaine; cyclomethycaine; lidocaine; prilocaine; propxycaine; proparacaine; tetracaine; tocainide; and trimecaine; methotrexate; cyclophosphamide; thalidomide; paclitaxel; pemetrexed; pentostatin; pipobroman; pixantrone; plicamycin; procarbazine; raltitrexed; rebeccamycin; rubitecan; SN-38; salinosporamide A; satraplatin; streptozotocin;

swainsonine; tariquidar; taxane; tegafur-uracil; temozolomide; testolactone; thioTEPA; tioguanine; topotecan; trabectedin; tretinoin; triplatin tetranitrate; tris(2-chloroethyl)amine; troxacitabine; uracil mustard; valrubicin; vinblastine; vincristine; vinorelbine; vorinostat; zosuquidar; carbamazepine; oxcarbazepine; phenytein; valproic acid; sodium valproate; cinnarizine; flunarizine; nimodipine; brain-derived neurotrophic factor (BDNF); ciliary neurotrophic factor (CNTF); glial cell-line derived neurotrophic factor (GDNF); neurotrophin-3; neurotrophin-4; fibroblast growth factor (FGF) receptor; insulin-like growth factor (IGF); or a combination thereof. In some embodiments, the targeting molecule further comprises a fluorescent moiety. In some embodiments, the targeting molecule further comprises a fluorescent moiety selected from: a fluorescent protein, a fluorescent peptide, a fluorescent dye, or a combination thereof. In some embodiments, the targeting molecule further comprises a fluorescent moiety selected from: a xanthene; a bimane; a coumarin; an aromatic amines; a benzofuran; a fluorescent cyanine; a carbazole; a dicyanomethylene pyrane; polymethine; oxabenzanthrane; pyrylium; carbostyl; perylene; acridone; quinacridone; rubrene; anthracene; coronene; phenanthrecene; pyrene; butadiene; stilbene; porphyrin; pthalocyanine; lanthanide metal chelate complexes; rare-earth metal chelate complexes; and derivatives thereof. In some embodiments, the targeting molecule further comprises a fluorescent moiety selected from: 5-carboxyfluorescein; fluorescein-5-isothiocyanate; 6-carboxyfluorescein; tetramethylrhodamine-6-isothiocyanate; 5-carboxytetramethylrhodamine; 5-carboxy rhodol derivatives; tetramethyl and tetraethyl rhodamine; diphenyldimethyl and diphenyldiethyl rhodamine; dinaphthyl rhodamine; rhodamine 101 sulfonyl chloride; Cy3, Cy3B, Cy3.5, Cy5, Cy5.5, Cy 7, indocyanine green, IR800CW or combinations thereof.

[0010] Disclosed herein, in certain embodiments, are methods of identifying a neuron or nerve, comprising contacting a neuron or nerve with a targeting molecule comprising (a) a peptide or an aptamer that specifically binds to a neuron, nerve, or component of either, and (b) a fluorescent moiety. In some embodiments, the peptide is selected from: AHHNSWKAKHHS (SEQ ID NO:1), TYTDWLNFWAWP (SEQ ID NO:2), KSLSRHDHIHHH (SEQ ID NO:3), NTQTLAKAPEHT (SEQ ID NO:4), DFTKTSPLGIH (SEQ ID NO:5), LTPIPLPTPKPP (SEQ ID NO:6), VSTMPMSNMNGP (SEQ ID NO:7), GIFERNFGAMLH (SEQ ID NO:8), ACLREYHNWC (SEQ ID NO:9), MHRQPIAPVSSL (SEQ ID NO:10), SFADPLLFLAPP (SEQ ID NO:11), ASAHHMFTPGFD (SEQ ID NO:12), VAPTKAPLHSPS (SEQ ID NO:13), NNLKTGTSAPTG (SEQ ID NO:14), HKTAQWPFIAFR (SEQ ID NO:15), RLTNAPAYQAPA (SEQ ID NO:16),

MQNPLNGKPGR (SEQ ID NO:17), THYSRSLTDGTR (SEQ ID NO:18), FSTSNNQSSPAI(SEQ ID NO:19), YPSPNRPPNLTN (SEQ ID NO:20), DIANPPPPPLYV (SEQ ID NO:21), ALQTDGPFAESA (SEQ ID NO:22), DNAQHSERFPVP (SEQ ID NO:23), and IPPTFPDRIRAPG (SEQ ID NO:24). In some embodiments, the fluorescent moiety is selected from: a fluorescent protein, a fluorescent peptide, a fluorescent dye, or a combination thereof. In some embodiments, the fluorescent moiety is selected from: a xanthene; a bimane; a coumarin; an aromatic amines; a benzofuran; a fluorescent cyanine; a carbazole; a dicyanomethylene pyrane; polymethine; oxabenzanthrane; pyrylium; carbostyl; perylene; acridone; quinacridone; rubrene; anthracene; coronene; phenanthrecene; pyrene; butadiene; stilbene; porphyrin; pthalocyanine; lanthanide metal chelate complexes; rare-earth metal chelate complexes; and derivatives thereof. In some embodiments, the fluorescent moiety is selected from: 5-carboxyfluorescein; fluorescein-5-isothiocyanate; 6-carboxyfluorescein; tetramethylrhodamine-6-isothiocyanate; 5-carboxytetramethylrhodamine; 5-carboxy rhodol derivatives; tetramethyl and tetraethyl rhodamine; diphenyldimethyl and diphenyldiethyl rhodamine; dinaphthyl rhodamine; rhodamine 101 sulfonyl chloride; Cy3, Cy3B, Cy3.5, Cy5, Cy5.5, Cy 7, indocyanine green, IR800CW or combinations thereof.

[0011] Disclosed herein, in certain embodiments, are methods of delivering a drug to a neuron or nerve, comprising contacting a neuron or nerve with a targeting molecule comprising (a) a peptide or an aptamer that specifically binds to a neuron, nerve, or component of either, and (b) a drug. In some embodiments, the peptide is selected from: AHHNSWKAKHHS (SEQ ID NO:1), TYTDWLNFWAWP (SEQ ID NO:2), KSLSRHDHIHHH (SEQ ID NO:3), NTQTLAKAPEHT (SEQ ID NO:4), DFTKTSPLGIH (SEQ ID NO:5), LTPIPLPTPKPP (SEQ ID NO:6), VSTMPMSNMNGP (SEQ ID NO:7), GIFERNFGAMLH (SEQ ID NO:8), ACLREYHNWC (SEQ ID NO:9), MHRQPIAPVSSL (SEQ ID NO:10), SFADPLLFLAPP (SEQ ID NO:11), ASAHHMFTPGFD (SEQ ID NO:12), VAPTKAPLHSPS (SEQ ID NO:13), NNLKTGTSAPTG (SEQ ID NO:14), HKTAQWPFIAFR (SEQ ID NO:15), RLTNAPAYQAPA (SEQ ID NO:16), MQNPLNGKPGR (SEQ ID NO:17), THYSRSLTDGTR (SEQ ID NO:18), FSTSNNQSSPAI (SEQ ID NO:19), YPSPNRPPNLTN (SEQ ID NO:20), DIANPPPPPLYV (SEQ ID NO:21), ALQTDGPFAESA (SEQ ID NO:22), DNAQHSERFPVP (SEQ ID NO:23), and IPPTFPDRIRAPG (SEQ ID NO:24). In some embodiments, the drug is selected from: an antihistamine, a GABA receptor modulator, a neurotransmitter reuptake inhibitor, a local anesthetic, an anticholinergic, a sodium channel blocker, a calcium channel blocker, a

thyrotropin-releasing hormone, a γ-secretase inhibitor, an AMPA receptor agonist or antagonist, an NMDA receptor agonist or antagonist, an mGlu receptor agonist or antagonist, a growth factor, an antiemetic agent, a corticosteroid; a cytotoxic agent; an antioxidant, an iron chelator, a mitochondrial modulator, a sirtuin modulator, a nitric oxide (NO) and/or nitric oxide synthase (NOS) modulator, a potassium channel agonist or antagonist, a purigenic receptor agonist or antagonist, or a combination thereof. In some embodiments, the drug is selected from: benzocaine; carticaine; cinchocaine; cyclomethycaine; lidocaine; prilocaine; propxycaine; proparacaine; tetracaine; tocainide; and trimecaine; methotrexate; cyclophosphamide; thalidomide; paclitaxel; pemetrexed; pentostatin; pipobroman; pixantrone; plicamycin; procarbazine; raltitrexed; rebeccamycin; rubitecan; SN-38; salinosporamide A; satraplatin; streptozotocin; swainsonine; tariquidar; taxane; tegafur-uracil; temozolomide; testolactone; thioTEPA; tioguanine; topotecan; trabectedin; tretinoin; triplatin tetranitrate; tris(2-chloroethyl)amine; troxacitabine; uracil mustard; valrubicin; vinblastine; vincristine; vinorelbine; vorinostat; zosuquidar; carbamazepine; oxcarbazepine; phenytein; valproic acid; sodium valproate; cinnarizine; flunarizine; nimodipine; brain-derived neurotrophic factor (BDNF); ciliary neurotrophic factor (CNTF); glial cell-line derived neurotrophic factor (GDNF); neurotrophin-3; neurotrophin-4; fibroblast growth factor (FGF) receptor; insulin-like growth factor (IGF); or a combination thereof.

[0012] Disclosed herein, in certain embodiments, are pharmaceutical compositions comprising: (a) a peptide or aptamer that specifically binds to a neuron, nerve, or component of either, and (b) a pharmaceutically acceptable excipient. In some embodiments, the peptide is selected from: AHHNSWKAKHHS (SEQ ID NO:1), TYTDWLNFWAWP (SEQ ID NO:2), KSLSRHDHIHHH (SEQ ID NO:3), NTQTLAKAPEHT (SEQ ID NO:4), DFTKTSPLGIH (SEQ ID NO:5), LTPIPLPTPKPP (SEQ ID NO:6), VSTMPMSNMNGP (SEQ ID NO:7), GIFERNFGAMLH (SEQ ID NO:8), ACLREYHNWC (SEQ ID NO:9), MHRQPIAPVSSL (SEQ ID NO:10), SFADPLLFLAPP (SEQ ID NO:11), ASAHHMFTPGFD (SEQ ID NO:12), VAPTKAPLHSPS (SEQ ID NO:13), NNLKTGTSAPTG (SEQ ID NO:14), HKTAQWPFIAFR (SEQ ID NO:15), RLTNAPAYQAPA (SEQ ID NO:16), MQNPLNGKPGR (SEQ ID NO:17), THYSRSLTDGTR (SEQ ID NO:18), FSTSNNQSSPAI (SEQ ID NO:19), YPSPNRPPNLTN (SEQ ID NO:20), DIANPPPPPLYV (SEQ ID NO:21), ALQTDGPFAESA (SEQ ID NO:22), DNAQHSERFPVP (SEQ ID NO:23), and IPPTFPDRIRAPG (SEQ ID NO:24). In some embodiments, the peptide or aptamer is bound to a drug. In some embodiments, the peptide or aptamer is bound to a fluorescent moiety.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] Figure 1. Peptide labeling of nerves. Fluorescence images of exposed sciatic nerves in living wild-type mice following administration of (A-B) acetyl-SHSNTQTLAKAPEHTGK(5,6FAM)-amide ("FAM-SEQ ID NO:4") derived from the *ex vivo* screen or (C) a control peptide acetyl-SHSSTARDLWPHGKEGK(5,6FAM)-amide ("FAM-NP43"). K(5,6FAM)-amide is the N^{ε}-[fluorescein-5(6)-carbonyl]-lysinamide at the C-terminus.

[0014] Figure 2. Nerve binding affinity of FAM-labeled peptides. A-F. Fluorescence images of exposed sciatic nerves in living mice following administration of (A) acetyl-SHSAHHNSWKAKHHSGK(5,6FAM)-amide ("FAM-SEQ ID NO:1"); (B) acetyl-SHSTYTDWLNFWAWPGK(5,6FAM)-amide ("FAM-SEQ ID NO:2"); (C) FAM-NP43; (D) acetyl-SHSKSLSRHDHIHHHGK(5,6FAM)-amide ("FAM-SEQ ID NO:3"); (E) FAM-SEQ ID NO:4; and (F) acetyl-SHSDFTKTSPLGIHGK(5,6FAM)-amide ("FAM-SEQ ID NO:5"). G-I. Systemic survey of nerves labeled in animals injected with FAM-SEQ ID NO:4, including (G) facial nerve; (H) brachial plexus; and (I) sciatic nerve.

[0015] Figure 3. Time course of FAM-SEQ ID NO:4 binding to nerve tissue. Fluorescence images of sciatic nerves and surrounding non-nerve tissue in living mice (A) prior to intravenous administration of FAM-SEQ ID NO:4; (B) 15 seconds post-injection; (C) 10 minutes post-injection; (D) 1 hr post-injection; (E) 3.5 hrs post-injection; and (F) 5.5 hrs post-injection.

[0016] Figure 4. Time course and dose response of FAM-SEQ ID NO:4 binding to nerve and non-nerve tissue. A. Amount of fluorescence uptake in nerve and non-nerve tissue in living mice was determined from the time of intravenous injection of FAM-SEQ ID NO:4 to 300 minutes post-injection. The half-life of nerve fluorescence was approximately 50 minutes, while the half-life of muscle fluorescence was approximately 20 minutes. B. Serum fluorescence was quantified from the time of intravenous injection to 2 hrs post-injection, measured as percentage of initial fluorescence. The half-life of serum fluorescence was approximately 10 minutes. C. Ratio of nerve fluorescence to muscle fluorescence was calculated from the time of intravenous injection to about 300 minutes post-injection. D. The dose response of peptide binding to nerve and muscle was determined by administering FAM-SEQ ID NO:4 at an amount ranging from 15 to 5,000 nmoles per mouse (average weight of mouse = 25g) and measuring ratio of nerve fluorescence to muscle fluorescence after 2 hrs.

[0017] Figure 5. Cy5-SEQ ID NO:4-(ACETYL- SHSNTQTLAKAPEHTG-(L-cys)-(cY5)-amide) labeling of sciatic nerve in thy1-YFP transgenic mice. A. Low power brightfield view of left exposed sciatic nerve. B. Same nerve as in A viewed with YFP fluorescence superimposed on the brightfield image showing the transgene expression of YFP in axons. C. Same nerve as in A and B viewed with Cy5 fluorescence superimposed on the brightfield image showing nerve labeling with Cy5-SEQ ID NO 4. D. Low magnification photomicrograph showing myelin within the sciatic nerve using Nomarski optics. E. Same nerve as in E showing YFP-labeled axons. F. Same nerve as in D and E, showing Cy5-SEQ ID NO 4 labeling of epineurium, perineurium and endoneurium. G. Composite image of E,D and F showing that SEQ ID NO 4 labeling does not colocalize with either myelin or axons. H-K, Higher magnification of panels E-G.

[0018] Figure 6. Nerve labeling with SEQ ID NO:4 following injury. Nerve labeling with SEQ ID NO:4 is diminished at 3 days following injury but recovers by 7 days after injury. A-F, SEQ ID NO:4 labeling of representative sciatic nerves in control nerves (A,C,E,G) and immediately after crushing (B), 1 day after crushing (D), 7 days after crushing (F) and after devascularization (H). I. Graph showing that a) nerve fluorescence does not significantly diminish as a function of distance from crush site and b)nerve fluorescence is significantly diminished by day 3 after crush but then recovers to that equal to contralateral control nerve by day 7 after crush.

[0019] Figure 7. Human nerve labeling with SEQ ID NO:4. (A) Fluorescence images of human recurrent laryngeal nerve and (B) human muscle freshly resected from patient undergoing total laryngectomy incubated with FAM-SEQ ID NO 4. Fluorescent photomicrograph of human nerve in cross-section (C) and longitudinal section (D). High-power fluorescent photomicrograph of human nerve (E,G). Hematoxylin/eosin stain of same sections (F,H).

[0020] Figure 8. Nerve conduction studies. A. Compound muscle action potentials (CMAP) were evoked with stimulating electrodes (orange) placed 2 mm lateral to the midline. The recording electrode was an ear-clip electrode placed on the digits of the hind foot and the reference electrode (purple) was placed on the heel of the foot. B. Representative CMAP tracing for control (left panel) and FAM-SEQ ID NO 4-treated (right panel) animals. C. 2-tailed Student's t test results showing that there is no significant difference between the CMAP amplitude and latency between control and SEQ ID NO 4-treated nerves.

[0021] **Figure 9.** Illustrates the chemical structure of one isomer of acetyl-SEQ ID NO 4-FAM-amide.

DETAILED DESCRIPTION OF THE INVENTION

Introduction

[0022] Preservation of neurons and nerves is one of the most important goals of any surgical procedure, because accidental transection of neuron or nerves leads to significant morbidity. Nerves are typically identified by their elongated whitish appearance and relationship to nearby structures or by electrophysiological studies. However, in instances such as trauma, tumor involvement, inflammation, or infection, nerve identification using these criteria can be difficult. Therefore, there is a need for methods of reliably and conclusively identifying neuron or nerves which overcome the deficiencies in the art.

[0023] Neuron or nerve identification prior to direct exposure during surgery or confirmation of neuron or nerve identity in instances of uncertainty following direct exposure is accomplished by electromyographic (EMG) monitoring. This technique, however, has the disadvantage of not providing visual feedback to the operating surgeon. Thus, even if a nerve has been identified in one location, either through accidental or purposeful stimulation, there is no visual guidance to the operating surgeon as to how far away from the stimulation site the nerve lies or the direction of travel the nerve takes away from the stimulation site. Furthermore, EMG only traces motor pathways, not sensory fibers. EMG fails if neuron or nerve conduction or neuromuscular transmission is temporarily blocked anywhere distal to the recording site. Such blockade easily occurs due to neuron or nerve compression, trauma, local anesthetics, or neuromuscular blockers.

[0024] Neuron or nerve labeling primarily depend on retrograde or anterograde tracing of individually identified axonal tracts via the use of fluorescent dyes. However, methods of labeling neuron or nerves by locally applied fluorescent tracers have several disadvantages. First, this technique can label only one neuron or nerve fiber tract at a time, depending on where the dye has been injected. Second, this technique results in only limited labeling of fluorescent dyes along the axonal tracts, because retrograde axonal tracers typically accumulate in the neural cell body. Third, retrograde transport is relatively slow (on the order of millimeters per day) and therefore takes a long time to label human neuron or nerves, which are often longer than a meter, such as in the case of the sciatic neuron or nerve and its arborizations. Fourth, the application of fluorescent dyes to innervation targets such as direct intramuscular injections to label motor neuron or nerves is typically messy with a variable amount of the tracer dye remaining at the injection site. As dissection of neuron or nerves

depends on accurate visualization of adjacent structures prior to encountering them, a surgical site that is contaminated with fluorescent dyes would not be desirable. Finally, the direct injection of the fluorescent dye itself may be damaging to the target organs or neuron or nerve of interest, either by mechanical damage or by the very high local concentration of dye and vehicle at the injection site.

Definitions

[0025] As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

[0026] As used herein, the term "targeting molecule" refers to any agent (*e.g.*, peptide, protein, nucleic acid polymer, aptamer, or small molecule) that specifically binds to a target of interest. The target of interest may be a tissue, a cell type, a cellular structure (*e.g.*, an organelle), a protein, a peptide, a polysaccharide, or a nucleic acid polymer. In some embodiments, the targeting molecule is any agent that specifically binds to one or more neurons or nerves of a subject.

[0027] As used herein, the term "aptamer" refers to a DNA or RNA molecule that has been selected from random pools based on their ability to bind other molecules with high affinity specificity based on non-Watson and Crick interactions with the target molecule (see, *e.g.*, Cox and Ellington, *Bioorg. Med. Chem.* 9:2525-2531 (2001); Lee *et al., Nuc. Acids Res.* 32:D95-D100 (2004)). Aptamers can be selected which bind nucleic acid, proteins, small organic compounds, vitamins, inorganic compounds, cells, and even entire organisms.

[0028] The terms "polypeptide," "peptide," and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to naturally occurring occurring amino acid polymers as well as amino acid polymers in which one or more amino acid residues is a non-naturally occurring amino acid *(e.g.*, an amino acid analog). The terms encompass amino acid chains of any length, including full length proteins (*i.e.*, antigens), wherein the amino acid residues are linked by covalent peptide bonds. As used herein, the term "peptide" refers to a polymer of amino acid residues typically ranging in length from 2 to about 50 residues. In certain embodiments the peptide ranges in length from about 2, 3, 4, 5, 7, 9, 10, or 11 residues to about 50, 45, 40, 45, 30, 25, 20, or 15 residues. In certain embodiments the peptide ranges in length from about 8, 9, 10, 11, or 12 residues to about 15, 20 or 25 residues. Where an amino acid sequence is provided herein, L-, D-, or beta amino acid versions of the sequence are also contemplated as well as retro, inversion, and retro-inversion isoforms. Peptides also include amino acid polymers in which one or more amino

acid residues is an artificial chemical analogue of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers. In addition, the term applies to amino acids joined by a peptide linkage or by other modified linkages (*e.g.*, where the peptide bond is replaced by an α-ester, a β-ester, a thioamide, phosphonamide, carbamate, hydroxylate, and the like (*see, e.g.,* Spatola, (1983) *Chem. Biochem. Amino Acids and Proteins* 7: 267-357), where the amide is replaced with a saturated amine (*see, e.g.,* Skiles et al., U.S. Pat. No. 4,496,542, which is incorporated herein by reference, and Kaltenbronn *et al.,* (1990) Pp. 969-970 in Proc. 11th American Peptide Symposium, ESCOM Science Publishers, The Netherlands, and the like)).

[0029] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, *e.g.,* hydroxyproline, γ-carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.,* homoserine, norleucine, methionine sulfoxide. Such analogs have modified R groups (*e.g.,* norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

[0030] Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0031] One of skill will recognize that individual substitutions, deletions or additions to a peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention.

[0032] The following eight groups each contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Glycine (G); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); 7) Serine (S), Threonine (T); and 8) Cysteine (C), Methionine (M) (*see, e.g.*, Creighton, *Proteins* (1984)).

[0033] As used herein, the terms "label" refers to a molecule that facilitates the visualization and/or detection of a targeting molecule disclosed herein. In some embodiments, the label is a fluorescent moiety.

[0034] The phrase "specifically binds" when referring to the interaction between a targeting molecule disclosed herein and a target (*e.g.*, purified protein, neuron or nerve tissue, neuron or nerves, cranial neuron or nerves, central neuron or nerves, myelinated or unmyelinated neuron or nerves, or connective tissue surrounding neuron or nerves), refers to the formation of a high affinity bond between the targeting molecule and the target. Further, the term means that the targeting molecule has low affinity for non-targets.

[0035] "Selective binding," "selectivity," and the like refer to the preference of agent to interact with one molecule as compared to another. Preferably, interactions between a targeting molecule disclosed herein and a target are both specific and selective. Note that in some embodiments an agent is designed to "specifically bind" and "selectively bind" two distinct, yet similar targets without binding to other undesirable targets.

[0036] The terms "individual," "patient," or "subject" are used interchangeably. As used herein, they mean any mammal (*i.e.* species of any orders, families, and genus within the taxonomic classification animalia: chordata: vertebrata: mammalia). In some embodiments, the mammal is a human. None of the terms require or are limited to situation characterized by the supervision (*e.g.* constant or intermittent) of a health care worker (*e.g.* a doctor, a registered nurse, a nurse practitioner, a physician's assistant, an orderly, or a hospice worker).

[0037] The terms "administer," "administering", "administration," and the like, as used herein, refer to the methods that may be used to enable delivery of agents or compositions to the desired site of biological action. These methods include, but are not limited to parenteral injection (e.g., intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular, intrathecal, intravitreal, infusion, or local). Administration techniques that are optionally employed with the agents and methods described herein, include e.g., as discussed in Goodman and Gilman, The Pharmacological Basis of Therapeutics, current ed.; Pergamon;

and Remington's, Pharmaceutical Sciences (current edition), Mack Publishing Co., Easton, Pa.

[0038] The term "pharmaceutically acceptable" as used herein, refers to a material that does not abrogate the biological activity or properties of the agents described herein, and is relatively nontoxic (*i.e.*, the toxicity of the material significantly outweighs the benefit of the material). In some instances, a pharmaceutically acceptable material may be administered to an individual without causing significant undesirable biological effects or significantly interacting in a deleterious manner with any of the components of the composition in which it is contained.

[0039] The term "surgery" as used herein, refers to any methods for that may be used to manipulate, change, or cause an effect by a physical intervention. These methods include, but are not limited to open surgery, endoscopic surgery, laparoscopic surgery, minimally invasive surgery, robotic surgery, any procedures that may affect any neuron or nerves such as placement of retractors during spinal surgery, cardiac neuron or nerve ablation, epidural injection, intrathecal injections, neuron or nerve blocks, implantation of devices such as neuron or nerve stimulators and implantation of pumps.

Targets

[0040] Disclosed herein, in certain embodiments, are targeting molecules that specifically bind to a target.

[0041] In some embodiments, the target is a neuron or nerve. The nerve is any nerve (*e.g.*, motor nerves, sensory nerves, sympathetic and parasympathetic nerves, periprostatic neurovascular bundle, sciatic nerves, cranial nerves including olfactory nerve, optic nerve, oculomotor nerve, trochlear nerve, trigeminal nerve, abducens nerve, facial nerve, vestibulocochlear nerve, glossopharyngeal nerve, vagus nerve, accessory nerve, hypoglossal nerve, spinal nerves, brachial plexus, or lumbrosacral plexus). The neuron is any neuron (e.g., sensory neurons (afferent neurons), motor neurons (efferent neurons), interneurons, unipolar neurons, bipolar neurons, multipolar neurons, basket cells, Betz cells, medium spiny neurons, Purkinje cells, pyramidal cells, Renshaw cells, Granule cells, anterior horn cells). In some embodiments, the neuron or nerve is myelinated. In some embodiments, the neuron or nerve is unmyelinated. In some embodiments, the neuron or nerve is demyelinated. In some embodiments, the neuron or nerve is undergoing demyelination.

[0042] In some embodiments, the target is a component of a neuron or nerve. The component of a neuron or nerve is any component of a neuron or nerve. In some

embodiments, the target is tissue within or surrounding a neuron or nerve (*e.g.*, epineurium, perineurium, or endoneurium). In some embodiments, the target is a component of myelin, (*e.g.*, myelin basic protein (MBP), myelin oligodendrocyte glycoprotein, or proteolipid protein). In some embodiments, the target is expressed by Schwann cells, (*e.g.*, MBP, glial fibrillary acidic protein, S-100, or myelin protein zero). In some embodiments, the target is a component of neuron or nerve tissue, (*e.g.*, elastin, fibrillin, e-cadherin, cytokeratin, vimentin, collagen I, collagen, III, collagen IV, or collagen V). In some embodiments, the target is a neurotrophic factor receptor expressed in neuron or nerves, (*e.g.*, tyrosine kinase receptors TrkA, TrkB, and TrkC, low affinity neuron or nerve growth receptor or p75 neurotrophin receptor, or GDNF family receptor alpha-1 or -2). In some embodiments, the target is a non-neurotrophic factor receptor expressed in a neuron or nerve tissue, (*e.g.*, epithelial growth factor receptors, transforming growth factor beta receptors, vascular endothelial growth factor receptors, endothelin A receptors, endothelin B receptors, and integrin receptors).

[0043] Determining whether a targeting molecule is capable of binding a neuron or nerve or component thereof is accomplished by any suitable method. In some embodiments, the method of determining whether a targeting molecule is capable of binding a neuron or nerve or component thereof involves contacting a targeting molecule (*e.g.*, peptide or aptamer) disclosed herein with a test agent for a period of time sufficient to allow the targeting molecule and test agent to form a binding complex. The binding complex is detected using any suitable method. Suitable binding assays can be performed *in vitro* or *in vivo* and include, but are not limited to, phage display, two-hybrid screens, co-precipitation, cross-linking, and expression cloning (see, e.g., Bennet, J.P. and Yamamura, H.I. (1985) "Neurotransmitter, Hormone or Drug Receptor Binding Methods," in *Neurotransmitter Receptor Binding* (Yamamura, H. I., et al., eds.), pp. 61-89. Other binding assays involve the use of mass spectrometry or NMR techniques to identify molecules bound to the target of interest. The targeting molecule utilized in such assays can be naturally expressed, cloned or synthesized.

[0044] In some embodiments, the targeting molecule is capable of crossing the blood-brain barrier in order to reach reach and bind the neuron or nerve of interest.

Targeting Molecules

Peptides and Aptamers

[0045] In some embodiments, the targeting molecule comprises a peptide sequence selected from: AHHNSWKAKHHS (SEQ ID NO:1), TYTDWLNFWAWP (SEQ ID NO:2), KSLSRHDHIHHH (SEQ ID NO:3), NTQTLAKAPEHT (SEQ ID NO:4), DFTKTSPLGIH (SEQ ID NO:5), LTPIPLPTPKPP (SEQ ID NO:6), VSTMPMSNMNGP (SEQ ID NO:7),

GIFERNFGAMLH(SEQ ID NO:8), ACLREYHNWC(SEQ ID NO:9), MHRQPIAPVSSL (SEQ ID NO:10), SFADPLLFLAPP (SEQ ID NO:11), ASAHHMFTPGFD (SEQ ID NO:12), VAPTKAPLHSPS (SEQ ID NO:13), NNLKTGTSAPTG (SEQ ID NO:14), HKTAQWPFIAFR (SEQ ID NO:15), RLTNAPAYQAPA (SEQ ID NO:16), MQNPLNGKPGR (SEQ ID NO:17), THYSRSLTDGTR, (SEQ ID NO:18), FSTSNNQSSPAI (SEQ ID NO:19), YPSPNRPPNLTN (SEQ ID NO:20), DIANPPPPPLYV (SEQ ID NO:21), ALQTDGPFAESA(SEQ ID NO:22), DNAQHSERFPVP (SEQ ID NO:23), and IPPTFPDRIRAPG (SEQ ID NO:24).

[0046] In some embodiments, the targeting molecule comprises a peptide sequence sharing 80% homology with a peptide sequence disclosed herein. In some embodiments, the targeting molecule comprises a peptide sequence sharing 85% homology with a peptide sequence disclosed herein. In some embodiments, the targeting molecule comprises a peptide sequence sharing 90% homology with a peptide sequence disclosed herein. In some embodiments, the targeting molecule comprises a peptide sequence sharing 95% homology with a peptide sequence disclosed herein. In some embodiments, the targeting molecule comprises a peptide sequence sharing 99% homology with a peptide sequence disclosed herein.

[0047] In some embodiments, the targeting molecule comprises an aptamer.

[0048] The peptides and aptamers of the present invention are synthesized by any suitable method. For example, targeting peptides and aptamers of the present invention can be chemically synthesized by solid phase peptide synthesis. Techniques for solid phase synthesis are described, for example, by Barany and Merrifield (1963) *Solid-Phase Peptide Synthesis;* pp. 3-284 *in The Peptides: Analysis, Synthesis, Biology. Vol. 2: Special Methods in Peptide Synthesis, Part A.*; Merrifield *et al.* (1963) *J. Am. Chem. Soc.,* 85: 2149-2156, and Stewart et al. (1984) *Solid Phase Peptide Synthesis,* 2nd ed. Pierce Chem. Co., Rockford, Ill.

Cargo

[0049] In some embodiments, the targeting molecule further comprises a cargo. In some embodiments, the peptide or aptamer is directly bound to a cargo. In some embodiments, the peptide or aptamer is indirectly (e.g., via a linker) bound to a cargo. In some embodiments, two or more peptides or aptamers are directly or indirectly bound to a cargo. In some embodiments, the cargo is a drug. In some embodiments, the cargo is a fluorescent moiety.

Drugs

[0050] In some embodiments, the targeting molecule further comprises a drug. All drugs that act on a neuron or nerve (or a component thereof) are encompassed within the term

"drug." Specific examples of drug given herein, are illustrative and are not meant to limit the drugs for use with the targeting molecules disclosed herein.

[0051] In some embodiments, the peptide or aptamer is directly bound to a drug. In some embodiments, the peptide or aptamer is indirectly (e.g., via a linker) bound to a drug. In some embodiments, two or more peptides or aptamers are directly or indirectly bound to a drug.

[0052] In some embodiments, the drug is selected from a drug that: induces cell death (apoptotic or necrotic), inhibits cell death (apoptotic or necrotic), inhibits the transmission of a neuron or nerve signal (i.e., an electrochemical impulse), inhibits the release of a neurotransmitter, agonizes the activity of a GABA receptor, partially or fully inhibits the repolarization of a neuron, disrupts the conduction of an ion channel, or a combination thereof.

[0053] In some embodiments, the drug is an antihistamine, a GABA receptor modulator, a neurotransmitter reuptake inhibitor, a local anesthetic, an anticholinergic, a sodium channel blocker, a calcium channel blocker, a thyrotropin-releasing hormone, a γ-secretase inhibitor, an AMPA receptor agonist or antagonist, an NMDA receptor agonist or antagonist, an mGlu receptor agonist or antagonist, a growth factor, an antiemetic agent, a corticosteroid; a cytotoxic agent; an antioxidant, an iron chelator, a mitochondrial modulator, a sirtuin modulator, a nitric oxide (NO) and/or nitric oxide synthase (NOS) modulator, a potassium channel agonist or antagonist, a purigenic receptor agonist or antagonist, or a combination thereof.

[0054] In some embodiments, the drug is meclizine, diphenhydramine, dimenhydrinate, loratadine, quetiapine, mepyramine, piperoxan, antazoline, carbinoxamine, doxylamine, clemastine, pheniramine, chlorphenamine, chlorpheniramine, dexchlorpheniramine, brompheniramine, triprolidine, cyclizine, chlorcyclizine, hydroxyzine, promethazine, alimemazine, trimeprazine, cyproheptadine, azatadine, ketotifen, oxatomide, meclizine hydrochloride, promethazine hydrochloride, cinnarizine, hydroxyzine pamoate, betahistine dihydrochloride, alprazolam, bromazepam, brotizolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flunitrazepam, flurazepam, loprazolam, lorazepam, lormetazepam, idazolam, nimetazepam, nitrazepam, oxazepam, prazepam, temazepam, triazolam, clonazepam, diazepam, lorazepam, furosemide, bumetanide, ethacrynic acid, gabapentin, pregabalin, muscimol, baclofen, amitriptyline, nortriptyline, trimipramine, fluoxetine, paroxetine, sertraline, glycopyrrolate, homatropine, scopolamine, atropine, benzocaine, carticaine, cinchocaine, cyclomethycaine, lidocaine, prilocaine, propxycaine,

proparacaine, tetracaine, tocainide, trimecaine, carbamazepine, oxcarbazepine, phenytein, valproic acid, sodium valproate, cinnarizine, flunarizine, nimodipine, thyrotropin-releasing hormone, amifostine (also known as WR-2721, or ETHYOL®); a carbamate compound (e.g., 2-phenyl-1,2-ethanediol monocarbomates and dicarbamates); LY450139 (hydroxylvaleryl monobenzocaprolactam); L685458 (1S-benzyl-4R[1-[1-S-carbamoyl-2-phenethylcarbamoyl)-1S-3-methylbutylcarbamoyl]-2R-hydroxy-5-phenylpentyl}carbamic acid tert-butyl ester); LY411575 (N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyethanoyl]-N^1[(7S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[bid]azepin-7yl]-L-alaninamide); MK-0752; tarenflurbil; BMS-299897 (2-[(1R)-1-[[(4-chlorophenyl) sulfony](2,5-difluorophenyl)amino]ethyl]-5-fluorobenzenepropanoic acid; CNQX (6-cyano-7-nitroquinoxaline-2,3-dione); NBQX (2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione); DNQX (6,7-dinitroquinoxaline-2,3-dione); kynurenic acid; 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo-[f]quinoxaline; 1-aminoadamantane; dextromethorphan; dextrorphan; ibogaine; ketamine; nitrous oxide; phencyclidine; riluzole; tiletamine; memantine; dizocilpine; aptiganel; remacimide; 7-chlorokynurenate; DCKA (5,7-dichlorokynurenic acid); kynurenic acid; 1-aminocyclopropanecarboxylic acid (ACPC); AP7 (2-amino-7-phosphonoheptanoic acid); APV (R-2-amino-5-phosphonopentanoate); CPPene (3-[(R)-2-carboxypiperazin-4-yl]-prop-2-enyl-1-phosphonic acid); (+)-(1S, 2S)-1-(4-hydroxy-phenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-pro-panol; (1S, 2S)-1-(4-hydroxy-3-methoxyphenyl)-2-(4-hydroxy-4-phenylpiperi-dino)-1-propanol; (3R, 4S)-3-(4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl-)-chroman-4;7-diol; (1R*, 2R*)-1-(4-hydroxy-3-methylphenyl)-2-(4-(4-fluoro-phenyl)-4-hydroxypiperidin-1-yl)-propan-1-ol-mesylate); LY389795 ((-)-2-thia-4-aminobicyclo-hexane-4,6-dicarboxylate); LY379268 ((-)-2-oxa-4-aminobicyclo-hexane-4,6-dicarboxylate); LY354740 ((+)-2-aminobicyclo-hexane-2,6dicarboxylate); DCG-IV ((2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)glycine); 2R,4R-APDC (2R,4R-4-aminopyrrolidine-2,4-dicarboxylate); (S)-3C4HPG ((S)-3-carboxy-4-hydroxyphenylglycine); (S)-4C3HPG ((S)-4-carboxy-3-hydroxyphenylglycine); L-CCG-I ((2S,1'S,2'S)-2-(carboxycyclopropyl)glycine); ACPT-I ((1S,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid); L-AP4 (L-(+)-2-Amino-4-phosphonobutyric acid); (S)-3,4-DCPG ((S)-3,4-dicarboxyphenylglycine); (RS)-3,4-DCPG ((RS)-3,4-dicarboxyphenylglycine); (RS)-4-phosphonophenylglycine ((RS)PPG); AMN082 (,N'-bis(diphenylmethyl)-1,2-ethanediamine dihydrochloride); DCG-IV ((2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)glycine); AMN082; brain-derived neurotrophic factor (BDNF); ciliary neurotrophic factor (CNTF); glial cell-line derived neurotrophic factor (GDNF); neurotrophin-3; neurotrophin-4; fibroblast growth factor (FGF) receptor; insulin-like growth factor (IGF); an aminoglycoside antibiotic (e.g., gentamicin and amikacin); a macrolide

antibiotic (e.g, erythromycin); a glycopeptide antibiotic (e.g. vancomycin); salicylic acid; nicotine; Eburnamenine-14-carboxylic acid ethyl ester; sipatrigine (2-(4-Methylpiperazin-1-yl)-5-(2,3,5-trichlorophenyl)-pyrimidin-4-amine); amiloride (3,5-diamino-N-(aminoiminomethyl)-6-chloropyrazinecarbox amide hydrochloride); carbamazepine (5H-dibenzo[b,f]azepine-5-carboxamide); TTX (octahydro-12-(hydroxymethyl)-2-imino-5,9:7,10a-dimethan o-10aH-[1,3]dioxocino[6,5-d]pyrimidine-4,7,10,11,12-pen tol); RS100642 (1-(2,6-dimethyl-phenoxy)-2-ethylaminopropane hydrochloride); mexiletine ((1-(2,6-dimethylphenoxy)-2-aminopropane hydrochloride)); QX-314 (N-(2,6-Dimethylphenylcarbamoylmethyl)triethylammonium bromide); phenytoin (5,5-diphenylimidazolidine-2,4-dione); lamotrigine (6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine); 4030W92 (2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethylpyrimidine); BW1003C87 (5-(2,3,5-trichlorophenyl) pyrimidine-2,4- 1.1 ethanesulphonate); QX-222 (2-[(2,6-dimethylphenyl)amino]-N,N,N-trimethyl-2-oxoetha niminium chloride); ambroxol (trans-4-[[(2-Amino-3,5-dibromophenyl)methyl]amino]cyclo hexanol hydrochloride); R56865 (N-[1-(4-(4-fluorophenoxy)butyl]-4-piperidinyl-N-methyl-2-benzo-thiazolamine); lubeluzole; ajmaline ((17R,21alpha)-ajmalan-17,21-diol); procainamide (4-amno-N-(2-diethylaminoethyl)benzamide hydrochloride); flecainide; riluzoleor; triamicinolone actenoide; Dexamethasone; promethazine; prochlorperazine; trimethobenzamide; triethylperazine; dolasetron; granisetron; ondansetron; tropisetron; and palonosetron; droperidol; meclizine; perphenazine; thiethyl perazine; domperidone; properidol; haloperidol; chlorpromazine; promethazine; prochlorperazine; metoclopramide; dronabinol; nabilone; sativex; scopolamine; dexamethasone; trimethobenzamine; emetrol; propofol; muscimol; acridine carboxamide; actinomycin; 17-N-allylamino-17-demethoxygeldanamycin; amsacrine; aminopterin; anthracycline; antineoplastic; antineoplaston; 5-azacytidine; azathioprine; BL22; bendamustine; biricodar; bleomycin; bortezomib; bryostatin; busulfan; calyculin; camptothecin; capecitabine; carboplatin; chlorambucil; cisplatin; cladribine; clofarabine; cytarabine; dacarbazine; dasatinib; daunorubicin; decitabine; dichloroacetic acid; discodermolide; docetaxel; doxorubicin; epirubicin; epothilone; eribulin; estramustine; etoposide; exatecan; exisulind; ferruginol; floxuridine; fludarabine; fluorouracil; fosfestrol; fotemustine; gemcitabine; hydroxyurea; IT-101; idarubicin; ifosfamide; imiquimod; irinotecan; irofulven; ixabepilone; laniquidar; lapatinib; lenalidomide; lomustine; lurtotecan; mafosfamide; masoprocol; mechlorethamine; melphalan; mercaptopurine; mitomycin; mitotane; mitoxantrone; nelarabine; nilotinib; oblimersen; oxaliplatin; PAC-1; methotrexate (RHEUMATREX®, Amethopterin); cyclophosphamide (CYTOXAN®);thalidomide (THALIDOMID®); paclitaxel; pemetrexed; pentostatin; pipobroman; pixantrone;

plicamycin; procarbazine; proteasome inhibitors (e.g.; bortezomib); raltitrexed; rebeccamycin; rubitecan; SN-38; salinosporamide A; satraplatin; streptozotocin; swainsonine; tariquidar; taxane; tegafur-uracil; temozolomide; testolactone; thioTEPA; tioguanine; topotecan; trabectedin; tretinoin; triplatin tetranitrate; tris(2-chloroethyl)amine; troxacitabine; uracil mustard; valrubicin; vinblastine; vincristine; vinorelbine; vorinostat; zosuquidar; N-acetylcysteine; vitamin E; vitamin C; vitamin A; lutein; selenium glutathione; melatonin; a polyphenol; a carotenoid; coenzyme Q-10; Ebselen (2-phenyl-1, 2-benzisoselenazol-3(2H)-one (also called PZ 51 or DR3305); L-methionine; azulenyl nitrones; L-(+)-Ergothioneine; CAPE (caffeic acid phenethyl ester); dimethylthiourea; dimethylsulfoxide; disufenton sodium; pentoxifylline; MCI-186; Ambroxol; U-83836E; MitoQ (mitoquinone mesylate); Idebenone (2-(10-hydroxydecyl)-5,6-dimethoxy-3-methyl-cyclohexa-2,5-diene-1,4-dione); desferrioxamine; hydroxybenzyl ethylene diamine; fullerenol-1, pyrrolidine dithiocarbamate; acetylcarnitine; lipoic acid; a stilbene; a chalcone; a flavone; an isoflavone; a flavanones; an anthocyanidin; a catechin; isonicotinamide; dipyridamole; ZM 336372; camptothecin; coumestrol; nordihydroguaiaretic acid; esculetin; SRT-1720; SRT-1460; SRT-2183; aminoguanidine; 1-Amino-2-hydroxyguanidine p-toluensulfate; GED; bromocriptine mesylate; dexamethasone; SDMA; ADMA; L-NMMA; L-NMEA; D-MMA; L-NIL; L-NNA; L-NPA; L-NAME; L-VNIO; diphenyleneiodonium chloride; 2-ethyl-2-thiopseudourea; haloperidol; L-NIO; MEG; SMT; SMTC; 7-Ni; nNOS inhibitor; 1,3-PBITU; L-thiocitrulline; TRIM; MTR-105; BBS-1; BBS-2; ONO-1714; GW273629; GW 274150; PPA250; AR-R17477; AR-R18512; spiroquinazolone; 1400W; S-NC; NTG; SNP; thapsigargin; VEGF; bradykinin; ATP; sphingosine-1-phosphate; estrogen; angiopoietin; acetylcholine; SIN-1; GEA 3162; GEA; GEA 5024; GEA 5538; SNAP; molsidomine; CNO-4; CNO-5; DEA/NO; IPA/NO; SPER/NO; SULFI/NO; OXI/NO; DETA/NO; nicorandil; minoxidil, levcromakalim; lemakalim; cromakalim; L-735,334; retigabine; flupirtine; BMS-204352; DMP-543; linopirdine; XE991; 4-AP; 3,4-DAP; E-4031; DIDS; Way 123,398; CGS-12066A; dofetilide; sotalol; apamin; amiodarone; azimilide; bretylium; clofilium; tedisamil; ibutilide; sematilide; nifekalant; tamulustoxin; ATP; ADP; UTP; UDP; UDP-glucose; adenosine; 2-MESATP; 2-MESADP; ABMEATP; DATPAS; ATPΓS; BZ-ATP; MRS2703; DENUFOSOL TETRASODIUM; MRS2365; MRS 2690; PSB 0474; A-317491; RO-3 (Roche); SURAMIN; PPADS; PPNDS; DIDS; pyridoxal-5-phosphate; 5-(3-bromophenyl)-1,3-dihydro-2H-benzofuro- [3,2-e]-1,4-diazepin-2-one; cibacron blue; basilen blue; ivermectin; A-438079; A-740003; NF023; NF449; NF110; NF157; MRS 2179; NF279; MRS 2211; MRS 2279; MRS 2500 tetrasodium salt; TNP-ATP; tetramethylpyrazine; Ip_5I; $\beta\gamma$-carboxymethylene ATP; $\beta\gamma$-chlorophosphomethylene ATP; KN-62; spinorphin;

minocycline; SB-203580 (4-(4-Fluorophenyl)-2-(4-methylsulfinyl phenyl)-5-(4-pyridyl) 1H-imidazole); PD 169316 (4-(4-Fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)-1H-imidazole); SB 202190 (4-(4-Fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)1H-imidazole); RWJ 67657 (4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol -2-yl]-3-butyn-1-ol); SB 220025 (5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinlyl)imidazole); D-JNKI-1 ((D)-hJIP$_{175-157}$-DPro-DPro-(D)-HIV-TAT$_{57-48}$); AM-111 (Auris); SP600125 (anthra[1,9-cd]pyrazol-6(2H)-one); JNK Inhibitor I ((L)-HIV-TAT$_{48-57}$-PP-JBD$_{20}$); JNK Inhibitor III ((L)-HIV-TAT$_{47-57}$-gaba-c-Junδ_{33-57}); AS601245 (1,3-benzothiazol-2-yl (2-[[2-(3-pyridinyl) ethyl] amino]-4 pyrimidinyl) acetonitrile); JNK Inhibitor VI (H_2N-RPKRPTTLNLF-NH_2); JNK Inhibitor VIII (N-(4-Amino-5-cyano-6-ethoxypyridin-2-yl)-2-(2,5-dimethoxyphenyl)acetamide); JNK Inhibitor IX (N-(3-Cyano-4,5,6,7-tetrahydro-1-benzothien-2-yl)-1-naphthamide); dicumarol (3,3′-Methylenebis(4-hydroxycoumarin)); SC-236 (4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzene-sulfonamide); CEP-1347 (Cephalon); CEP-11004 (Cephalon); an artificial protein comprising at least a portion of a Bcl-2 polypeptide; a recombinant FNK;V5 (also known as Bax inhibitor peptide V5); Bax channel blocker ((±)-1-(3,6-Dibromocarbazol-9-yl)-3-piperazin-1-yl-propan-2-ol); Bax inhibiting peptide P5 (also known as Bax inhibitor peptide P5); Kp7-6; FAIM(S) (Fas apoptosis inhibitory molecule-short); FAIM(L) (Fas apoptosis inhibitory molecule-long); Fas:Fc; FAP-1; NOK2; F2051; F1926; F2928; ZB4; Fas M3 mAb; EGF; 740 Y-P; SC 3036 (KKHTDDGYMPMSPGVA); PI 3-kinase Activator (Santa Cruz Biotechnology, Inc.); Pam_3Cys ((S)-(2,3-bis(palmitoyloxy)-(2RS)-propyl)-N-palmitoyl-(R)-Cys-(S)-Ser(S)-Lys4-OH, trihydrochloride); Act1 (NF-kB activator 1); an anti-IkB antibody; Acetyl-11-keto-b-Boswellic Acid; Andrographolide; Caffeic Acid Phenethyl Ester (CAPE); Gliotoxin; Isohelenin; NEMO-Binding Domain Binding Peptide (DRQIKIWFQNRRMKWKKTALDWSWLQTE); NF-kB Activation Inhibitor (6-Amino-4-(4-phenoxyphenylethylamino)quinazoline); NF-kB Activation Inhibitor II (4-Methyl-N1-(3-phenylpropyl)benzene-1,2-diamine); NF-kB Activation Inhibitor III (3-Chloro-4-nitro-N-(5-nitro-2-thiazolyl)-benzamide); NF-kB Activation Inhibitor IV ((E)-2-Fluoro-4′-methoxystilbene); NF-kB Activation Inhibitor V (5-Hydroxy-(2,6-diisopropylphenyl)-1H-isoindole-1,3-dione); NF-kB SN50 (AAVALLPAVLLALLAPVQRKRQKLMP); Oridonin; Parthenolide; PPM-18 (2-Benzoylamino-1,4-naphthoquinone); Ro106-9920; Sulfasalazine; TIRAP Inhibitor Peptide (RQIKIWFNRRMKWKKLQLRDAAPGGAIVS); Withaferin A; Wogonin; BAY 11-7082 ((E)3-[(4-Methylphenyl)sulfonyl]-2-propenenitrile); BAY 11-7085 ((E)3-[(4-t-Butylphenyl)sulfonyl]-2-propenenitrile); (E)-Capsaicin; Aurothiomalate (ATM or AuTM); Evodiamine; Hypoestoxide; IKK Inhibitor III (BMS-345541); IKK Inhibitor VII;

IKK Inhibitor X; IKK Inhibitor II; IKK-2 Inhibitor IV; IKK-2 Inhibitor V; IKK-2 Inhibitor VI; IKK-2 Inhibitor (SC-514); IkB Kinase Inhibitor Peptide; IKK-3 Inhibitor IX; ARRY-797 (Array BioPharma); SB-220025 (5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinlyl)imidazole); SB-239063 (trans-4-[4-(4-Fluorophenyl)-5-(2-methoxy-4-pyrimidinyl) -1H-imidazol-1-yl]cyclohexanol); SB-202190 (4-(4-Fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)1H-imidazole); JX-401 (-[2-Methoxy-4-(methylthio)benzoyl]-4-(phenylmethyl)piperidine); PD-169316 (4-(4-Fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)-1H-imidazole); SKF-86002 (6-(4-Fluorophenyl)-2,3-dihydro-5-(4-pyridinyl)imidazo[2 ,1-b]thiazole dihydrochloride); SB-200646 (N-(1-Methyl-1H-indol-5-yl)-N'-3-pyridinylurea); CMPD-1 (2'-Fluoro-N-(4-hydroxyphenyl)-[1,1'-biphenyl]-4-butanamide); EO-1428 ((2-Methylphenyl)-[4-[(2-amino-4-bromophenyl)amino]-2-chlorophenyl]methanone);SB-253080 (4-[5-(4-Fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-1H-i midazol-4-yl]pyridine); SD-169 (1H-Indole-5-carboxamide); SB-203580 (4-(4-Fluorophenyl)-2-(4-methylsulfinyl phenyl)-5-(4-pyridyl) 1H-imidazole); TZP-101 (Tranzyme Pharma); TZP-102 (Tranzyme Pharma); GHRP-6 (growth hormone-releasing peptide-6); GHRP-2 (growth hormone-releasing peptide-2); EX-1314 (Elixir Pharmaceuticals); MK-677 (Merck); L-692,429 (Butanamide, 3-amino-3-methyl-N-(2,3,4,5-tetrahydro-2-oxo-1-((2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl)-1H-1-benzazepin-3-yl)-, (R)-); EP1572 (Aib-DTrp-DgTrp-CHO); diltiazem; metabolites of diltiazem; BRE (Brain and Reproductive organ-Expressed protein); verapamil; nimodipine; diltiazem; omega-conotoxin; GVIA; amlodipine; felodipine; lacidipine; mibefradil; NPPB (5-Nitro-2-(3-phenylpropylamino)benzoic Acid); flunarizine; erythropoietin; piperine; hemin; brazilin; z-VAD-FMK (Benzyloxycarbonyl-Val-Ala-Asp(OMe)-fluoromethylketone); z-LEHD-FMK (benzyloxycarbonyl-Leu-Glu(OMe)-His-Asp(OMe)-fluoromethylketone); B-D-FMK (boc-aspartyl(Ome)-fluoromethylketone); Ac-LEHD-CHO (N-acetyl-Leu-Glu-His-Asp-CHO); Ac-IETD-CHO (N-acetyl-Ile-Glu-Thr-Asp-CHO); z-IETD-FMK (benzyloxycarbonyl-Ile-Glu(OMe)-Thr-Asp(OMe)-fluoromethy lketone); FAM-LEHD-FMK (benzyloxycarbonyl Leu-Glu-His-Asp-fluoromethyl ketone); FAM-LETD-FMK (benzyloxycarbonyl Leu-Glu-Thr-Asp-fluoromethyl ketone); Q-VD-OPH (Quinoline-Val-Asp-CH_2-O-Ph); XIAP; cIAP-1; cIAP-2; ML-IAP; ILP-2; NAIP; Survivin; Bruce; IAPL-3; fortilin; leupeptine; PD-150606 (3-(4-Iodophenyl)-2-mercapto-(Z)-2-propenoic acid); MDL-28170 (Z-Val-Phe-CHO); calpeptin; acetyl-calpastatin; MG 132 (N-[(phenylmethoxy)carbonyl]-L-leucyl-N-[(1S)-1-formyl-3 -methylbutyl]-L-leucinamide); MYODUR; BN 82270 (Ipsen); BN 2204 (Ipsen); AHLi-11 (Quark Pharmaceuticals), an mdm2 protein, pifithrin-α (1-(4-Methylphenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2H)-benzothiazolyl)ethanone); trans-stilbene; cis-stilbene; resveratrol; piceatannol; rhapontin;

deoxyrhapontin; butein; chalcon; isoliquirtigen; butein; 4,2',4'-trihydroxychalcone; 3,4,2',4',6'-pentahydroxychalcone; flavone; morin; fisetin; luteolin; quercetin; kaempferol; apigenin; gossypetin; myricetin; 6-hydroxyapigenin; 5-hydroxyflavone; 5,7,3',4',5'-pentahydroxyflavone; 3,7,3',4',5'-pentahydroxyflavone; 3,6,3',4'-tetrahydroxyflavone; 7,3',4',5'-tetrahydroxyflavone; 3,6,2',4'-tetrahydroxyflavone; 7,4'-dihydroxyflavone; 7,8,3',4'-tetrahydroxyflavone; 3,6,2',3'-tetrahydroxyflavone; 4'-hydroxyflavone; 5-hydroxyflavone; 5,4'-dihydroxyflavone; 5,7-dihydroxyflavone; daidzein; genistein; naringenin; flavanone; 3,5,7,3',4'-pentahydroxyflavanone; pelargonidin chloride; cyanidin chloride; delphinidin chloride; (−)-epicatechin (Hydroxy Sites: 3,5,7,3′,4′); (−)-catechin (Hydroxy Sites: 3,5,7,3′,4′); (−)-gallocatechin (Hydroxy Sites: 3,5,7,3′,4′,5′) (+)-catechin (Hydroxy Sites: 3,5,7,3′,4′); (+)-epicatechin (Hydroxy Sites: 3,5,7,3′,4′); Hinokitiol (b-Thujaplicin; 2-hydroxy-4-isopropyl-2,4,6-cycloheptatrien-1-one); L-(+)-Ergothioneine ((S)-a-Carboxy-2,3-dihydro-N,N,N-trimethyl-2-thioxo-1H-imidazole4-ethanaminium inner salt); Caffeic Acid Phenyl Ester; MCI-186 (3-Methyl-1-phenyl-2-pyrazolin-5-one); HBED (N,N′-Di-(2-hydroxybenzyl)ethylenediamine-N,N′-diacetic acid•H2O); Ambroxol (trans-4-(2-Amino-3,5-dibromobenzylamino)cyclohexane-HCl; and U-83836E ((−)-2-((4-(2,6-di-1-Pyrrolidinyl-4-pyrimidinyl)-1-piperzainyl)methyl)-3,4-dihydro-2,5,7,8-tetramethyl-2H-1-benzopyran-6-ol•2HCl); β-1′-5-methyl-nicotinamide-2′-deoxyribose; β-D-1′-5-methyl-nico-tinamide-2′-deoxyribofuranoside; β-1′-4,5-dimethyl-nicotinamide-2′-de-oxyribose; β-D-1′-4,5-dimethyl-nicotinamide-2′-deoxyribofuranoside; 1-Naphthyl PP1 (1-(1,1-Dimethylethyl)-3-(1-naphthalenyl)-1H-pyrazolo[3, 4-d]pyrimidin-4-amine); Lavendustin A (5-[[(2,5-Dihydroxyphenyl)methyl][(2-hydroxyphenyl)methy l]amino]-2-hydroxybenzoic acid); MNS (3,4-Methylenedioxy-b-nitrostyrene); PP1 (1-(1,1-Dimethylethyl)-1-(4-methylphenyl)-1H-pyrazolo[3, 4-d]pyrimidin-4-amine); PP2 (3-(4-chlorophenyl) 1-(1,1-dimethylethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine); KX1-004 (Kinex); KX1-005 (Kinex); KX1-136 (Kinex); KX1-174 (Kinex); KX1-141 (Kinex); KX2-328 (Kinex); KX1-306 (Kinex); KX1-329 (Kinex); KX2-391 (Kinex); KX2-377 (Kinex); ZD4190 (Astra Zeneca; N-(4-bromo-2-fluorophenyl)-6-methoxy-7-(2-(1H-1,2,3-triazol-1-yl)ethoxy)quinazolin-4-amine); AP22408 (Ariad Pharmaceuticals); AP23236 (Ariad Pharmaceuticals); AP23451 (Ariad Pharmaceuticals); AP23464 (Ariad Pharmaceuticals); AZD0530 (Astra Zeneca); AZM475271 (M475271; Astra Zeneca); Dasatinib (N-(2-chloro-6-methylphneyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino) thiazole-5-carboxamide); GN963 (trans-4-(6,7-dimethoxyquinoxalin-2ylamino)cyclohexanol sulfate); Bosutinib (4-((2,4-dichloro-5-methoxyphenyl)amino)-6-methoxy-7-(3-(4-methyl-1-piperazinyl)propoxy)-3-quinolinecarbonitrile); or combinations thereof.

Fluorescent Moieties

[0055] In some embodiments, the targeting molecule further comprises a fluorescent moiety (e.g., a fluorescent protein, peptide, or fluorescent dye molecule). All fluorescent moieties are encompassed within the term "fluorescent moiety." Specific examples of fluorescent moieties given herein, are illustrative and are not meant to limit the fluorescent moieties for use with the targeting molecules disclosed herein.

[0056] In some embodiments, the peptide or aptamer is directly bound to a fluorescent moiety. In some embodiments, the peptide or aptamer is indirectly (e.g., via a linker) bound to a fluorescent moiety. In some embodiments, two or more peptides or aptamers are directly or indirectly bound to a single fluorescent moiety.

[0057] Examples of fluorescent dyes include, but are not limited to, xanthenes (e.g., rhodamines, rhodols and fluoresceins, and their derivatives); bimanes; coumarins and their derivatives (e.g., umbelliferone and aminomethyl coumarins); aromatic amines (e.g., dansyl; squarate dyes); benzofurans; fluorescent cyanines; carbazoles; dicyanomethylene pyranes; polymethine; oxabenzanthrane; xanthene; pyrylium; carbostyl; perylene; acridone; quinacridone; rubrene; anthracene; coronene; phenanthrecene; pyrene; butadiene; stilbene; porphyrin; pthalocyanine; lanthanide metal chelate complexes; rare-earth metal chelate complexes; and derivatives of such dyes.

[0058] In some embodiments, the fluorescent moiety is a fluorescein dye. Examples of fluorescein dyes include, but are not limited to, 5-carboxyfluorescein, fluorescein-5-isothiocyanate and 6-carboxyfluorescein.

[0059] In some embodiments, the fluorescent moiety is a rhodamine dye. Examples of rhodamine dyes include, but are not limited to, tetramethylrhodamine-6-isothiocyanate, 5-carboxytetramethylrhodamine, 5-carboxy rhodol derivatives, tetramethyl and tetraethyl rhodamine, diphenyldimethyl and diphenyldiethyl rhodamine, dinaphthyl rhodamine, rhodamine 101 sulfonyl chloride (sold under the tradename of TEXAS RED®).

[0060] In some embodiments, the fluorescent moiety is a cyanine dye. Examples of cyanine dyes include, but are not limited to, Cy3, Cy3B, Cy3.5, Cy5, Cy5.5, Cy 7.

[0061] In some embodiments, the fluorescent moiety is a peptide. In some embodiments, the fluorescent moiety is Green Fluorescent Protein (GFP). In some embodiments, the fluorescent moiety is a derivative of GFP (e.g., EBFP, EBFP2, Azurite, mKalama1, ECFP, Cerulean, CyPet, YFP, Citrine, Venus, YPet).

[0062] Fluorescent labels are detected by any suitable method. For example, a fluorescent label may be detected by exciting the fluorochrome with the appropriate wavelength of light and detecting the resulting fluorescence, e.g., by microscopy, visual inspection, via photographic film, by the use of electronic detectors such as charge coupled devices (CCDs), photomultipliers, etc.

[0063] In some embodiments, the fluorescent moiety is conjugated to high molecular weight molecule, such as water soluble polymers including, but not limited to, dextran, PEG, serum albumin, or poly(amidoamine) dendrimer.

Linkers

[0064] In some embodiments, a cargo (*e.g.*, a fluorescent moiety or drug) is directly attached to the targeting molecule, *e.g.* at the end of the targeting peptide. Alternatively, in some embodiments, a cargo (*e.g.*, a fluorescent moiety or drug) is indirectly attached to a targeting molecule disclosed herein (*e.g.* ,via a linker).

[0065] As used herein, a "linker" is any molecule capable of binding (e.g., covalently) to a targeting molecule disclosed herein. Linkers include, but are not limited to, straight or branched-chain carbon linkers, heterocyclic carbon linkers, peptide linkers, and polyether linkers. For example, poly(ethylene glycol) linkers are available from Quanta Biodesign, Powell, OH. These linkers optionally have amide linkages, sulfhydryl linkages, or heterofunctional linkages.

[0066] In some embodiments, the linker binds to a targeting molecule disclosed herein by a covalent linkage. In some embodiments, the covalent linkage comprises an ether bond, thioether bond, amine bond, amide bond, carbon-carbon bond, carbon-nitrogen bond, carbon-oxygen bond, or carbon-sulfur bond.

[0067] In some embodiments, the linker is flexible. In some embodiments, the linker is rigid.

[0068] In some embodiments, the linker comprises a linear structure. In some embodiments, the linker comprises a non-linear structure. In some embodiments, the linker comprises a branched structure. In some embodiments, the linker comprises a cyclic structure.

[0069] In some embodiments, the linker is an alkyl. In some embodiments, the linker is heteroalkyl.

[0070] In some embodiments, the linker is an alkylene. In some embodiments, the linker is an alkenylene. In some embodiments, the linker is an alkynylene. In some embodiments, the linker is a heteroalkylene.

[0071] An "alkyl" group refers to an aliphatic hydrocarbon group. The alkyl moiety may be a saturated alkyl or an unsaturated alkyl. Depending on the structure, an alkyl group can be a monoradical or a diradical (i.e., an alkylene group).

[0072] The"alkyl" moiety may have 1 to 10 carbon atoms (whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; *e.g.*, "1 to 10 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group could also be a "lower alkyl" having 1 to 6 carbon atoms. The alkyl group of the compounds described herein may be designated as "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from: methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, and the like.

[0073] In some embodiments, the linker comprises a ring structure (e.g., an aryl). As used herein, the term "ring" refers to any covalently closed structure. Rings include, for example, carbocycles (e.g., aryls and cycloalkyls), heterocycles (e.g., heteroaryls and non-aromatic heterocycles), aromatics (e.g. aryls and heteroaryls), and non-aromatics (e.g., cycloalkyls and non-aromatic heterocycles). Rings can be optionally substituted. Rings can be monocyclic or polycyclic.

[0074] As used herein, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl rings can be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited to phenyl, naphthalenyl, phenanthrenyl, anthracenyl, fluorenyl, and indenyl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group).

[0075] The term "cycloalkyl" refers to a monocyclic or polycyclic non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. Cycloalkyls may be saturated, or partially unsaturated. Cycloalkyl groups include groups having from 3 to

10 ring atoms. Cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

[0076] In some embodiments, the ring is a cycloalkane. In some embodiments, the ring is a cycloalkene.

[0077] In some embodiments, the ring is an aromatic ring. The term "aromatic" refers to a planar ring having a delocalized π-electron system containing 4n+2 π electrons, where n is an integer. Aromatic rings can be formed from five, six, seven, eight, nine, or more than nine atoms. Aromatics can be optionally substituted. The term "aromatic" includes both carbocyclic aryl (*e.g.*, phenyl) and heterocyclic aryl (or "heteroaryl" or "heteroaromatic") groups (*e.g.*, pyridine). The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups.

[0078] In some embodiments, the ring is a heterocycle. The term "heterocycle" refers to heteroaromatic and heteroalicyclic groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups include groups having only 3 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 3-membered heterocyclic group is aziridinyl. An example of a 4-membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5-membered heterocyclic group is thiazolyl. An example of a 6-membered heterocyclic group is pyridyl, and an example of a 10-membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl,

benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups, may be C-attached or *N*-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems and ring systems substituted with one or two oxo (=O) moieties such as pyrrolidin-2-one. Depending on the structure, a heterocycle group can be a monoradical or a diradical (i.e., a heterocyclene group).

[0079] In some embodiments, the ring is fused. The term "fused" refers to structures in which two or more rings share one or more bonds. In some embodiments, the ring is a dimer. In some embodiments, the ring is a trimer. In some embodiments, the ring is a substituted.

[0080] The term "carbocyclic" or "carbocycle" refers to a ring wherein each of the atoms forming the ring is a carbon atom. Carbocycle includes aryl and cycloalkyl. The term thus distinguishes carbocycle from heterocycle ("heterocyclic") in which the ring backbone contains at least one atom which is different from carbon (i.e., a heteroatom). Heterocycle includes heteroaryl and heterocycloalkyl. Carbocycles and heterocycles can be optionally substituted.

[0081] In some embodiments, the linker is substituted. The term "optionally substituted" or "substituted" means that the referenced group may be substituted with one or more additional group(s) individually and independently selected from C_1-C_6alkyl, C_3-C_8cycloalkyl, aryl, heteroaryl, C_2-C_6heteroalicyclic, hydroxy, C_1-C_6alkoxy, aryloxy, C_1-C_6alkylthio, arylthio, C_1-C_6alkylsulfoxide, arylsulfoxide, C_1-C_6alkylsulfone, arylsulfone, cyano, halo, C_2-C_8acyl, C_2-C_8acyloxy, nitro, C_1-C_6haloalkyl, C_1-C_6fluoroalkyl, and amino, including C_1-C_6alkylamino, and the protected derivatives thereof. By way of example, an optional substituents may be L^sR^s, wherein each L^s is independently selected from a bond, -O-, -C(=O)-, -S-, -S(=O)-, -$S(=O)_2$-, -NH-, -NHC(=O)-, -C(=O)NH-, $S(=O)_2NH$-, -$NHS(=O)_2$-, -OC(=O)NH-, -NHC(=O)O-, -(C_1-C_6alkyl)-, or -(C_2-C_6alkenyl)-; and each R^s is independently selected from H, (C_1-C_4alkyl), (C_3-C_8cycloalkyl), heteroaryl, aryl, and C_1-C_6heteroalkyl. Optionally substituted non-aromatic groups may be substituted with one or more oxo (=O). The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art.

[0082] In some embodiments, a bifunctional linker having one functional group reactive with a group on one molecule (*e.g.*, a targeting molecule), and another group reactive on the other molecule (*e.g.*, a fluorescent moiety or a drug), is used to form the desired conjugate. Alternatively, in some embodiments, derivatization is performed to provide functional groups. Thus, for example, procedures for the generation of free sulfhydryl groups on peptides are also known (See U.S. Pat. No. 4,659,839). A linker may alternatively comprise a heterobifunctional crosslinker comprising two or more different reactive groups that form a heterocyclic ring that can interact with a targeting molecule. For example, a heterobifunctional crosslinker such as cysteine may comprise an amine reactive group and a thiol-reactive group can interact with an aldehyde on a derivatized targeting molecule. Additional combinations of reactive groups suitable for heterobifunctional crosslinkers include, for example, amine- and sulfhydryl reactive groups; carbonyl and sulfhydryl reactive groups; amine and photoreactive groups; sulfhydryl and photoreactive groups; carbonyl and photoreactive groups; carboxylate and photoreactive groups; and arginine and photoreactive groups.

[0083] In some embodiments, a peptide linker consisting of one or more amino acids is used to join the targeting molecule and a fluorescent moiety or drug. Generally the peptide linker will have no specific biological activity other than to join the molecules or to preserve some minimum distance or other spatial relationship between them. However, the constituent amino acids of the linker may be selected to influence some property of the molecule such as the folding, net charge, or hydrophobicity. In some embodiments the peptide linker is relatively short, typically less than about 10 amino acids, preferably less than about 8 amino acids and more preferably less than 5 amino acids. Non-limiting illustrative examples include glycine and glycine-serine linkers which can be added to the C-terminus of a targeting peptide.

Further Modifications

[0084] In some embodiments, the targeting molecules of the present invention are optionally conjugated to high molecular weight molecules that increase the multivalency and avidity of labeling. In some embodiments, the high molecular weight molecules are water-soluble polymers. Examples of suitable water-soluble polymers include, but are not limited to, peptides, saccharides, poly(vinyls), poly(ethers), poly(amines), poly(carboxylic acids) and the like. In some embodiments, the water-soluble polymers is dextran, polyethylene glycol (PEG), polyoxyalkylene, polysialic acid, starch, or hydroxyethyl starch. Any suitable method

is used to conjugate peptides to water-soluble polymers (*see* Hermanson G., *Bioconjugate Techniques 2nd Ed.*, Academic Press, Inc. 2008).

[0085] In some embodiments, the targeting molecules of the present invention are conjugated to factors having neurotrophic properties (*e.g.*, neurotrophic proteins such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), glial cell line-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF) as well as non-protein small molecules with neurotrophic properties).

Methods

Labeling

[0086] Disclosed herein, in certain embodiments, are methods of labeling a neuron or nerve (or component of either) by contacting a neuron or nerve with a targeting molecule described.

[0087] In some embodiments, the contacting occurs *in vivo*. In some embodiments, the contacting occurs *in vitro*.

[0088] In some embodiments, a neuron or nerve (or component thereof) is labeled for identification during surgery. In some embodiments, the method comprises administering a targeting molecule disclosed herein to a subject that will undergo surgery. In some embodiments, the method comprises administering a targeting molecule disclosed herein to a subject that is undergoing surgery. In some embodiments, a targeting molecule disclosed herein is administered to a patient systemically. In some embodiments, a targeting molecule disclosed herein is administered to a patient locally.

Drug Delivery

[0089] Disclosed herein, in certain embodiments, are methods of targeted drug delivery. In some embodiments, a targeting molecule disclosed herein delivers a drug to a specific target. In some embodiments, a targeting molecule disclosed herein delivers a drug to a neuron or nerve.

[0090] In some embodiments, the drug is an agent that reduces pain (either the perception of pain or activity of a painful stimulant). In some embodiments, the drug is an anesthetic. In some embodiments, the drug is benzocaine; carticaine; cinchocaine; cyclomethycaine; lidocaine; prilocaine; propxycaine; proparacaine; tetracaine; tocainide; and trimecaine; or a combination thereof.

[0091] In some embodiments, the drug is an agent that modulates death (e.g., via apoptosis or necrosis) of a neuron or nerve. In some embodiments, the drug is a cytotoxic agent. In some embodiments, the drug is methotrexate (RHEUMATREX®, Amethopterin); cyclophosphamide (CYTOXAN®);thalidomide (THALIDOMID®); paclitaxel; pemetrexed; pentostatin; pipobroman; pixantrone; plicamycin; procarbazine; proteasome inhibitors (e.g.; bortezomib); raltitrexed; rebeccamycin; rubitecan; SN-38; salinosporamide A; satraplatin; streptozotocin; swainsonine; tariquidar; taxane; tegafur-uracil; temozolomide; testolactone; thioTEPA; tioguanine; topotecan; trabectedin; tretinoin; triplatin tetranitrate; tris(2-chloroethyl)amine; troxacitabine; uracil mustard; valrubicin; vinblastine; vincristine; vinorelbine; vorinostat; zosuquidar; or a combination thereof. In some embodiments, the drug is a pro-apoptotic agent. In some embodiments, the drug is an anti-apoptotic agent. In some embodiments, the drug is selected from: minocycline; SB-203580 (4-(4-Fluorophenyl)-2-(4-methylsulfinyl phenyl)-5-(4-pyridyl) 1H-imidazole); PD 169316 (4-(4-Fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)-1H-imidazole); SB 202190 (4-(4-Fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)1H-imidazole); RWJ 67657 (4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol -2-yl]-3-butyn-1-ol); SB 220025 (5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinlyl)imidazole); D-JNKI-1 ((D)-hJIP$_{175-157}$-DPro-DPro-(D)-HIV-TAT$_{57-48}$); AM-111 (Auris); SP600125 (anthra[1,9-cd]pyrazol-6(2H)-one); JNK Inhibitor I ((L)-HIV-TAT$_{48-57}$-PP-JBD$_{20}$); JNK Inhibitor III ((L)-HIV-TAT$_{47-57}$-gaba-c-Junδ_{33-57}); AS601245 (1,3-benzothiazol-2-yl (2-[[2-(3-pyridinyl) ethyl] amino]-4 pyrimidinyl) acetonitrile); JNK Inhibitor VI (H_2N-RPKRPTTLNLF-NH_2); JNK Inhibitor VIII (N-(4-Amino-5-cyano-6-ethoxypyridin-2-yl)-2-(2,5-dimethoxyphenyl)acetamide); JNK Inhibitor IX (N-(3-Cyano-4,5,6,7-tetrahydro-1-benzothien-2-yl)-1-naphthamide); dicumarol (3,3′-Methylenebis(4-hydroxycoumarin)); SC-236 (4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzene-sulfonamide); CEP-1347 (Cephalon); CEP-11004 (Cephalon); an artificial protein comprising at least a portion of a Bcl-2 polypeptide; a recombinant FNK;V5 (also known as Bax inhibitor peptide V5); Bax channel blocker ((±)-1-(3,6-Dibromocarbazol-9-yl)-3-piperazin-1-yl-propan-2-ol); Bax inhibiting peptide P5 (also known as Bax inhibitor peptide P5); Kp7-6; FAIM(S) (Fas apoptosis inhibitory molecule-short); FAIM(L) (Fas apoptosis inhibitory molecule-long); Fas:Fc; FAP-1; NOK2; F2051; F1926; F2928; ZB4; Fas M3 mAb; EGF; 740 Y-P; SC 3036 (KKHTDDGYMPMSPGVA); PI 3-kinase Activator (Santa Cruz Biotechnology, Inc.); Pam$_3$Cys ((S)-(2,3-bis(palmitoyloxy)-(2RS)-propyl)-N-palmitoyl-(R)-Cys-(S)-Ser(S)-Lys4-OH, trihydrochloride); Act1 (NF-kB activator 1); an anti-IkB antibody; Acetyl-11-keto-b-Boswellic Acid; Andrographolide; Caffeic Acid Phenethyl Ester (CAPE); Gliotoxin;

Isohelenin; NEMO-Binding Domain Binding Peptide (DRQIKIWFQNRRMKWKKTALDWSWLQTE); NF-kB Activation Inhibitor (6-Amino-4-(4-phenoxyphenylethylamino)quinazoline); NF-kB Activation Inhibitor II (4-Methyl-N1-(3-phenylpropyl)benzene-1,2-diamine); NF-kB Activation Inhibitor III (3-Chloro-4-nitro-N-(5-nitro-2-thiazolyl)-benzamide); NF-kB Activation Inhibitor IV ((E)-2-Fluoro-4′-methoxystilbene); NF-kB Activation Inhibitor V (5-Hydroxy-(2,6-diisopropylphenyl)-1H-isoindole-1,3-dione); NF-kB SN50 (AAVALLPAVLLALLAPVQRKRQKLMP); Oridonin; Parthenolide; PPM-18 (2-Benzoylamino-1,4-naphthoquinone); Ro106-9920; Sulfasalazine; TIRAP Inhibitor Peptide (RQIKIWFNRRMKWKKLQLRDAAPGGAIVS); Withaferin A; Wogonin; BAY 11-7082 ((E)3-[(4-Methylphenyl)sulfonyl]-2-propenenitrile); BAY 11-7085 ((E)3-[(4-t-Butylphenyl)sulfonyl]-2-propenenitrile); (E)-Capsaicin; Aurothiomalate (ATM or AuTM); Evodiamine; Hypoestoxide; IKK Inhibitor III (BMS-345541); IKK Inhibitor VII; IKK Inhibitor X; IKK Inhibitor II; IKK-2 Inhibitor IV; IKK-2 Inhibitor V; IKK-2 Inhibitor VI; IKK-2 Inhibitor (SC-514); IkB Kinase Inhibitor Peptide; IKK-3 Inhibitor IX; ARRY-797 (Array BioPharma); SB-220025 (5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinlyl)imidazole); SB-239063 (trans-4-[4-(4-Fluorophenyl)-5-(2-methoxy-4-pyrimidinyl) -1H-imidazol-1-yl]cyclohexanol); SB-202190 (4-(4-Fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)1H-imidazole); JX-401 (-[2-Methoxy-4-(methylthio)benzoyl]-4-(phenylmethyl)piperidine); PD-169316 (4-(4-Fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)-1H-imidazole); SKF-86002 (6-(4-Fluorophenyl)-2,3-dihydro-5-(4-pyridinyl)imidazo[2 ,1-b]thiazole dihydrochloride); SB-200646 (N-(1-Methyl-1H-indol-5-yl)-N'-3-pyridinylurea); CMPD-1 (2'-Fluoro-N-(4-hydroxyphenyl)-[1,1'-biphenyl]-4-butanamide); EO-1428 ((2-Methylphenyl)-[4-[(2-amino-4-bromophenyl)amino]-2-ch lorophenyl]methanone);SB-253080 (4-[5-(4-Fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-1H-i midazol-4-yl]pyridine); SD-169 (1H-Indole-5-carboxamide); SB-203580 (4-(4-Fluorophenyl)-2-(4-methylsulfinyl phenyl)-5-(4-pyridyl) 1H-imidazole); TZP-101 (Tranzyme Pharma); TZP-102 (Tranzyme Pharma); GHRP-6 (growth hormone-releasing peptide-6); GHRP-2 (growth hormone-releasing peptide-2); EX-1314 (Elixir Pharmaceuticals); MK-677 (Merck); L-692,429 (Butanamide, 3-amino-3-methyl-N-(2,3,4,5-tetrahydro-2-oxo-1-((2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl)-1H-1-benzazepin-3-yl)-, (R)-); EP1572 (Aib-DTrp-DgTrp-CHO); diltiazem; metabolites of diltiazem; BRE (Brain and Reproductive organ-Expressed protein); verapamil; nimodipine; diltiazem; omega-conotoxin; GVIA; amlodipine; felodipine; lacidipine; mibefradil; NPPB (5-Nitro-2-(3-phenylpropylamino)benzoic Acid); flunarizine; erythropoietin; piperine; hemin; brazilin; z-VAD-FMK (Benzyloxycarbonyl-Val-Ala-Asp(OMe)-fluoromethylketone); z-LEHD-FMK (benzyloxycarbonyl-Leu-Glu(OMe)-

His-Asp(OMe)-fluoromethylketone); B-D-FMK (boc-aspartyl(Ome)-fluoromethylketone); Ac-LEHD-CHO (N-acetyl-Leu-Glu-His-Asp-CHO); Ac-IETD-CHO (N-acetyl-Ile-Glu-Thr-Asp-CHO); z-IETD-FMK (benzyloxycarbonyl-Ile-Glu(OMe)-Thr-Asp(OMe)-fluoromethy lketone); FAM-LEHD-FMK (benzyloxycarbonyl Leu-Glu-His-Asp-fluoromethyl ketone); FAM-LETD-FMK (benzyloxycarbonyl Leu-Glu-Thr-Asp-fluoromethyl ketone); Q-VD-OPH (Quinoline-Val-Asp-CH_2-O-Ph); XIAP; cIAP-1; cIAP-2; ML-IAP; ILP-2; NAIP; Survivin; Bruce; IAPL-3; fortilin; leupeptine; PD-150606 (3-(4-Iodophenyl)-2-mercapto-(Z)-2-propenoic acid); MDL-28170 (Z-Val-Phe-CHO); calpeptin; acetyl-calpastatin; MG 132 (N-[(phenylmethoxy)carbonyl]-L-leucyl-N-[(1S)-1-formyl-3 -methylbutyl]-L-leucinamide); MYODUR; BN 82270 (Ipsen); BN 2204 (Ipsen); AHLi-11 (Quark Pharmaceuticals), an mdm2 protein, pifithrin-α (1-(4-Methylphenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2H)-benzothiazolyl)ethanone); trans-stilbene; cis-stilbene; resveratrol; piceatannol; rhapontin; deoxyrhapontin; butein; chalcon; isoliquirtigen; butein; 4,2',4'-trihydroxychalcone; 3,4,2',4',6'-pentahydroxychalcone; flavone; morin; fisetin; luteolin; quercetin; kaempferol; apigenin; gossypetin; myricetin; 6-hydroxyapigenin; 5-hydroxyflavone; 5,7,3',4',5'-pentahydroxyflavone; 3,7,3',4',5'-pentahydroxyflavone; 3,6,3',4'-tetrahydroxyflavone; 7,3',4',5'-tetrahydroxyflavone; 3,6,2',4'-tetrahydroxyflavone; 7,4'-dihydroxyflavone; 7,8,3',4'-tetrahydroxyflavone; 3,6,2',3'-tetrahydroxyflavone; 4'-hydroxyflavone; 5-hydroxyflavone; 5,4'-dihydroxyflavone; 5,7-dihydroxyflavone; daidzein; genistein; naringenin; flavanone; 3,5,7,3',4'-pentahydroxyflavanone; pelargonidin chloride; cyanidin chloride; delphinidin chloride; (−)-epicatechin (Hydroxy Sites: 3,5,7,3′,4′); (−)-catechin (Hydroxy Sites: 3,5,7,3′,4′); (−)-gallocatechin (Hydroxy Sites: 3,5,7,3′,4′,5′) (+)-catechin (Hydroxy Sites: 3,5,7,3′,4′); (+)-epicatechin (Hydroxy Sites: 3,5,7,3′,4′); Hinokitiol (b-Thujaplicin; 2-hydroxy-4-isopropyl-2,4,6-cycloheptatrien-1-one); L-(+)-Ergothioneine ((S)-a-Carboxy-2,3-dihydro-N,N,N-trimethyl-2-thioxo-1H-imidazole4-ethanaminium inner salt); Caffeic Acid Phenyl Ester; MCI-186 (3-Methyl-1-phenyl-2-pyrazolin-5-one); HBED (N,N′-Di-(2-hydroxybenzyl)ethylenediamine-N,N′-diacetic acid•H2O); Ambroxol (trans-4-(2-Amino-3,5-dibromobenzylamino)cyclohexane-HCl; and U-83836E ((−)-2-((4-(2,6-di-1-Pyrrolidinyl-4-pyrimidinyl)-1-piperzainyl)methyl)-3,4-dihydro-2,5,7,8-tetramethyl-2H-1-benzopyran-6-ol•2HCl); β-1′-5-methyl-nicotinamide-2′-deoxyribose; β-D-1′-5-methyl-nicotinamide-2′-deoxyribofuranoside; β-1′-4,5-dimethyl-nicotinamide-2′-de-oxyribose; β-D-1′-4,5-dimethyl-nicotinamide-2′-deoxyribofuranoside; 1-Naphthyl PP1 (1-(1,1-Dimethylethyl)-3-(1-naphthalenyl)-1H-pyrazolo[3, 4-d]pyrimidin-4-amine); Lavendustin A (5-[[(2,5-Dihydroxyphenyl)methyl][(2-hydroxyphenyl)methy l]amino]-2-hydroxybenzoic acid); MNS (3,4-Methylenedioxy-b-nitrostyrene); PP1 (1-(1,1-Dimethylethyl)-1-(4-methylphenyl)-1H-

pyrazolo[3, 4-d]pyrimidin-4-amine); PP2 (3-(4-chlorophenyl) 1-(1,1-dimethylethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine); KX1-004 (Kinex); KX1-005 (Kinex); KX1-136 (Kinex); KX1-174 (Kinex); KX1-141 (Kinex); KX2-328 (Kinex); KX1-306 (Kinex); KX1-329 (Kinex); KX2-391 (Kinex); KX2-377 (Kinex); ZD4190 (Astra Zeneca; N-(4-bromo-2-fluorophenyl)-6-methoxy-7-(2-(1H-1,2,3-triazol-1-yl)ethoxy)quinazolin-4-amine); AP22408 (Ariad Pharmaceuticals); AP23236 (Ariad Pharmaceuticals); AP23451 (Ariad Pharmaceuticals); AP23464 (Ariad Pharmaceuticals); AZD0530 (Astra Zeneca); AZM475271 (M475271; Astra Zeneca); Dasatinib (N-(2-chloro-6-methylphneyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino) thiazole-5-carboxamide); GN963 (trans-4-(6,7-dimethoxyquinoxalin-2ylamino)cyclohexanol sulfate); Bosutinib (4-((2,4-dichloro-5-methoxyphenyl)amino)-6-methoxy-7-(3-(4-methyl-1-piperazinyl)propoxy)-3-quinolinecarbonitrile); or combinations thereof.

[0092] In some embodiments, the drug is an agent that reduces undesired neuron or nerve impulses. In some embodiments, the drug reduces one or more symptoms of dyskinesia or synkinesia. In some embodiments, the drug is carbamazepine, oxcarbazepine, phenytein, valproic acid, sodium valproate, cinnarizine, flunarizine, or nimodipine, or combinations thereof.

[0093] In some embodiments, the drug is an agent that promotes regeneration of neuron or nerve tissue. In some embodiments, the drug is a growth factor. In some embodiments, the drug is selected from: brain-derived neurotrophic factor (BDNF); ciliary neurotrophic factor (CNTF); glial cell-line derived neurotrophic factor (GDNF); neurotrophin-3; neurotrophin-4; fibroblast growth factor (FGF) receptor; insulin-like growth factor (IGF); or a combination thereof.

Pharmaceutical Compositions

[0094] Disclosed herein, in certain embodiments, are pharmaceutical compositions comprising a targeting molecule disclosed herein. Pharmaceutical compositions herein are formulated using one or more physiologically acceptable carriers including excipients and auxiliaries which facilitate processing of the active agents into preparations which are used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions is found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage

Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins, 1999).

[0095] In certain embodiments, a pharmaceutical composition disclosed herein further comprises a pharmaceutically acceptable diluent(s), excipient(s), or carrier(s). In some embodiments, the pharmaceutical compositions includes other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, and/or buffers. In addition, the pharmaceutical compositions also contain other therapeutically valuable substances.

[0096] In certain embodiments, a pharmaceutical composition disclosed herein is administered to a subject by any suitable administration route, including but not limited to, parenteral (intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular, intrathecal, intravitreal, infusion, or local) administration.

[0097] Formulations suitable for intramuscular, subcutaneous, or intravenous injection include physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and non-aqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, cremophor and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity is maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. Formulations suitable for subcutaneous injection also contain optional additives such as preserving, wetting, emulsifying, and dispensing agents.

[0098] For intravenous injections, an active agent is optionally formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer.

[0099] Parenteral injections optionally involve bolus injection or continuous infusion. Formulations for injection are optionally presented in unit dosage form, e.g., in ampoules or in multi dose containers, with an added preservative. In some embodiments, the pharmaceutical composition described herein are in a form suitable for parenteral injection as a sterile suspensions, solutions or emulsions in oily or aqueous vehicles, and contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of an active agent in

water soluble form. Additionally, suspensions are optionally prepared as appropriate oily injection suspensions.

[0100] In some embodiments, the pharmaceutical composition described herein is in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of an active agent disclosed herein. In some embodiments, the unit dosage is in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged tablets or capsules, and powders in vials or ampoules. In some embodiments, aqueous suspension compositions are packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition. By way of example only, formulations for parenteral injection are presented in unit dosage form, which include, but are not limited to ampoules, or in multi dose containers, with an added preservative.

Examples

Example 1: Identification and Characterization of Peptides Having Nerve Binding Affinity

Identification of peptides having specific nerve affinity

[0101] Phage display screens were performed to identify peptides that bind myelinated nerves and therefore could be useful for systemic *in vivo* labeling of nerves during fluorescence assisted surgery. *In vitro* selection strategies were performed with either excised murine nerves or purified myelin basic protein (MBP), and an *in vivo* selection was performed by injecting the phage library into living mice and harvesting nerve tissue for phage isolation.

[0102] In the *in vitro* selection against MBP, after 5 binding and wash cycles, 80% of isolated phage represented a single phage with its variable sequence coding for the peptide TYTDWLNFWAWP (SEQ ID NO:2) (Table 1). Additional unique sequence that were isolated after 4-5 rounds of selection for binding to MBP were LTPIPLPTPKPP (SEQ ID NO:6), VSTMPMSNMNGP (SEQ ID NO:7), GIFERNFGAMLH (SEQ ID NO:8), ACLREYHNWC (SEQ ID NO:9), MHRQPIAPVSSL (SEQ ID NO:10), SFADPLLFLAPP (SEQ ID NO:11), ASAHHMFTPGFD (SEQ ID NO:12).

[0103] The *in vitro* selection against excised nerves yielded three sequences that were repeated. Of 14 specific phage sequences at the end of 7 rounds of selection, 5 coded for the peptide NTQTLAKAPEHT (SEQ ID NO:4), 3 for the peptide KSLSRHDHIHHH (SEQ ID

NO:3), and 2 for the peptide DFTKTSPLGIH (SEQ ID NO:5), with the remaining phage sequences being represented only once (Table 1).

[0104] In two additional selections, phage populations from the late round selections for either binding to MBP or to *in vitro* nerve were used for a secondary selection using the alternative selection strategy. (*i.e.* phage populations selected for MBP were selected for nerve binding and phage populations selected for nerve binding phage were selected for binding to MBP. From this selection 8 additional unique sequences were identified in addition to the sequences identified previously. The sequences of these phages were: VAPTKAPLHSPS (SEQ ID NO:13), NNLKTGTSAPTG (SEQ ID NO:14), HKTAQWPFIAFR (SEQ ID NO:15), RLTNAPAYQAPA (SEQ ID NO:16), MQNPLNGKPGR (SEQ ID NO:17), THYSRSLTDGTR (SEQ ID NO:18), FSTSNNQSSPAI (SEQ ID NO:19), YPSPNRPPNLTN (SEQ ID NO:20).

[0105] The *in vivo* selection did not yield any duplicated phage after 8 rounds of selection, perhaps because fluid circulation around nerves *in vivo* may not be strong enough to discriminate specifically bound phage from mechanically trapped or accidentally lodged phage. However, one *in vivo* selected sequence, AHHNSWKAKHHS (SEQ ID NO:1), was chosen for further testing (peptide synthesis and conjugation) because it contained multiple histidines reminiscent of the sequence KSLSRHDHIHHH from the *in vitro* selection against excised nerves (Table 1). Additional unique sequences identified using this *in vivo* selection were: DIANPPPPPLYV (SEQ ID NO:21), ALQTDGPFAESA (SEQ ID NO:22), DNAQHSERFPVP (SEQ ID NO:23), IPPTFPDRIRAPG (SEQ ID NO:24).

Table 1. Peptides selected from phage display screen

Selection strategy	Peptide sequence	Name
In vivo	AHHNSWKAKHHS	SEQ ID NO:1
In vitro against MBP	TYTDWLNFWAWP	SEQ ID NO:2
In vitro against excised nerves	KSLSRHDHIHHH	SEQ ID NO:3
	NTQTLAKAPEHT	SEQ ID NO:4
	DFTKTSPLGIH	SEQ ID NO:5
Control random sequence	STARDLWPHGKE	NP43

[0106] Phage selected sequences were resynthesized as peptides for in vitro and in vivo testing. For the initial synthesis of these peptides, several amino acids were added to preserve the context of which sequences were screened on phage and to add a flexible linker between the peptide and dye. Specifically, at the N-terminus SHS contained within the phage linker was added to conserve some of the context in which the peptides were screened as fusion

proteins on the phage surface. In addition, a C-terminus glycine was included to provide a flexible linker between the dye and the peptide. Removal of these residues could result in either an increase or decrease in nerve binding. A control sequence STARDLWPHGKE was designed to be similar to the sequences that were made into peptides, although in a scrambled order.

[0107] To test the nerve binding affinity of each of the isolated peptide sequences *in vitro*, dissected nerve tissue was removed from mice and incubated for one hour with 100 nM of each peptide, including a control peptide made up of amino acids that were contained within the various phages selected and sequenced, but in a mixed-up order and designed without repeating any single amino acid except for glycine (which was added to the C-terminus as a flexible linker). Peptide with sequence TYTDWLNFWAWP (designated as SEQ ID NO:2) showed about little increase in uptake compared to no peptide or control peptide. We did detect a 10-fold increase in binding of this peptide to MBP crosslinked beads compared to control beads (with no MBP) confirming specific binding of TYTDWLNFWAWP to MBP. For the remaining peptides AHHNSWKAKHHS (SEQ ID NO:1), KSLSRHDHIHHH (SEQ ID NO:3), NTQTLAKAPEHT (SEQ ID NO:4), and DFTKTSPLGIH (SEQ ID NO:5), binding ranged from a two-fold increase over control to no difference from control.

[0108] To test the nerve binding affinity of each of the isolated peptide sequences *in vivo*, carboxyfluorescein (FAM)-labeled peptides were injected intravenously into living mice. Following a wash-out period, the contrast between nerve and muscle binding of the labeled peptides was evaluated. Figure 1 shows fluorescence images of exposed sciatic nerves in living mice injected with FAM-SEQ ID NO:4 as compared to the control FAM-NP43. In SEQ ID NO:4-labeled mice (Figures 1A-1B), the nerves show a 4-fold higher fluorescence than adjacent non-neural tissue, while NP43-labeled mice (Figure 1C) show a 2-fold increase in fluorescence in nerves; the low level of labeling in NP43 control mice is likely due, at least in part, to the nonspecific binding of the fluorescein fluorophore to a variety of tissues. For the sequence identified through the *in vivo* selection (SEQ ID NO:1, Figure 2A) and the sequence identified through *in vitro* selection against MBP (SEQ ID NO:2, Figure 2B), little significant nerve-to muscle contrast was observed, as both peptides yielded high background binding to the surrounding non-neural tissue, similar to that of the control scrambled sequence (NP43, Figure 2C). The peptide sequence with the best nerve to non-nerve contrast was SEQ ID NO:4, the sequence identified through the *in vitro* selection against excised nerves with the highest repeats (Figure 2E). The other two sequences identified through this same selection strategy (SEQ ID NO:3 and SEQ ID NO:5) also exhibited nerve to muscle

contrast, although at a lower level than that of SEQ ID NO:4 (Figures 2D and 2F). A systemic survey of animals injected with FAM- SEQ ID NO:4 revealed that all nerves were brightly labeled including cranial nerves (Figure 2G-I). However, examination of nerves in the central nervous system (CNS) showed no evidence of labeling, perhaps due to lack of affinity of SEQ ID NO:4 for nerves in the CNS or the inability of the fluorescently labeled SEQ ID NO:4 to penetrate the blood brain barrier.

Peptide binding characteristics

[0109] To evaluate the time course of peptide binding to nerve tissue, sciatic nerves and surrounding non-nerve tissue in living mice were imaged before and after intravenous administration of FAM- SEQ ID NO:4. Prior to administration of FAM- SEQ ID NO:4 (Figure 3A), there was little contrast of the nerve (arrowheads) in relation to surrounding non-nerve tissue. Within seconds following intravenous administration of FAM- SEQ ID NO:4 (Figure 3B), the fluorescent injectate could be seen leaking from capillaries (arrows), including capillaries associated with the sciatic nerves (insert). Nerve fluorescence peaked at around 10 minutes post-administration (Figure 3C), and exhibited a steep decline thereafter (Figure 4A; half life ~50 minutes). Useful contrast between nerve and surrounding muscle begins to develop by 2-3 hours after intravenous injection (Figure 3E) and lasts several hours (Figure 3F). In contrast, muscle fluorescence was highest immediately following intravenous administration of the peptide, with a half life of ~20 minutes (Figure 4A). Serum half-life was calculated at ~10 minutes. Nerve to muscle contrast ratio appeared to increase with time, with a contrast of 8-10 fold by 4-5 hours (Figure 4C. By 24 hrs post-injection, all visible contrast between nerve and muscle had disappeared.

[0110] To determine the dose response of peptide binding, the nerve to muscle contrast ratio was measured as a function of the amount of peptide administered (Figure 4D). It was found that nerve to muscle contrast ratio correlates to the amount of peptide administered in a sigmoidal fashion over the range of 15 to 5,000 nmoles injected per mouse (average weight 25g).

Toxicity and motor function

[0111] To evaluate generalized toxicity following peptide administration, the generalized activity, behavior and weight gain of mice after a single intravenous injection of 15-5,000 nmoles of FAM-SEQ ID NO:4 was studied. It was found that the mice did not have any apparent changes in behavior, generalized activity or weight gain following injection with FAM-NP41 at any of doses given, as compared to uninjected mice, for up to 8 weeks of

monitoring (n=2 at 15 nmoles; n=2 at 45 nmoles; n=60 at 150 nmoles; n=2 at 450 nmoles; and n=2 at 5,000 nmoles).

[0112] To evaluate nerve function after the administration of SEQ ID NO:4, we performed nerve conduction studies to evaluate maximal compound muscle action potential (CMAP) amplitude and latency (Figure 8A). We found that the shape of the CMAP curve is similar between control and SEQ ID NO:4-treated animals (Figure 8B). CMAP amplitude and latency were also similar between control and SEQ ID NO:4-treated animals (Figure 8C).

Peptide metabolism

[0113] To evaluate the biodistribution of the peptide following systemic administration, organs were harvested from mice treated with SEQ ID NO:4 and fluorescence uptake was evaluated. The majority of the peptide accumulated in the kidney and was excreted into the urine. To evaluate the metabolism of the peptide as it passed through the renal system, liquid chromatography–mass spectrometry (LC-MS, Agilent) tracing was used to compare urine obtained from mice injected with FAM-SEQ ID NO:4 or Cy5-SEQ ID NO:4 intravenously versus urine from normal mice spiked with the native FAM-SEQ ID NO:4 or Cy5-SEQ ID NO:4. It was found that FAM-SEQ ID NO:4 and Cy5-SEQ ID NO:4 were modified as they passed through the renal system, as none of the native FAM-SEQ ID NO:4 or Cy5-SEQ ID NO:4 was detectable in urine from mice injected intravenously with FAM-SEQ ID NO:4 or Cy5-SEQ ID NO:4. Next, matrix-assisted laser desorption/ionization (MALDI) was used to evaluate the nature of the modification to the peptide as it was metabolized. The only fluorescently labeled entity identified was the lysine-FAM or cysteine-Cy5, suggesting either that the entire peptide had been degraded or that there was cleavage precisely between the terminal glycine amino acid and the lysine-FAM or cysteine-Cy5.

Effect of nerve injury on labeling

[0114] The ability of peptides to label peripheral nerves following nerve crush injury was evaluated in mice using FAM-SEQ ID NO:4. We found that nerve labeling was intact compared to the contralateral control nerve 1 day after crush injury, decreased by 40% 3 days after injury, and returned to control levels 7 days after injury (Figure 6A-F,I). We plan to perform systemic evaluation of proteins that are downregulated following crush injury with a similar time course to obtain insight into the binding target for SEQ ID NO:4. (Occasionally, nerve labeling immediately at the site of injury was slightly diminished compared to nerve labeling several centimeters away from the site of injury (Figure 6D), but this observation was highly variable (Figures 6B,F) and not statistically significant (Figure 6I)). Nerve

fluorescence was highly diminished compared to the contralateral control side immediately following nerve devascularization (by intentional injury to the feeding vessels, Figure 6G-H), presumably due to the lack of peptide access to the nerve from the devascularization procedure.

Histology

[0115] To evaluate the localization of SEQ ID NO:4 binding in nerves, we treated thy1-YFP transgenic mice whose axons are genetically encoded with YFP under a neuron specific promoter (Feng *et al*, Imaging neuronal subsets in transgenic mice expressing multiple spectral variants of GFP. *Neuron*, 2000) with Cy5 labeled SEQ ID NO:4. We found that Cy5-SEQ ID NO:4 (Figure 5C) precisely labels nerves that are genetically encoded with YFP (Figure 5B) and as seen with brightfield imaging (Figure 5A). In addition, because Cy5-SEQ ID NO:4 has deeper tissue penetration compared to imaging in the visible range (brightfield or YFP), we were able to observe nerves that were branching deep into the muscle, away from the field of view in the Cy5-labeled SEQ ID NO:4 animals (Figure 5C, insert arrows). These deeper nerve structures were not easily seen either with brightfield (Figure 5A, insert) or YFP (Figure 5B, insert) imaging. To evaluate the localization of SEQ ID NO:4 binding on a cellular level, we imaged cryosections (3-5μm) of nerves and attached muscles from thy1-YFP animals treated with Cy5-SEQ ID NO:4. We found that Cy5-SEQ ID NO:4 appears to be most localized to the epineurium of the nerves with some labeling of the perineurium and endoneurium (Figure 5F,J). We also found that SEQ ID NO:4 labeling (Figure 5F,J) does not appear to colocalize with either myelin (Figure 5D, H) or axons (Figure 5 E,I). We plan to perform a systemic evaluation of proteins that exhibit a similar pattern of localization to obtain insight into the binding target for SEQ ID NO:4.

Human nerve labeling

[0116] To evaluate whether or not FAM-SEQ ID NO:4 could selectively bind human nerves as compared to non-nerve tissue, freshly resected recurrent laryngeal nerves and adjacent muscle obtained from patients undergoing total laryngectomy for laryngeal cancer were incubated with FAM-SEQ ID NO:4. Selective binding of FAM-SEQ ID NO:4 to nerves as compared to adjacent muscle was observed (Figure 7A-B). Histological examination of tissue sections showed that the pattern of nerve binding in human tissue appeared to be to the connective tissue surrounding the nerve, *i.e.* epineurium, perineurium, and endoneurium (Figure 7C-H). This binding pattern is similar to the binding pattern observed in mice.

Example 2: Materials and Methods

Peptide selection with phage display

[0117] Phage display screens were used for *in vitro* selection of peptides binding to excised murine peripheral nerves or purified myelin basic protein (MBP) and for an *in vivo* selection screen in which the phage library was injected in the tail vein of mice followed by dissection of nerve tissue and isolation of phage.

[0118] For the *in vitro* selection, m13 phage libraries expressing random 12 amino acid sequences on the N-terminus of gIII (New England Biolabs) were processed through two parallel selections for binding to either purified MBP or to excised murine peripheral nerves. In the selection against MBP, phage expressing a library of peptide were selected through multiple cycles for binding to biotinylated MBP using avidin agarose to isolate selected phage. Specifically, phage library was mixed with biotinylated MBP and allowed to bind for 1 hour. Avidin agarose was added and incubated for an additional hour. Non-binding phage were removed by washing agarose 3 times with phosphate buffered saline solution (PBS), and the supernatant was plated for titer and amplification for subsequent cycles. This process was repeated 5 times; once repeat sequences appeared, these were synthesized for affinity testing.

[0119] In the selection against excised murine peripheral nerves, phage from the same library as the selection against MBP were isolated based on differential binding to excised murine peripheral nerves and not to adjacent muscles and fat tissue. Phage were processed through multiple cycles of selection, with representative phage being isolated and sequenced after each cycle. Specifically, for positive selection using nerve tissue, neural tissue was dissected/washed and mixed with phage library. Following incubation, the mixture (containing mostly intact nerves with phage particles that had variable affinity for nerves) was centrifuged and the pellet washed with PBS. The pellet was homogenized and plated for titering and re-amplification. For negative selection using non-nerve tissues (*e.g.*, muscle and fat), non-nerve tissues were dissected from normal mice and incubated with the phage library obtained from the positive selection. Following the incubation period, the mixture was centrifuged and the supernatant plated for titer and sequencing. Once individual sequences started to appear repetitively, these were re-synthesized for affinity testing.

[0120] For the *in vivo* selection, the same phage library as for the *in vitro* selections was injected in the tail vein of mice followed by dissection of nerve tissue and isolation of phage. In each case isolated phage were re-amplified and re-injected to iterate each selection step up

to 8 times. Specifically, phages were injected into wild-type mice. Following a binding/washout period of 2-4 hours, the mice were sacrificed and nerve tissue (sciatic, brachial plexus, cranial nerves) were dissected, washed, and homogenized. Homogenates were plated for titering and re-amplified for subsequent injections. Sample phage were sequenced after each round of selection. Once repeat sequences appeared, they were synthesized for affinity testing.

[0121] Amino acid sequences derived from sequences of selected phage were chemically synthesized as peptides by solid-phase synthesis and labeled with fluorescein or Cy5 for *in vitro* testing and *in vivo* labeling of nerves. Selected peptides were additionally attached to other fluorescent dyes and in some case conjugated to a large molecular weight carrier such as (dextran) to increase the multivalency and avidity of the peptide. Derivatives of SEQ ID NO:4 peptides that were made and tested are listed in Table 2.

Table 2. Nerve contrast with derivatives of peptide SEQ ID NO:4

Peptide	Nerve contrast
acetyl- SHSNTQTLAKAPEHTGK (5,6FAM)-amide	High
acetyl- SHSNTQTLA-(acetyl-lysine)-APEHTGK (5,6FAM)-amide	Medium/High
All D-amino acid acetyl- SHSNTQTLAKAPEHT-GK-(5,6FAM)-amide	Medium
acetyl- SHSNTQTLAKAPEHTG(L-cys)(5,6FAM)-amide	Medium/High
Free amine- SHSNTQTLAKAPEHTG-(L-cys)-(5,6FAM)-amide	Medium/High
acetyl- SHSNTQTLAKAPEHTG-(D-cys)-(5,6FAM)-amide	Medium
acetyl- SHSNTQTLAKAPEHTG-(L-cys)-(cy5)-amide	Medium/High
acetyl- SHSNTQTLAKAPEHTG-(D-cys)-(cy5)-amide	Medium
acetyl- SHSNTQTLAKAPEHTG-(L-cys)-(IR800CW)	Low
acetyl- SHSNTQTLAKAPEHTG-(L-cys-)-(TAMRA)-amide	Medium
acetyl- SHSNTQTLAKAPEHTG-(L-cys)-(Texas Red)-amide	Medium
acetyl- SHSNTQTLAKAPEHTG-(L-cys)-(indocyanine green derivative)	Low
acetyl- SHSNTQTLAKAPEHTG-(L-cys)-(heptamethinecyanine derivative)	Low

Testing of nerve binding with fluorescently labeled peptides

[0122] Wild-type albino C57BL6 (Jackson Laboratory) or SKH1 (Charles River Laboratories) mice were treated intravenously with 150nmoles of fluorescently labeled SEQ ID NO:4 via tail vein injection. Following a 2-3 hour wash-out period for FAM-SEQ ID NO:4 or 5-6 hours for Cy5-SEQ ID NO:4, mice were anesthetized with ketamine and midazolam (80mg/kg intraperitoneally), a skin incision was made over the dorsal surface of the hind legs and the sciatic nerves exposed bilaterally. Fluorescent images were acquired with a dissecting microscope (Lumar Zeiss) and a monochrome camera (Coolsnap), excitation 470/40 nm, emission 525/50 nm for FAM-SEQ ID NO:4 and excitation 620/60,

emission 700/75 for Cy5-SEQ ID NO:4, 5-10 second exposure. Nerves and adjacent non-nerve tissue was delineated with Image J and relative fluorescence was measured. Following background subtraction using dark current measurements and measurements of a standard, the ratios of peptide binding to nerve versus adjacent non-nerve tissue were calculated.

Time course of nerve binding

[0123] Female 8 week-old SKH1 mice were anesthetized with ketamine and midazolam and a skin incision was made over the dorsal surface of the hind legs and the sciatic nerves exposed. A preinjection image was taken a dissecting microscope (Lumar Zeiss) and a monochrome camera (Coolsnap). The mice were treated intravenously with 150 nmoles of FAM labeled SEQ ID NO:4 via tail vein injection. Sequential fluorescence imaging was then performed as described above: excitation 470/40 nm, emission 525/50 nm, exposure 15 milliseconds – 5 seconds. Nerves and adjacent non-nerve tissue were delineated with Image J and relative fluorescence was measured. Quantification of fluorescence was then performed following subtraction of dark current and normalizing to a standard.

Dose response of peptide binding

[0124] Female 8 week-old SKH1 mice (average weight 25 g) were treated with varying amounts of FAM-labeled SEQ ID NO:4 ranging from 15–5,000 nmoles. After a 2 hour washout period, mice were sacrificed and sciatic nerves exposed. Nerves and adjacent non-nerve tissue were delineated with Image J and relative fluorescence was measured. Quantification of fluorescence was then performed following subtraction of dark current and normalizing to a standard. For the mice injected with 5,000 nmoles of SEQ ID NO:4, it was noted that background fluorescence was still very high at 2 hours, making the contrast ratio low even though the absolute nerve fluorescence was high. For these mice, the skin incisions were repaired and the mice were allowed to awaken from anesthesia, then at 6 hours following initial SEQ ID NO:4 administration, the mice were sacrificed and the sciatic nerves exposed and analyzed as above.

Toxicity and motor function

[0125] Female 8 week-old SKH1 mice (average weight 25 g) were treated with varying amounts of FAM-labeled SEQ ID NO:4 ranging from 15–5,000 nmoles. Generalized activity, behavior and weight gain were evaluated following single intravenous injection of 15–5,000 nmoles of SEQ ID NO:4 on a daily basis for 3 days following injection. Thereafter, the mice were monitored three times per week for 8 weeks. We found that

generalized activity, behavior and weight gain were similar between SEQ ID NO 4-treated and control mice.

Nerve Conduction Studies

[0126] Maximal compound muscle action potential amplitude (CMAP) and nerve conduction latency were measured as described in Osuchowski et al, Noninvasive model of sciatic nerve conduction in healthy and septic mice: reliability and normative data, *Muscle Nerve*, 2009). Briefly, control female 8 week-old SKH1 mice and mice treated with FAM-SEQ ID NO:4 were anesthetized with ketamine-midazolam and placed in a prone position. CMAP potentials were evoked (Grass stimulator) with stimulating electrode (Medtronics) placed 2 mm lateral to the midline. The recording electrode was an ear-clip electrode (Life-tech.com) placed on the digits of the hind foot and the reference electrode was placed on the heel of the foot. Maximal CMAPs were generated by gradually increasing the stimulation (5-10V, 1 pulse per second, paired, 0.5-2sec duration) until a maximal, artifact free tracing was obtained. The CMAP traces were captured on a digital oscilloscope (Tektronic). Nerve conduction latency was measured from the beginning of the stimulation to the start of the upslope. CMAP amplitude was measured from the start of the upslope to the peak.

Peptide metabolism

[0127] To evaluate the biodistribution of the peptide following systemic administration, organs were harvested from mice treated with SEQ ID NO:4 and fluorescence uptake was evaluated. The majority of the peptide accumulated in the kidney and was excreted into the urine. To evaluate the metabolism of the peptide as it passed through the renal system, liquid chromatography–mass spectrometry (LC-MS, Agilent) tracing was used to compare urine obtained from mice injected with FAM-SEQ ID NO:4 and Cy5-SEQ ID NO:4 intravenously versus urine from normal mice spiked with the native FAM-SEQ ID NO:4. It was found that FAM-SEQ ID NO:4 and Cy5-SEQ ID NO:4 were modified as they passed through the renal system, as none of the native FAM-SEQ ID NO:4 or Cy5-SEQ ID NO:4 was detectable in urine from mice injected intravenously with FAM-SEQ ID NO:4 or Cy5-SEQ ID NO:4. Next, matrix-assisted laser desorption/ionization (MALDI) was used to evaluate the nature of the modification to the peptide as it was metabolized. The only fluorescently labeled entity identified was the lysine-FAM or cysteine-Cy5 respectively, suggesting either that the entire peptide had been degraded or that there was cleavage precisely between the terminal glycine amino acid and the lysine-FAM or cysteine-Cy5.

Effect of nerve injury on labeling

[0128] Wild type mice were anesthetized and the left sciatic nerve exposed and crushed with microforceps for 3-5 seconds. Muscular contractions during the crush after immediately afterwards were monitored to ensure uniformity of the injury. The skin incision was then closed and mice returned to their cages to recover. At varying times after crush injury, intravenous FAM-SEQ ID NO:4 (150nmoles) was administered. Two to three hours after intravenous FAM-SEQ ID NO:4 treatment, the mice were anesthetized, bilateral sciatic nerves exposed and quantitative fluorescence microscopy was used to measure nerve fluorescence. Nerve and adjacent muscle fluorescence were measured using Image J software by measuring standardized boxed regions. Crushed and contralateral control nerve fluorescence were compared for each animal.

Human nerve labeling

[0129] To evaluate whether or not FAM-SEQ ID NO:4 could selectively bind human nerves as compared to non-nerve tissue, freshly resected recurrent laryngeal nerves and adjacent muscle obtained from patients undergoing total laryngectomy for laryngeal cancer were incubated with FAM-SEQ ID NO:4 at 50μmfor 15 minutes and washed in saline for 15 minutes each. The nerve and muscle segments were then placed on a black non-fluorescent plate and imaged (Maestro, CRI). The nerve segments were then embedded in Tissue-Tek®, frozen and cryosectioned. 7-10μm cryosections were then imaged with standard fluorescence microscopy. Adjacent sections were stained with hematoxylin and eosin (H&E) and imaged.

Example 3: Selection of aptamers for nerve labeling

[0130] For the *in vivo* and *in vitro* selection, three aptamer libraries were processed through two parallel selections for binding to either excised murine nerves or in-vivo uptake into nerves after IV injection.

a. Library 1: (N60) EcoR1-N60-EcoR1
GGACGCGGAATTCCGACTCGNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNCTCATCGGAATTCCGCG
TCC

b. Library 2 (N50)- EcoR1-N50-EcoR1
GGACGCGGAATTCCGATTACNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNCAGACCGGAATTCCGCTCC

c. Library 3 (3N20) EcoR1-N20-Xba-N20-Xba-N20EcoR1
GGACGCGGAATTCCGCCGTCNNNNNNNNNNNNNNNNNNGCTCTAGAG
CNNNNNNNNNNNNNNNNNNNGCTCTAGAGCNNNNNNNNNNNNNNNN
NNNGATACCGGAATTCCGCGTCC

[0131] For *in vitro* selection of nerve binding aptamers, aptamer were selected for binding to excised nerves over multiple rounds of iterative selection. Specifically, excised nerves (both cranial and peripheral) were mixed separately with each of the 3 aptamer libraries and allowed to bind to nerve under fixed condition followed by washing and re-amplification. For rounds 1-3 nerves and aptamers were incubated at 4°C for 18 hours followed by three wash cycles in PBS at 4°C, For rounds 4-6 nerves and aptamers were incubated a 21°C for 2 hours followed by 5 washes with PBS at 21°C. In each case aptamers were eluted from nerve by heating for 10 min to 95°C in PBS with Chelex, an ion exchange resin which removes polyvalent metal ions. After selection and elution, aptamers were reamplified prior to the next round of selection. Post PCR aptamers were boiled and rapidly cooled prior to re-injection. After 5 rounds of binding and re-amplification single representative were sequenced. A partial list is listed below. Sequences of aptamers recovered from the EcoR1-N50-EcoR1 aptamer library (*i.e.*
GGACGCGGAATTCCGATTACNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNCAGACCGGAATTCCGCTCC) selection were:

a. MC-m2-a
1. GAATTC CGGTCTG GAGGACCGGATGGCAAAAATATCTAAAAAA CACAGAATAA AACGTTATTG
2. GTAATCGGAATTC

b. MC-m2-b
1. GAATTC CGATTAC CACAAATTCGTTACATGCTC CTCTATCGCG
2. CCTTCCTTCC GTCCGC
3. CAGACCGGAATTC

c. MC-m2-c
1. GAATTCCGGTCTG
2. GGAACAGACC GGCCTCTTAT TGTGGTTTCG GCTTGGTTAG CGGGTG
3. GTAATCGGAATTC

d. MC-m2-d
1. GGAATTCCGATTAC
2. CGACGTGTCTACCTTCATTTACTGTCCCCATCGTCCCCCGGGTTGGTCCCA GACCGGAATTC

e. MC-m2-e
1. GAATTCCGATTAC
2. CATAGTTATGTCGTGTCTCTAGGTCATCCTTCCTCGTCATTCCCGGTCCCA
3. GACCGGAATTC

[0132] Sequences of aptamers (variable library region in non-bold) recovered from the EcoR1-N20-Xba-N20-Xba-N20-EcoR1 aptamer library (*i.e.* GGACGCGGAATTCCGCCGTCNNNNNNNNNNNNNNNNNNNNGCTCTAGAGCNNNNNNNNNNNNNNNNNNNNNNGCTCTAGAGCNNNNNNNNNNNNNNNNNNNNGATACCGGAATTCCGCGTCC) selections were:

a. MC-m3-a
1. GAATTCCGCCGTC
2. GGCGGGACCTGGGCTATGTT
3. GCTTTAGAG
4. CCCGGAAGGCAGGGGTAATA
5. GCTCTAGAG
6. CCAGGAGAGGTGTGGGGGGTG
7. GATACCGGAATTC

b. MC-m3-b
1. GAATTCCGCCGTC
2. GGCGGACGACCCTCAGTTCG
3. GCTCTAGGAG
4. CAATATTAATCCTCATGGGCC
5. GCTCTAGAG
6. CTCGCACTTTTTTGTAATGTT
7. GATACCGGAATTCC

[0133] Sequences of aptamers (variable library region in non-bold) recovered from the EcoR1-N60-EcoR1 aptamer library (*i.e.* GGACGCGGAATTCCGACTCGNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNCTCATCGGAATTCCGCGTCC) selection were:

a. m1a
1. GAATTCCGATGAG
2. CACAATCTCAACCACGTCCCCAAGCAATGTAGCTTCCACGATTTATGGCCCGACTCGTCC
3. CGAGTCGGAATTCC

b. m1b
1. GAATTCCGATGAG
2. CACAATCTCAACCACGTCCCCAAGCAATGTAGCTTCCACGATTTATGGCCCGACTCGTCC
3. CGAGTCGGAATTCC

[0134] Aptamers (as either pool or single sequences) were labeled with fluorescein using fluorescently labeled PCR primers and tested for binding to dissected nerve versus muscle tissue.

[0135] *In vivo* selection for aptamer binding to nerves: For the *in vivo* selection the N60 aptamer library was injected in the tail vein of mice followed by dissection of nerve tissue. Dissected tissues were washed mixed with chelex, boiled and used for PCR reamplification. After selection and elution, aptamers were reamplified prior to the next round of selection.

[0136] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference. Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

WHAT IS CLAIMED IS:

1. A targeting molecule comprising a peptide or an aptamer that specifically binds to a neuron or nerve, or component of either.

2. The molecule of claim 1, wherein the peptide is at least 85% homologous to a peptide selected from: AHHNSWKAKHHS (SEQ ID NO:1), TYTDWLNFWAWP (SEQ ID NO:2), KSLSRHDHIHHH (SEQ ID NO:3), NTQTLAKAPEHT (SEQ ID NO:4), DFTKTSPLGIH (SEQ ID NO:5), LTPIPLPTPKPP(SEQ ID NO:6), VSTMPMSNMNGP (SEQ ID NO:7), GIFERNFGAMLH (SEQ ID NO:8), ACLREYHNWC (SEQ ID NO:9), MHRQPIAPVSSL (SEQ ID NO:10), SFADPLLFLAPP (SEQ ID NO:11), ASAHHMFTPGFD (SEQ ID NO:12), VAPTKAPLHSPS (SEQ ID NO:13), NNLKTGTSAPTG (SEQ ID NO:14), HKTAQWPFIAFR (SEQ ID NO:15), RLTNAPAYQAPA (SEQ ID NO:16), MQNPLNGKPGR (SEQ ID NO:17), THYSRSLTDGTR,(SEQ ID NO:18), FSTSNNQSSPAI (SEQ ID NO:19), YPSPNRPPNLTN (SEQ ID NO:20), DIANPPPPPLYV (SEQ ID NO:21), ALQTDGPFAESA (SEQ ID NO:22), DNAQHSERFPVP (SEQ ID NO:23), and IPPTFPDRIRAPG (SEQ ID NO:24).

3. The molecule of claim 1, further comprising a drug.

4. The molecule of claim 1, further comprising a drug selected from: an antihistamine, a GABA receptor modulator, a neurotransmitter reuptake inhibitor, a local anesthetic, an anticholinergic, a sodium channel blocker, a calcium channel blocker, a thyrotropin-releasing hormone, a γ-secretase inhibitor, an AMPA receptor agonist or antagonist, an NMDA receptor agonist or antagonist, an mGlu receptor agonist or antagonist, a growth factor, an antiemetic agent, a corticosteroid; a cytotoxic agent; an antioxidant, an iron chelator, a mitochondrial modulator, a sirtuin modulator, a nitric oxide (NO) and/or nitric oxide synthase (NOS) modulator, a potassium channel agonist or antagonist, a purigenic receptor agonist or antagonist, or a combination thereof.

5. The molecule of claim 1, further comprising a drug selected from: benzocaine; carticaine; cinchocaine; cyclomethycaine; lidocaine; prilocaine; propxycaine; proparacaine; tetracaine; tocainide; and trimecaine; methotrexate; cyclophosphamide; thalidomide; paclitaxel; pemetrexed; pentostatin; pipobroman; pixantrone; plicamycin;

procarbazine; raltitrexed; rebeccamycin; rubitecan; SN-38; salinosporamide A; satraplatin; streptozotocin; swainsonine; tariquidar; taxane; tegafur-uracil; temozolomide; testolactone; thioTEPA; tioguanine; topotecan; trabectedin; tretinoin; triplatin tetranitrate; tris(2-chloroethyl)amine; troxacitabine; uracil mustard; valrubicin; vinblastine; vincristine; vinorelbine; vorinostat; zosuquidar; carbamazepine; oxcarbazepine; phenytein; valproic acid; sodium valproate; cinnarizine; flunarizine; nimodipine; brain-derived neurotrophic factor (BDNF); ciliary neurotrophic factor (CNTF); glial cell-line derived neurotrophic factor (GDNF); neurotrophin-3; neurotrophin-4; fibroblast growth factor (FGF) receptor; insulin-like growth factor (IGF); or a combination thereof.

6. The molecule of claim 1, further comprising a fluorescent moiety.

7. The molecule of claim 1, further comprising a fluorescent moiety selected from: a fluorescent protein, a fluorescent peptide, a fluorescent dye, or a combination thereof.

8. The molecule of claim 1, further comprising a fluorescent moiety selected from: a xanthene; a bimane; a coumarin; an aromatic amines; a benzofuran; a fluorescent cyanine; a carbazole; a dicyanomethylene pyrane; polymethine; oxabenzanthrane; pyrylium; carbostyl; perylene; acridone; quinacridone; rubrene; anthracene; coronene; phenanthrecene; pyrene; butadiene; stilbene; porphyrin; pthalocyanine; lanthanide metal chelate complexes; rare-earth metal chelate complexes; and derivatives thereof.

9. The molecule of claim 1, further comprising a fluorescent moiety selected from: 5-carboxyfluorescein; fluorescein-5-isothiocyanate; 6-carboxyfluorescein; tetramethylrhodamine-6-isothiocyanate; 5-carboxytetramethylrhodamine; 5-carboxy rhodol derivatives; tetramethyl and tetraethyl rhodamine; diphenyldimethyl and diphenyldiethyl rhodamine; dinaphthyl rhodamine; rhodamine 101 sulfonyl chloride; Cy3, Cy3B, Cy3.5, Cy5, Cy5.5, Cy 7, indocyanine green, IR800CW or combinations thereof.

10. A method of identifying a neuron or nerve, comprising contacting the neuron or nerve with a targeting molecule comprising (a) a peptide or an aptamer that specifically binds to the neuron or nerve, or component of either, and (b) a fluorescent moiety.

11 . The method of claim 10, wherein the peptide is at least 85% homologous to a peptide selected from: AHHNSWKAKHHS (SEQ ID NO:1),

TYTDWLNFWAWP (SEQ ID NO:2), KSLSRHDHIHHH (SEQ ID NO:3), NTQTLAKAPEHT (SEQ ID NO:4), DFTKTSPLGIH (SEQ ID NO:5), LTPIPLPTPKPP (SEQ ID NO:6), VSTMPMSNMNGP (SEQ ID NO:7), GIFERNFGAMLH (SEQ ID NO:8), ACLREYHNWC (SEQ ID NO:9), MHRQPIAPVSSL (SEQ ID NO:10), SFADPLLFLAPP (SEQ ID NO:11), ASAHHMFTPGFD (SEQ ID NO:12), VAPTKAPLHSPS (SEQ ID NO:13), NNLKTGTSAPTG (SEQ ID NO:14), HKTAQWPFIAFR (SEQ ID NO:15), RLTNAPAYQAPA (SEQ ID NO:16), MQNPLNGKPGR (SEQ ID NO:17), THYSRSLTDGTR (SEQ ID NO:18), FSTSNNQSSPAI (SEQ ID NO:19), YPSPNRPPNLTN (SEQ ID NO:20), DIANPPPPPLYV (SEQ ID NO:21), ALQTDGPFAESA (SEQ ID NO:22), DNAQHSERFPVP (SEQ ID NO:23), and IPPTFPDRIRAPG (SEQ ID NO:24).

12. The method of claim 10, wherein the fluorescent moiety is selected from: a fluorescent protein, a fluorescent peptide, a fluorescent dye, or a combination thereof.

13. The method of claim 10, wherein the fluorescent moiety is selected from: a xanthene; a bimane; a coumarin; an aromatic amines; a benzofuran; a fluorescent cyanine; a carbazole; a dicyanomethylene pyrane; polymethine; oxabenzanthrane; pyrylium; carbostyl; perylene; acridone; quinacridone; rubrene; anthracene; coronene; phenanthrecene; pyrene; butadiene; stilbene; porphyrin; pthalocyanine; lanthanide metal chelate complexes; rare-earth metal chelate complexes; and derivatives thereof.

14. The method of claim 10, wherein the fluorescent moiety is selected from: 5-carboxyfluorescein; fluorescein-5-isothiocyanate; 6-carboxyfluorescein; tetramethylrhodamine-6-isothiocyanate; 5-carboxytetramethylrhodamine; 5-carboxy rhodol derivatives; tetramethyl and tetraethyl rhodamine; diphenyldimethyl and diphenyldiethyl rhodamine; dinaphthyl rhodamine; rhodamine 101 sulfonyl chloride; Cy3, Cy3B, Cy3.5, Cy5, Cy5.5, Cy 7, indocyanine green, IR800CW or combinations thereof.

15. A method of delivering a drug to a neuron or nerve, comprising contacting the neuron or nerve with a targeting molecule comprising (a) a peptide or an aptamer that specifically binds to the neuron or nerve, or component of either., and (b) a drug.

16. The method of claim 15, wherein the peptide is at least 85% homologous to a peptide selected from: AHHNSWKAKHHS (SEQ ID NO:1), TYTDWLNFWAWP (SEQ ID NO:2), KSLSRHDHIHHH (SEQ ID NO:3), NTQTLAKAPEHT (SEQ ID NO:4), DFTKTSPLGIH (SEQ ID NO:5), LTPIPLPTPKPP

(SEQ ID NO:6), VSTMPMSNMNGP (SEQ ID NO:7), GIFERNFGAMLH (SEQ ID NO:8), ACLREYHNWC (SEQ ID NO:9), MHRQPIAPVSSL (SEQ ID NO:10), SFADPLLFLAPP (SEQ ID NO:11), ASAHHMFTPGFD (SEQ ID NO:12), VAPTKAPLHSPS (SEQ ID NO:13), NNLKTGTSAPTG (SEQ ID NO:14), HKTAQWPFIAFR (SEQ ID NO:15), RLTNAPAYQAPA (SEQ ID NO:16), MQNPLNGKPGR (SEQ ID NO:17), THYSRSLTDGTR (SEQ ID NO:18), FSTSNNQSSPAI (SEQ ID NO:19), YPSPNRPPNLTN (SEQ ID NO:20), DIANPPPPPLYV (SEQ ID NO:21), ALQTDGPFAESA (SEQ ID NO:22), DNAQHSERFPVP (SEQ ID NO:23), and IPPTFPDRIRAPG (SEQ ID NO:24).

17. The method of claim 15, wherein the drug is selected from: an antihistamine, a GABA receptor modulator, a neurotransmitter reuptake inhibitor, a local anesthetic, an anticholinergic, a sodium channel blocker, a calcium channel blocker, a thyrotropin-releasing hormone, a γ-secretase inhibitor, an AMPA receptor agonist or antagonist, an NMDA receptor agonist or antagonist, an mGlu receptor agonist or antagonist, a growth factor, an antiemetic agent, a corticosteroid; a cytotoxic agent; an antioxidant, an iron chelator, a mitochondrial modulator, a sirtuin modulator, a nitric oxide (NO) and/or nitric oxide synthase (NOS) modulator, a potassium channel agonist or antagonist, a purigenic receptor agonist or antagonist, or a combination thereof.

18. The method of claim 15, wherein the drug is selected from: benzocaine; carticaine; cinchocaine; cyclomethycaine; lidocaine; prilocaine; propxycaine; proparacaine; tetracaine; tocainide; and trimecaine; methotrexate; cyclophosphamide; thalidomide; paclitaxel; pemetrexed; pentostatin; pipobroman; pixantrone; plicamycin; procarbazine; raltitrexed; rebeccamycin; rubitecan; SN-38; salinosporamide A; satraplatin; streptozotocin; swainsonine; tariquidar; taxane; tegafur-uracil; temozolomide; testolactone; thioTEPA; tioguanine; topotecan; trabectedin; tretinoin; triplatin tetranitrate; tris(2-chloroethyl)amine; troxacitabine; uracil mustard; valrubicin; vinblastine; vincristine; vinorelbine; vorinostat; zosuquidar; carbamazepine; oxcarbazepine; phenytein; valproic acid; sodium valproate; cinnarizine; flunarizine; nimodipine; brain-derived neurotrophic factor (BDNF); ciliary neurotrophic factor (CNTF); glial cell-line derived neurotrophic factor (GDNF); neurotrophin-3; neurotrophin-4; fibroblast growth factor (FGF) receptor; insulin-like growth factor (IGF); or a combination thereof.

19. A pharmaceutical composition comprising: (a) a peptide or aptamer that specifically binds to a neuron, nerve, or component of either, and (b) a pharmaceutically acceptable excipient.

20. The composition of claim 19, wherein the peptide is at least 85% homologous to a peptide selected from: AHHNSWKAKHHS (SEQ ID NO:1), TYTDWLNFWAWP (SEQ ID NO:2), KSLSRHDHIHHH (SEQ ID NO:3), NTQTLAKAPEHT (SEQ ID NO:4), DFTKTSPLGIH (SEQ ID NO:5), LTPIPLPTPKPP (SEQ ID NO:6), VSTMPMSNMNGP (SEQ ID NO:7), GIFERNFGAMLH (SEQ ID NO:8), ACLREYHNWC (SEQ ID NO:9), MHRQPIAPVSSL (SEQ ID NO:10), SFADPLLFLAPP (SEQ ID NO:11), ASAHHMFTPGFD (SEQ ID NO:12), VAPTKAPLHSPS (SEQ ID NO:13), NNLKTGTSAPTG (SEQ ID NO:14), HKTAQWPFIAFR (SEQ ID NO:15), RLTNAPAYQAPA (SEQ ID NO:16), MQNPLNGKPGR (SEQ ID NO:17), THYSRSLTDGTR (SEQ ID NO:18), FSTSNNQSSPAI (SEQ ID NO:19), YPSPNRPPNLTN (SEQ ID NO:20), DIANPPPPPLYV (SEQ ID NO:21), ALQTDGPFAESA (SEQ ID NO:22), DNAQHSERFPVP (SEQ ID NO:23), and IPPTFPDRIRAPG (SEQ ID NO:24).

21. The composition of claim 19, wherein the peptide or aptamer is bound to a drug or fluorescent moiety.

Figure 1

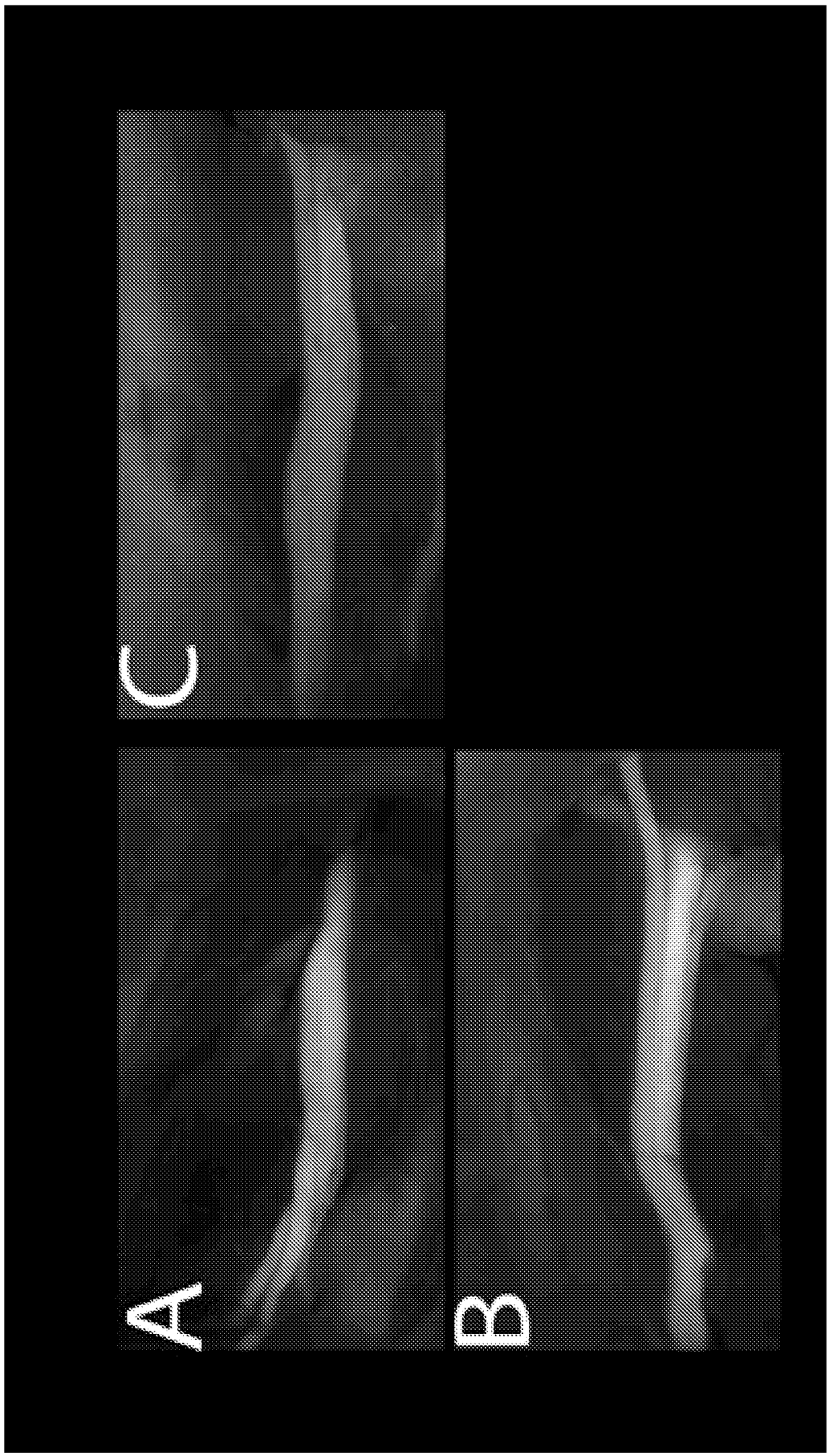


Figure 2

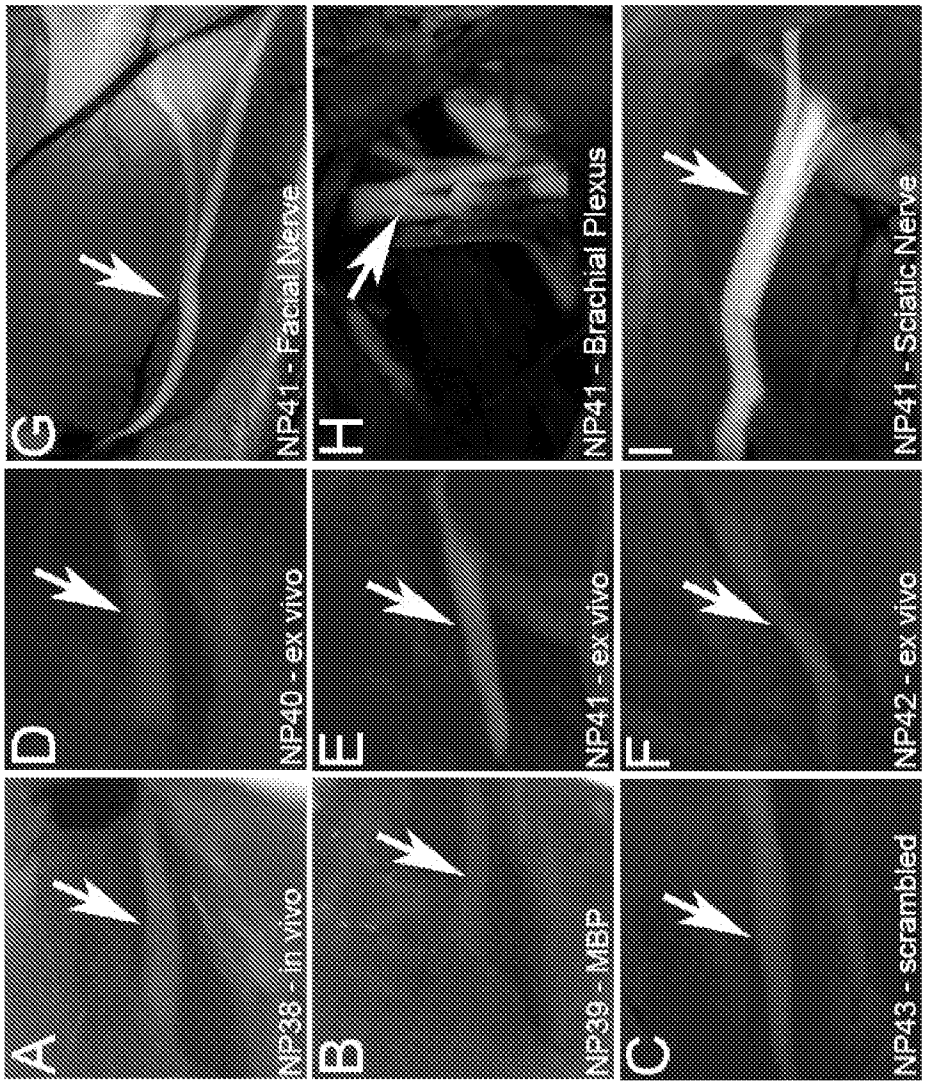

A
NP38 - In Vivo
D
NP40 - ex vivo
G
NP41 - Facial Nerve
B
NP39 - MBP
E
NP41 - ex vivo
H
NP41 - Brachial Plexus
C
NP43 - scrambled
F
NP42 - ex vivo
I
NP41 - Sciatic Nerve

Figure 3

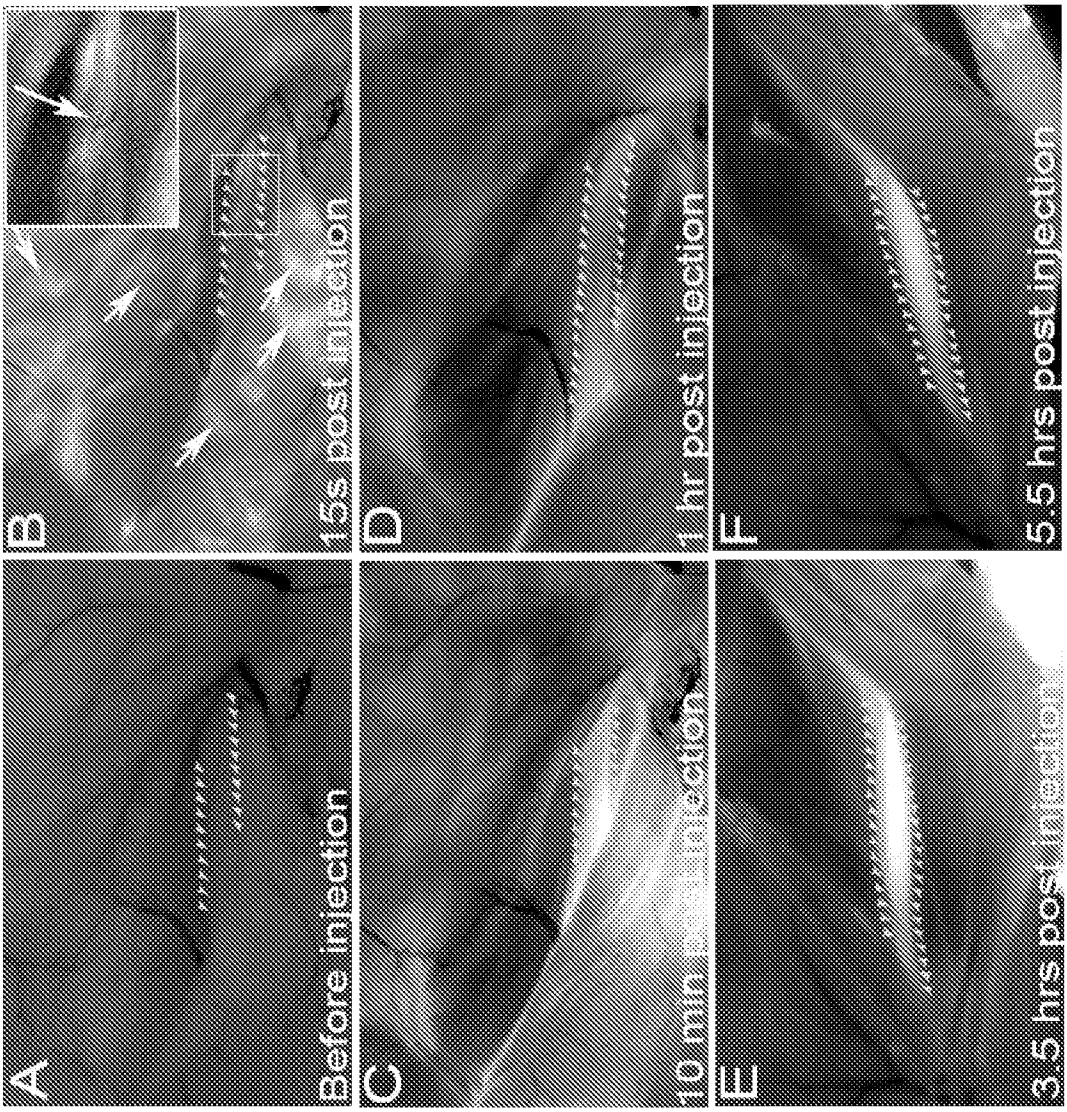

A
Before injection
B
15s post injection
C
10 min post injection
D
1 hr post injection
E
3.5 hrs post injection
F
5.5 hrs post injection

Figure 4

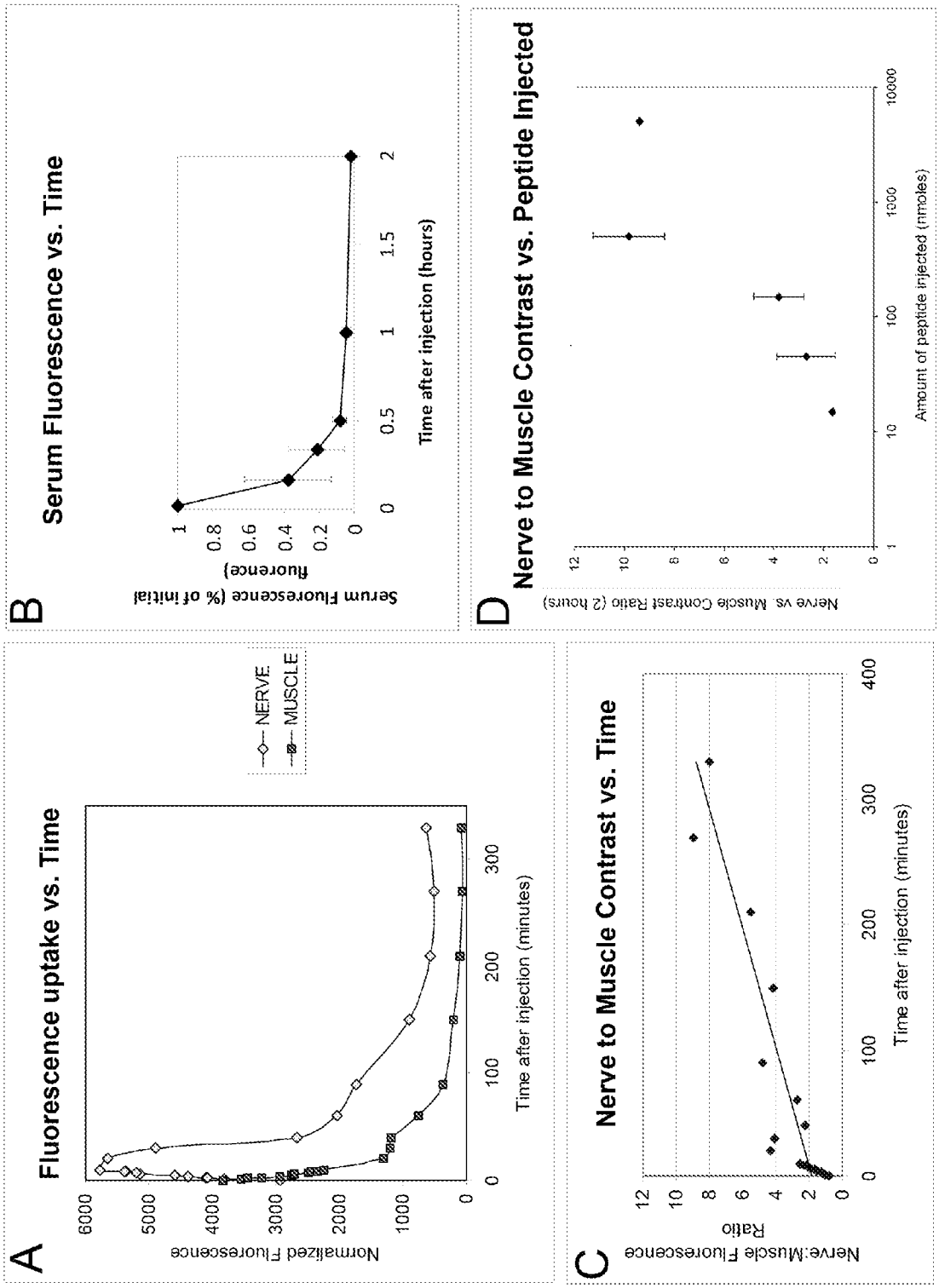

A
Fluorescence uptake vs. Time
NERVE
MUSCLE
Normalized Fluorescence
Time after injection (minutes)
B
Serum Fluorescence vs. Time
Serum Fluorescence (% of initial fluorence)
Time after injection (hours)
C
Nerve to Muscle Contrast vs. Time
Nerve:Muscle Fluorescence Ratio
Time after injection (minutes)
D
Nerve to Muscle Contrast vs. Peptide Injected
Nerve vs. Muscle Contrast Ratio (2 hours)
Amount of peptide injected (nmoles)

Figure 5

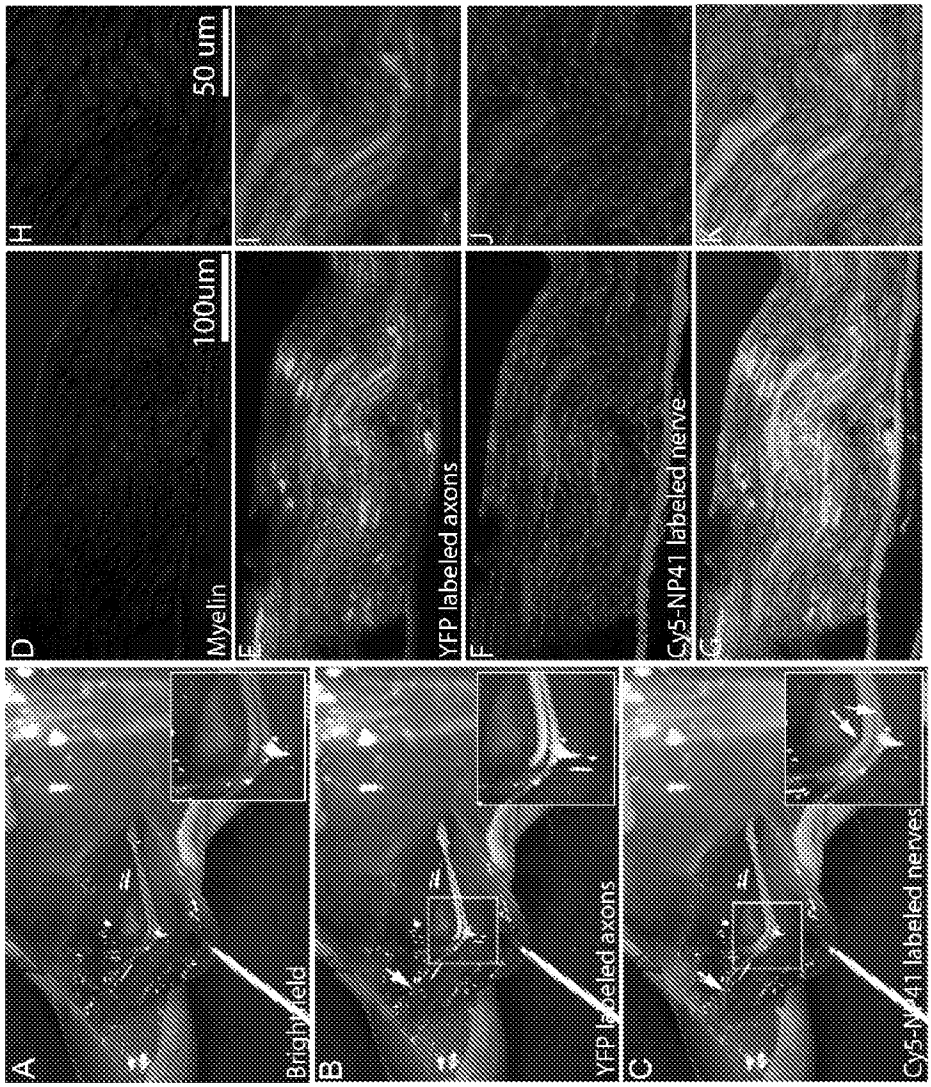

A
B
C
D
E
F
G
H
I
J
K
Brightfield
YFP labeled axons
Cy5-NP41 labeled nerves
Myelin
YFP labeled axons
Cy5-NP41 labeled nerve
100um
50 um

Figure 6

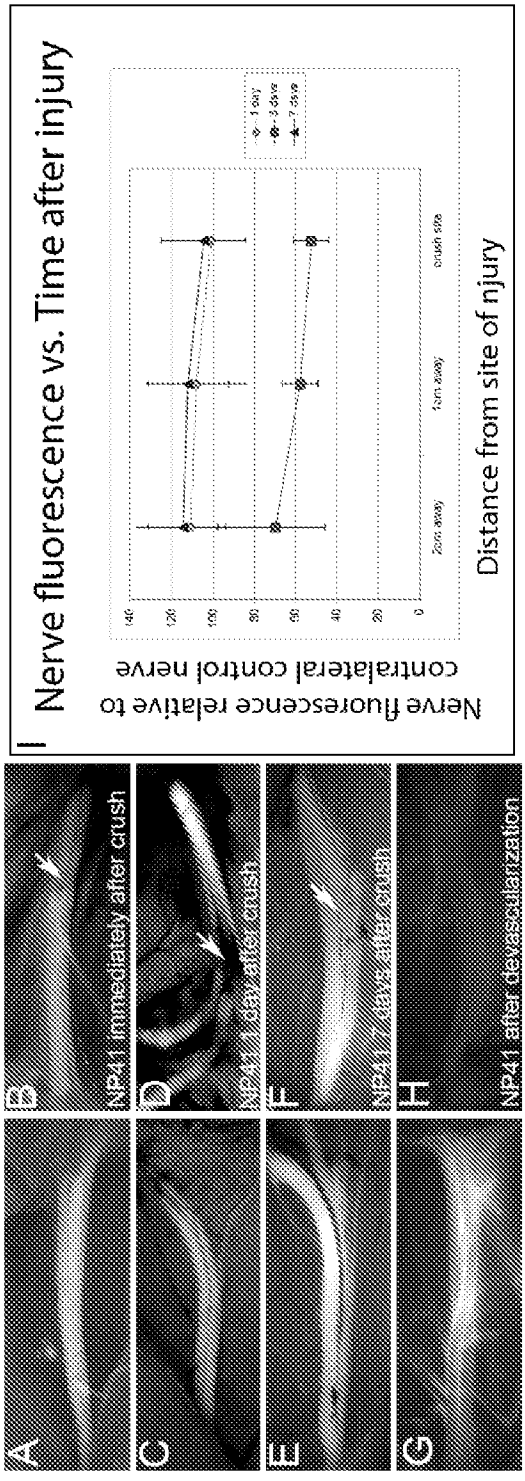

A
B
NP41 immediately after crush
C
D
NP41 1 day after crush
E
F
NP41 7 days after crush
G
H
NP41 after devascularization
I
Nerve fluorescence vs. Time after injury
Nerve fluorescence relative to contralateral control nerve
Distance from site of njury
1 day
3 days
7 days
Zone away
1cm away
crush site

Figure 7

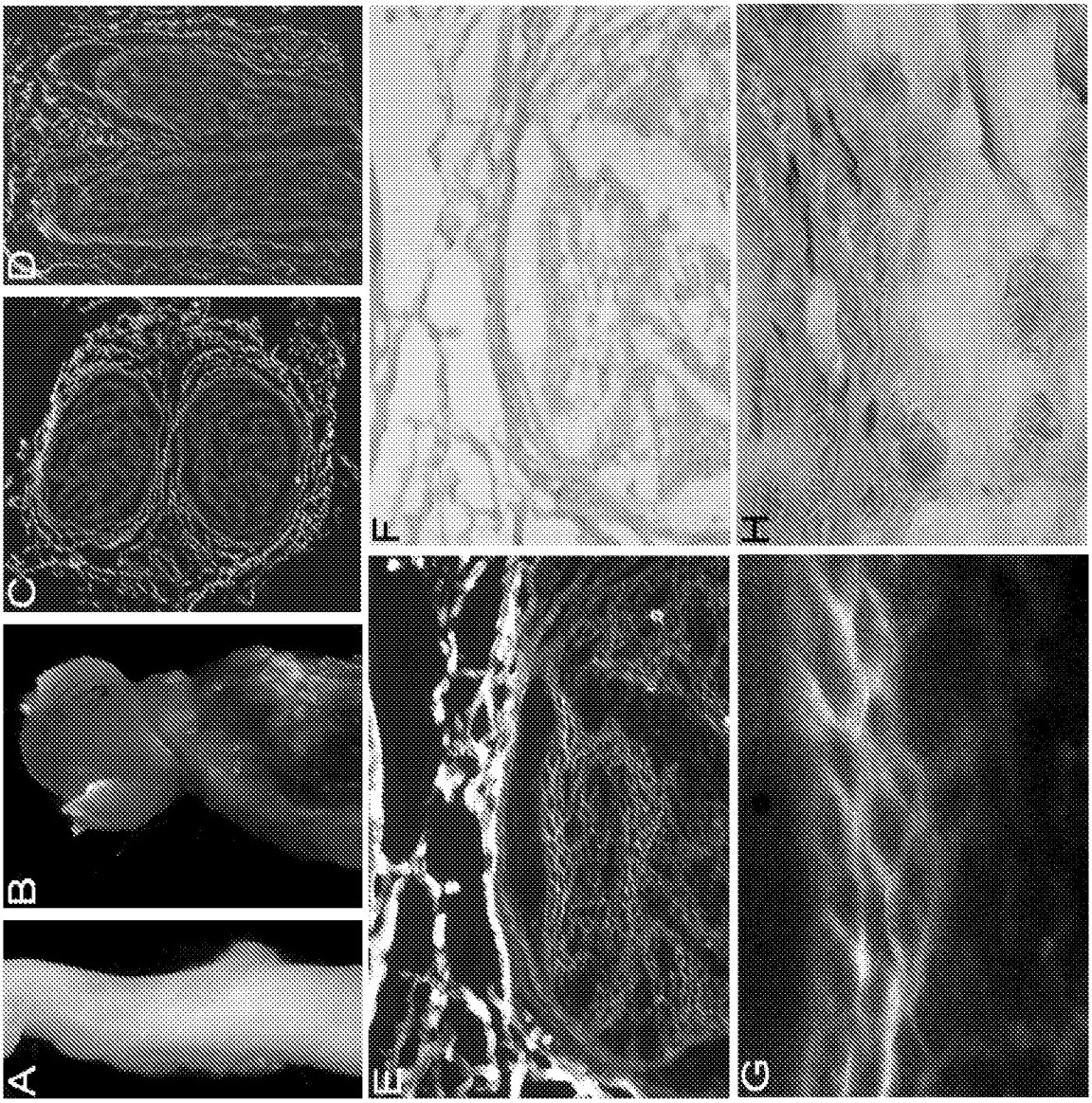
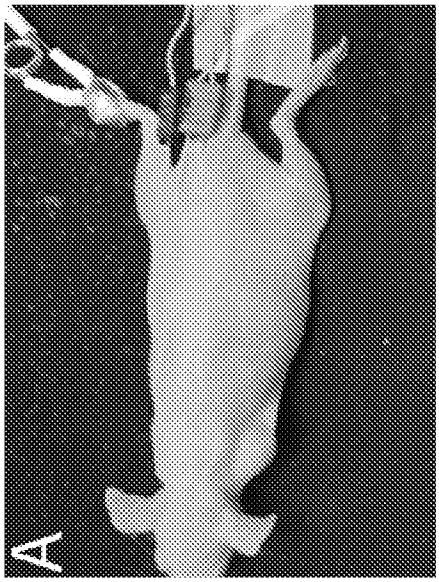
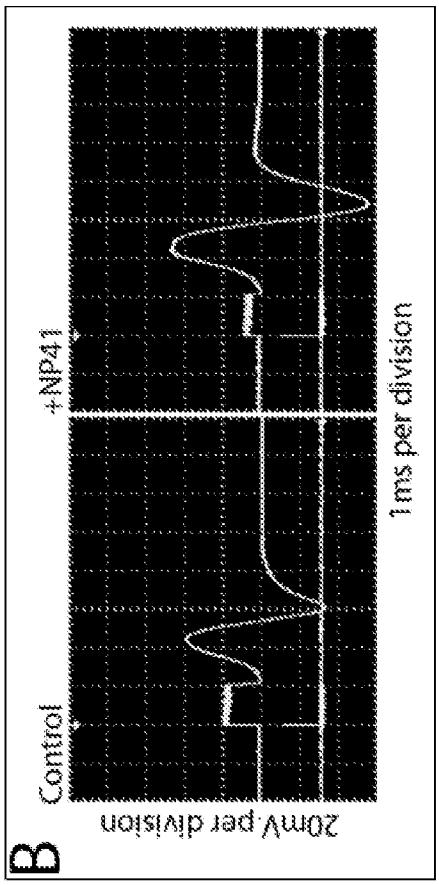


Figure 8

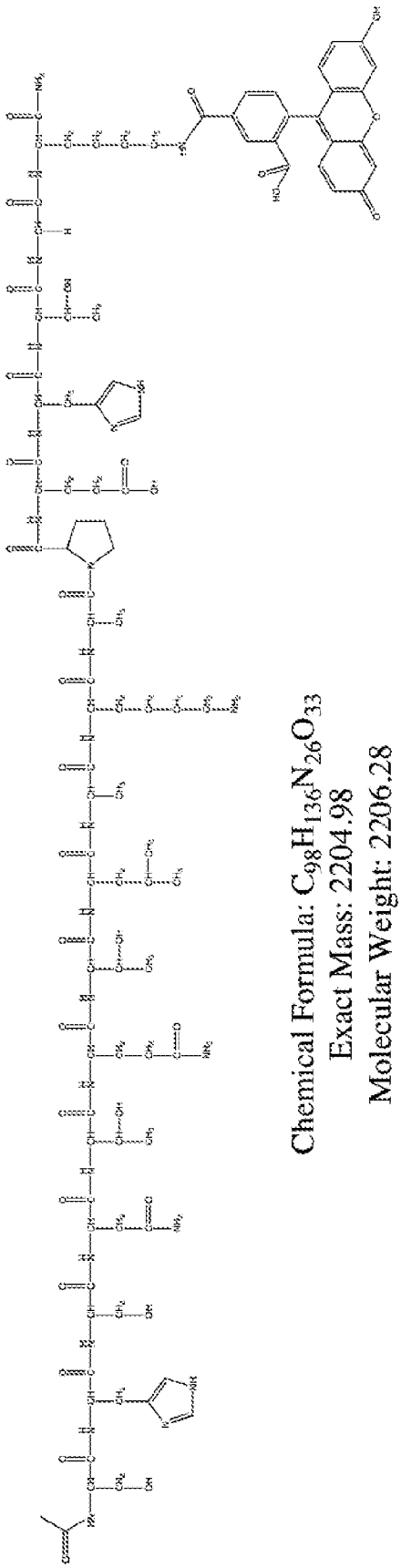




C

	CMAP Amplitude (mV)	Latency (msec)
Control (n = 4 mice, 8 nerves)	31.88 ± 8.39	1.18±0.15
+NP41 (n = 4 mice, 8 nerves)	40.50 ± 9.36	1.09±0.08
2-tailed Student's t test	0.073	0.169

Figure 9



Chemical Formula: $C_{98}H_{136}N_{26}O_{33}$
Exact Mass: 2204.98
Molecular Weight: 2206.28