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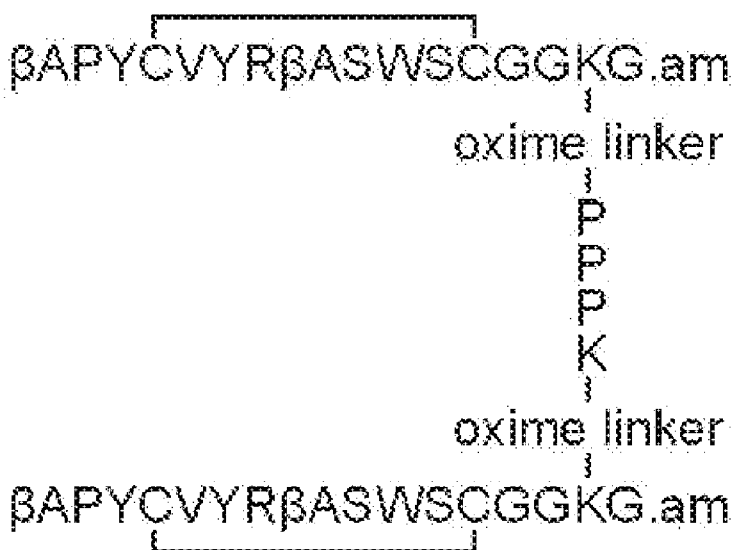
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[Continued on next page]

- (54) **Title:** MODIFIED EPHA4 CYCLIC PEPTIDE ANTAGONISTS FOR NEUROPROTECTION AND NEURAL REPAIR

FIG. 1A



(57) **Abstract:** The present specification discloses modified APY cyclic peptides having EphA4 antagonistic activity, pharmaceutical compositions containing such EphA4 antagonists, and methods and uses of treating an EphA4-based disease, disorder or pathology in an individual using such modified APY cyclic peptides or pharmaceutical compositions.



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**MODIFIED EPHA4 CYCLIC PEPTIDE ANTAGONISTS FOR NEUROPROTECTION AND NEURAL
REPAIR**

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[001] This application claims the benefit of priority and the filing date pursuant to 35 U.S.C. § 119(e) of U.S. Provisional Patent Application 62/193,010, filed on July 15, 2015, the contents of which are hereby incorporated by reference in its entirety.

GOVERNMENT LICENSE RIGHTS

[002] This invention was made with government support under 5P01CA138390 awarded by the National Institutes of Health; under R01GM098871 awarded by the National Institutes of Health; under R01NS087070 awarded by the National Institutes of Health; under P30CA030199 awarded by the National Institutes of Health. The government has certain rights in the invention.

REFERENCE TO SEQUENCE LISTING

[003] Submitted as part of this patent application is a Sequence Listing file named 3IPSB1-0001WOSeqList.txt having a file size of 44 KB, the content of which is hereby expressly incorporated by reference in its entirety.

BACKGROUND

[004] The Ephrin (Eph) receptors are a large family of receptor tyrosine kinases with many functions in physiology and disease. They bind their activating ligands, the ephrins, mainly through a high-affinity binding pocket located in the N-terminal ephrin-binding domain. Each of the five ephrin-A ligands can bind to most of the nine EphA receptors and each of the three ephrin-B ligands can bind to the five EphB receptors. A cysteine-rich region and two fibronectin type III domains connect the ephrin-binding domain to the transmembrane segment. The cytoplasmic portion of the Eph receptors includes a juxtamembrane segment, the kinase domain, a sterile-alpha-motif (SAM) domain and a C-terminal PDZ domain-binding motif. Interaction between Eph receptors and ephrin ligands, which are attached to the cell surface through a GPI-anchor (ephrin-As) or a transmembrane domain (ephrin-Bs), typically occurs at sites of cell-cell contact. Ephrin binding promotes activation of the receptor's kinase domain, triggering "forward" signals. Ephrin ligands engaged with Eph receptors can also affect the cells in which they are expressed by mediating "reverse" signals.

[005] Ephrin type-A receptor 4 (EphA4) signaling can be activated by all ephrin ligands, including the five GPI-linked ephrin-As and the three transmembrane ephrin-Bs. Highly expressed in the nervous system, EphA4 tyrosine kinase activity and downstream signaling leads to inhibition of axon growth and retraction of synaptic structures known as dendritic spines. The repulsive effects of EphA4 in neurons help guide the growth of developing axons towards their synaptic targets and may contribute to inhibition

of axon regeneration following injury. In addition, EphA4 interaction with the ephrin-A3 ligand expressed in astrocytes stimulates "reverse" signals through the ephrin that limit the uptake of the extracellular neurotransmitter glutamate, thus modulating synaptic transmission. EphA4 is also highly expressed in adult hippocampal neurons, where it controls synaptic morphology and plasticity. Furthermore, EphA4 appears to contribute to the maintenance of brain neural stem cells in an undifferentiated state. This is in contrast to muscle, where EphA4 may contribute to myoblast differentiation.

[006] Dysregulation of EphA4 activity and/or function has been implicated in the pathophysiology of neurodegenerative disorders, the promotion of neurotoxicity, the inhibition of nerve differentiation and regeneration, and in the progression of cancer. For example, low EphA4 expression and loss-of-function mutations are linked to late onset and prolonged survival in amyotrophic lateral sclerosis (ALS), a fatal diseases that still lack any means for effective therapeutic intervention. Even partial EphA4 gene inactivation has shown beneficial effects in animal models of ALS, making EphA4 inhibition an attractive strategy for counteracting neurodegeneration. In addition, EphA4 was identified as a possible inhibitor of nerve regeneration after spinal cord injury. Experiments in mice suggest a role for EphA4 in the behavioral responses to cocaine administration. Further evidence also supports the involvement of EphA4 in the pathogenesis of spinal cord injury and other neurological diseases such as Alzheimer's disease, multiple sclerosis, stroke and traumatic brain injury. These pathological roles of EphA4 in the diseased nervous system are regarded as being linked to its increased expression and activation by ephrin ligands or A β -oligomers in the Alzheimer's brain, leading to abnormal inhibition of axon growth, synaptic function and neuronal survival. Furthermore, EphA4 signaling prevents the generation of cochlear sensory hair cells suggesting that inhibition of EphA4 activity could be an effective therapy in the treatment of hearing loss. Finally, increasing evidence also implicates EphA4 in various types of cancer, including glioblastoma, gastric cancer, pancreatic cancer, prostate cancer and breast cancer. For example, EphA4 downregulation studies have suggested a role for EphA4 in leukemia, prostate cancer, pancreatic cancer and gastric cancer cell growth and in liver cancer metastasis. High EphA4 expression has also been correlated with shorter survival in breast and gastric cancer patients, although the opposite correlation was found in lung cancer patients. EphA4 is also highly upregulated in Sezary syndrome, a leukemic variant of cutaneous T-cell lymphomas. Finally, EphA4 can enhance the oncogenic effects of fibroblast growth factor receptor 1 in glioblastoma cells. Hence, inhibiting EphA4-ephrin interaction could be useful for promoting axon regeneration and neural repair, providing neuroprotection and regulating synaptic plasticity in the nervous system as well as inhibiting the progression of cancer.

[007] The two main strategies to block ephrin-induced EphA4 receptor signaling are inhibition of EphA4 kinase activity using kinase inhibitors and inhibition of ephrin binding to the EphA4 ligand binding domain using antagonists. Kinase inhibitors are hampered by low selectivity because they typically target multiple kinases due to the high conservation of the ATP binding pocket. As such, it is very difficult to identify kinase inhibitors selective for EphA4. In contrast, the ephrin-binding pocket in the extracellular EphA4 ligand binding domain has unique features that can be exploited for more selective antagonist targeting. However, the ephrin-binding pocket is very broad (exceeding 900 Å²) and shallow for high affinity binding of small molecules, and small molecule EphA4 antagonists found to date are not very

potent and exhibit problematic features that make them unsuitable for therapeutic applications. On the other hand, peptide antagonists have been identified that are highly selective for the ephrin-binding pocket of EphA4. The most potent peptide antagonist identified to date was the linear dodecapeptide KYLPYWPVLSSL (KYL; SEQ ID NO: 1) which was shown to specifically inhibit EphA4 signaling in culture systems and animal models. The KYL peptide significantly dampened ALS pathogenesis in the classic rat SOD1 G93A ALS model. In addition, recent data have shown that KYL peptide can inhibit the toxic effects of A β oligomers in in vitro and in vivo mouse models of Alzheimer's disease. The KYL peptide was also shown to promote axon sprouting and recovery of limb function in a rat model of spinal cord injury. Thus, the KYL peptide clearly demonstrated the therapeutic potential of EphA4 antagonistic agents. However, with a K_D value of about 800-1000 nM, the linear KYL peptide lacks desired features, and as such, is not ideally suited as a platform for therapeutic development. In addition, both a phage display screen of a cyclic nonapeptide library and an NMR-based screen for smaller EphA4 peptidomimetic antagonists failed to yield peptides more potent than KYL.

[008] In addition, to identifying EphA4 peptide antagonists of clinical relevancy, there is also a need to ensure these peptides are designed in a manner that prevents or reduces proteolysis in the circulating blood, prevents or reduces premature clearance through the kidneys, and/or prevents or reduces immunogenicity and the generation of neutralizing antibodies. Furthermore, issues regarding low bioavailability, including the peptide's inability to easily cross membrane barriers such as the intestinal and blood-brain barriers should also be addressed when developing EphA4 peptide antagonists useful for therapeutic applications. To date, no known EphA4 peptide antagonist appears to satisfy these physiological stability and bioavailability criteria to the extent that these peptides are recognized as clinically useful drugs.

[009] Therefore there is still a need to identify EphA4 peptide antagonists that possess the required potency and stability in biological systems to make them suitable therapeutic agents in the treatment of neurodegenerative disorders, neurotoxicity, nerve regeneration and cancer.

SUMMARY

[010] Aspects of the present specification disclose a modified EphA4 receptor antagonist. A modified EphA4 receptor antagonist can comprise a cyclic peptide comprising, consisting essentially of, or consisting of the sequence X₁-X₂-X₃-C₄-X₅-X₆-X₇- β A₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 3), or X₂-X₃-C₄-X₅-X₆-X₇- β A₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 4), or X₃-C₄-X₅-X₆-X₇- β A₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 5), wherein X₁ is independently Ahx, Ava, γ Abu, β A, Sar, DAla (D-A), A, E, G, Q, D, L, S, F, or Y; X₂ is independently P, A, G, Ahx, Ava, γ Abu, β A or Sar; X₃ is independently Y, F, W, V, L, H or I; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently any amino acid; X₉ is independently any amino acid; and X₁₁ is independently any amino acid; wherein C₄ and C₁₂ form a disulfide bridge; wherein C₁₂ is optionally amidated and wherein the amino-terminus may optionally be acetylated. The length of the having a length of the cyclic peptide may be 10 to 20 amino acids in length. In addition, a cyclic peptide disclosed herein contains a modification designed to increase binding affinity, increase binding selectivity, and/or

increase stability. Modification useful to increase binding affinity, binding selectivity, and/or stability of a cyclic peptide disclosed herein include, without limitation, lipidation, PEGylation, polysialylation, a Blood-Brain Barrier (BBB) shuttle, hyperglycosylation, N-(2-hydroxypropyl) methacrylamide (HPMA) copolymers, and polyglutamic acid, poly(lactic acid) (PLA) polymers, poly(glycolic acid) (PGA) polymers and poly(D,L-lactic-coglycolic-acid) (PLGA) polymers. The length of the cyclic peptide may be 10 to 16 amino acids in length or more.

[011] Other aspects of the present specification disclose a pharmaceutical composition comprising one or more modified EphA4 receptor antagonists disclosed herein. A pharmaceutical composition disclosed can further comprises one or more pharmaceutical acceptable carriers.

[012] Other aspects of the present specification disclose a method of treating an EphA4-based disease, disorder or pathology. The disclosed method can comprise administering a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein to an individual in need thereof. Administration of a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein reduces one or more symptoms associated with the EphA4-based disease, disorder or pathology. An EphA4-based disease, disorder or pathology includes, without limitation, a neurodegenerative disease, a hearing loss, a promotion of nerve regeneration, a promotion of neuroprotection, or a cancer.

[013] Other aspects of the present specification disclose a method of treating a neurodegenerative disease. The disclosed method can comprise administering a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein to an individual in need thereof. Administration of a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein reduces one or more symptoms associated with the neurodegenerative disease.

[014] Other aspects of the present specification disclose a method of treating a hearing loss. The disclosed method can comprise administering a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein to an individual in need thereof. Administration of a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein reduces one or more symptoms associated with the hearing loss.

[015] Other aspects of the present specification disclose a method of promoting nerve regeneration. The disclosed method can comprise administering a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein to an individual in need thereof. Administration of a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein stimulates or facilitates neuronal differentiation and/or growth, thereby promoting nerve regeneration.

[016] Other aspects of the present specification disclose a method of promoting neuroprotection. The disclosed method can comprise administering a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein to an individual in need thereof. Administration of a

modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein protects neurons or nerve tissue from damage, thereby promoting neuroprotection.

[017] Other aspects of the present specification disclose a method of treating a cancer. The disclosed method can comprise administering a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein to an individual in need thereof. Administration of a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein reduces one or more symptoms associated with the cancer.

[018] Other aspects of the present specification disclose a use of a modified EphA4 receptor antagonist disclosed herein in the manufacture of a medicament for treating an EphA4-based disease, disorder or pathology. Other aspects of the present specification disclose a use of a modified EphA4 receptor antagonist disclosed herein in the manufacture of a medicament for treating a neurodegenerative disease. Other aspects of the present specification disclose a use of a modified EphA4 receptor antagonist disclosed herein in the manufacture of a medicament for treating a hearing loss. Other aspects of the present specification disclose a use of a modified EphA4 receptor antagonist disclosed herein in the manufacture of a medicament for treating a cancer.

[019] Other aspects of the present specification disclose a use of a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein in the treatment of an EphA4-based disease, disorder or pathology. Other aspects of the present specification disclose a use of a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein in the treatment of a neurodegenerative disease. Other aspects of the present specification disclose a use of a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein in the treatment of a hearing loss. Other aspects of the present specification disclose a use of a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein in the treatment of a cancer.

[020] Other aspects of the present specification disclose a use of a modified EphA4 receptor antagonist disclosed herein in the manufacture of a medicament for promoting nerve regeneration. Other aspects of the present specification disclose a use of a modified EphA4 receptor antagonist disclosed herein in the manufacture of a medicament for promoting neuroprotection.

[021] Other aspects of the present specification disclose a use of a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein in the promotion of nerve regeneration. Other aspects of the present specification disclose a use of a modified EphA4 receptor antagonist disclosed herein or a pharmaceutical composition disclosed herein in the promotion of neuroprotection.

BREIF DESCRIPTION OF THE DRAWING

[022] FIG. 1A shows the structure of an APY cyclic peptide dimer disclosed herein using a PPPK(amide)G linker (SEQ ID NO: 84); FIG. 1B shows the structure of an APY cyclic peptide dimer disclosed herein using a PPPPK(amide)G linker (SEQ ID NO: 85); and FIG. 1C shows the structure of an APY cyclic peptide dimer disclosed herein using a PPPPK(amide)G linker (SEQ ID NO: 86).

[023] FIG. 2A shows the structure of an APY cyclic peptide dimer disclosed herein using a K(amide)Y linker; FIG. 2B shows the structure of an APY cyclic peptide dimer disclosed herein using a PPPK(amide)Y linker (SEQ ID NO: 102); FIG. 2C shows the structure of an APY cyclic peptide dimer disclosed herein using a PPPPK(amide)Y linker (SEQ ID NO: 103); and FIG. 2D shows the structure of an APY cyclic peptide dimer disclosed herein using a PPPPK(amide)Y linker (SEQ ID NO: 104).

DETAILED DESCRIPTION

[024] EphA4 is a particularly promiscuous receptor that can bind both ephrin-A and ephrin-B ligands. The difficulties in obtaining submicromolar EphA4 antagonists are likely due to the nature of the ephrin-binding pocket of EphA4 to accommodate the binding of multiple ligands. For example, ephrin-binding pocket of EphA4 is very broad (exceeding an estimated 900 Å²), lacks sufficient hot spot regions and is highly dynamic, being able to assume multiple conformations. These features reduce the potential free energy gain for the binding of small molecules and flexible linear peptide ligands. In contrast to linear peptides, cyclic peptides are more structured in their unbound form, which can improve binding affinity and pharmacokinetic properties. Furthermore, cyclic peptides are able to better occupy a wide cavity such as the ephrin-binding pocket of EphA4 due to their circular conformation.

[025] Towards this end, improved APY cyclic peptide derivatives of APYCVYRGSWSC (APY; SEQ ID NO: 2) were developed that exhibited better potency and stability than any previously known EphA4 peptide antagonist. The more potent APY cyclic peptide derivatives disclosed herein can serve as therapeutic agents for targeting EphA4 in neurodegenerative disorders, neurotoxicity, nerve regeneration and cancer. In addition, to enhance the therapeutic potential of these APY cyclic peptide derivatives, several different modifications were created and examined in an effort to create peptides having greater stability, efficacy and bioavailability. This analysis identified several different modifications that resulted in APY cyclic peptide derivatives having better stability, efficacy and/or bioavailability.

[026] Aspects of the present specification disclose, in part, a modified EphA4 receptor antagonist. A modified EphA4 receptor antagonist disclosed herein (also referred to as a modified EphA4 antagonist) is a cyclic peptide that selectively reduce or inhibit EphA4 receptor signaling activity and/or reduce or inhibit any other functionality of an EphA4 receptor. In aspects of this embodiment, a modified EphA4 receptor antagonist comprising a cyclic peptide completely inhibits EphA4 receptor signaling activity and/or other functionality of an EphA4 receptor. In aspects of this embodiment, a modified EphA4 receptor antagonist comprising a cyclic peptide may selectively reduce or inhibit EphA4 receptor signaling activity and/or

other functionality of an EphA4 receptor by, e.g., about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 60%, or about 100%. In other aspects of this embodiment, a modified EphA4 receptor antagonist comprising a cyclic peptide may selectively reduce or inhibit EphA4 receptor signaling activity and/or other functionality of an EphA4 receptor by, e.g., at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 60%, or at least 100%. In yet other aspects of this embodiment, a modified EphA4 receptor antagonist comprising a cyclic peptide may selectively reduce or inhibit EphA4 receptor signaling activity and/or other functionality of an EphA4 receptor by, e.g., at most 10%, at most 20%, at most 30%, at most 40%, at most 50%, at most 60%, at most 70%, at most 80%, at most 60%, or at most 100%. In still another aspect of this embodiment, a modified EphA4 receptor antagonist comprising a cyclic peptide may reduce or inhibit EphA4 receptor signaling activity and/or other functionality of an EphA4 receptor by, e.g., about 10% to about 20%, about 10% to about 30%, about 10% to about 40%, about 10% to about 50%, about 10% to about 60%, about 10% to about 70%, about 10% to about 80%, about 10% to about 90%, about 10% to about 100%, about 20% to about 30%, about 20% to about 40%, about 20% to about 50%, about 20% to about 60%, about 20% to about 70%, about 20% to about 80%, about 20% to about 90%, about 20% to about 100%, about 30% to about 40%, about 30% to about 50%, about 30% to about 60%, about 30% to about 70%, about 30% to about 80%, about 30% to about 90%, about 30% to about 100%, about 40% to about 50%, about 40% to about 60%, about 40% to about 70%, about 40% to about 80%, about 40% to about 90%, about 40% to about 100%, about 50% to about 60%, about 50% to about 70%, about 50% to about 80%, about 50% to about 90%, about 50% to about 100%, about 60% to about 70%, about 60% to about 80%, about 60% to about 90%, about 60% to about 100%, about 70% to about 80%, about 70% to about 90%, about 70% to about 100%, about 80% to about 90%, about 80% to about 100%, or about 90% to about 100%.

[027] Aspects of the present specification disclose, in part, a cyclic peptide. Cyclic peptides disclosed herein are peptides derived from APY (SEQ ID NO: 2), a 12 amino acid peptide with a disulfide bridge between the two cysteines (Cys) at positions 4 and 12. All APY cyclic peptides disclosed herein contain a disulfide bridge, which helps impart the cyclic structure of the peptide. All APY cyclic peptides disclosed herein are useful as a modified EphA4 receptor antagonist. An APY cyclic peptide disclosed herein can be chemically synthesized using standard techniques such as liquid-phase synthesis or solid-phase synthesis including Fmoc and Boc.

[028] In aspects of this embodiment, an APY cyclic peptide may have an amino acid length of, e.g., about 9 residues, about 10 residues, about 11 residues, about 12 residues, about 13 residues, about 14 residues or about 15 residues. In other aspects of this embodiment, an APY cyclic peptide may have an amino acid length of, e.g., at least 9 residues, at least 10 residues, at least 11 residues, at least 12 residues, at least 13 residues, at least 14 residues, at least 15 residues, at least 16 residues, at least 17 residues, at least 18 residues, at least 19 residues or at least 20 residues. In yet other aspects of this embodiment, an APY cyclic peptide may have an amino acid length of, e.g., at most 9 residues, at most 10 residues, at most 11 residues, at most 12 residues, at most 13 residues, at most 14 residues, at most 15 residues, at most 16 residues, at most 17 residues, at most 18 residues, at most 19 residues or at

most 20 residues. In still other aspects of this embodiment, an APY cyclic peptide may have an amino acid length of, e.g., about 9 to about 10 residues, about 9 to about 11 residues, about 9 to about 12 residues, about 9 to about 13 residues, about 9 to about 14 residues, about 9 to about 15 residues, about 9 to about 16 residues, about 9 to about 17 residues, about 9 to about 18 residues, about 9 to about 19 residues, about 9 to about 20 residues, about 10 to about 11 residues, about 10 to about 12 residues, about 10 to about 13 residues, about 10 to about 14 residues, about 10 to about 15 residues, about 10 to about 16 residues, about 10 to about 17 residues, about 10 to about 18 residues, about 10 to about 19 residues, about 10 to about 20 residues, about 11 to about 12 residues, about 11 to about 13 residues, about 11 to about 14 residues, about 11 to about 15 residues, about 11 to about 16 residues, about 11 to about 17 residues, about 11 to about 18 residues, about 11 to about 19 residues, about 11 to about 20 residues, about 12 to about 13 residues, about 12 to about 14 residues, about 12 to about 15 residues, about 12 to about 16 residues, about 12 to about 17 residues, about 12 to about 18 residues, about 12 to about 19 residues, about 12 to about 20 residues, about 13 to about 14 residues, about 13 to about 15 residues, about 13 to about 16 residues, about 13 to about 17 residues, about 13 to about 18 residues, about 13 to about 19 residues, about 13 to about 20 residues, about 14 to about 15 residues, about 14 to about 16 residues, about 14 to about 17 residues, about 14 to about 18 residues, about 14 to about 19 residues, about 14 to about 20 residues, about 15 to about 16 residues, about 15 to about 17 residues, about 15 to about 18 residues, about 15 to about 19 residues, about 15 to about 20 residues, about 16 to about 17 residues, about 16 to about 18 residues, about 16 to about 19 residues, or about 16 to about 20 residues.

[029] Aspects of the present specification disclose, in part, an APY cyclic peptide disclosed herein that is modified by amidation (am). Amidation is a chemical reaction that results in the addition of an amide functional group to the free carboxyl group of an amino acid. In C-terminal amidation, an amide group is added to the free carboxyl group of the C-terminal residue of a peptide. C-terminal amidation increases peptide stability because it eliminates a potential charge, thereby further protecting the peptide from rapid degradation by ubiquitous exopeptidases. In an aspect of this embodiment, an APY cyclic peptide disclosed herein is amidated by adding an amide group to the free carboxyl group of the C-terminal amino acid. In aspects, an APY cyclic peptide disclosed herein is C-terminally amidated at position 12, 13, 14, 15, 16, 17, 18, 19 or 20. In an aspect of this embodiment, an APY cyclic peptide disclosed herein is C-terminally amidated at a cysteine. In another aspect of this embodiment, an APY cyclic peptide disclosed herein is amidated at the cysteine located at position 12. In an aspect of this embodiment, an APY cyclic peptide disclosed herein is C-terminally amidated at a glycine. In another aspect of this embodiment, an APY cyclic peptide disclosed herein is amidated at the glycine located at position 14.

[030] Aspects of the present specification disclose, in part, an APY cyclic peptide disclosed herein that is optionally modified by acetylation (ac). Acetylation is a chemical reaction that results in the addition of an acetyl functional group to the free amino group of an amino acid. In N-terminal acetylation, an acetyl group is added to the free amino group of the N-terminal residue of a peptide. N-terminal acetyl increases peptide stability because it eliminates a potential charge, thereby further protecting the peptide from rapid degradation by ubiquitous exopeptidases. In an aspect of this embodiment, an APY cyclic peptide disclosed herein is acetylated by adding an acetyl group to the free amino group of the N-terminal

amino acid. In another aspect of this embodiment, an APY cyclic peptide disclosed herein is acetylated at position 1. In yet another aspect of this embodiment, an APY cyclic peptide disclosed herein is not acetylated at the free amino group of the N-terminal amino acid.

[031] Aspects of the present specification disclose, in part, an APY cyclic peptide disclosed herein that is optionally modified at the amino terminus. Besides acetylation, an APY peptide disclosed herein may optionally be modified by other functional groups in order to increase peptide stability. In an aspect of this embodiment, an APY cyclic peptide disclosed herein may be modified at the N-terminus by carboxybenzyl (Cbz). In yet another aspect of this embodiment, an APY cyclic peptide disclosed herein is not modified at the N-terminus by carboxybenzyl (Cbz).

[032] In another aspect of this embodiment, an APY cyclic peptide disclosed herein is modified to include a positive charge at the N-terminus portion. Such modification can increase the affinity of an APY cyclic peptide for the EphE4 receptor. In aspects of this embodiment, a positive charge may be added to the N-terminus (X₁) of an APY cyclic peptide and/or the penultimate N-terminal residue (X₂) of an APY cyclic peptide. A positive charge can be introduced by substituting X₁ or X₂ with an Ahx, Ava, γAbu, βA, Gly or Sar.

[033] In an embodiment, an APY cyclic peptide has the sequence X₁-X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 3), X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 4) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 5), wherein X₁ is independently Ahx, Ava, γAbu, βA, Sar, D-A, A, E, G, Q, D, L, S, F, or Y; X₂ is independently P, A, G, Ahx, Ava, γAbu, βA or Sar; X₃ is independently Y, F, W, V, L, H or I; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently any amino acid; X₉ is independently any amino acid; and X₁₁ is independently any amino acid. Residues C₄ and C₁₂ of an APY cyclic peptide disclosed herein form a disulfide bridge. In an aspect of this embodiment, residue C₁₂ is optionally amidated. In another aspect of this embodiment, the amino-terminal residue is optionally acetylated.

[034] In aspects of this embodiment, an APY cyclic peptide has the sequence X₁-X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 3), X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 4) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 5), wherein in any residue position combination thereof X₁ is independently βA, D-A, A, E, G or Q; X₂ is independently P or A; X₃ is independently Y, F, W, V, L or H; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently any amino acid except P; X₉ is independently any amino acid except P; and X₁₁ is independently any amino acid except P. In other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 3), X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 4) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 5), wherein in any residue position combination thereof X₁ is independently βA, D-A, A, E, G or Q; X₂ is independently P or A; X₃ is independently Y, F, W, V, L or H; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently R, T, N, D, S, Q, Y, K, A, G or E; X₉ is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X₁₁ is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 3), X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID

NO: 4) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 5), wherein in any residue position combination thereof X₁ is independently βA, D-A, A, E, G or Q; X₂ is independently P or A; X₃ is independently Y, F, W, V, L or H; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, W, R, L, D, Y; and X₁₁ is independently S, E, L, N, T, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 3), X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 4) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 5), wherein in any residue position combination thereof X₁ is independently βA, D-A, A, E, G or Q; X₂ is independently P or A; X₃ is independently Y, F, W, V, L or H; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, D, Y; and X₁₁ is independently S, E, L, N, K, V, I or H. In other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 3), X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 4) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 5), wherein in any residue position combination thereof X₁ is independently βA, D-A, A, E, G or Q; X₂ is independently P or A; X₃ is independently Y, F, W, V, L or H; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently R, T, or N; X₉ is independently S, E, T or V; and X₁₁ is independently S, E, L or N.

[035] In aspects of this embodiment, an APY cyclic peptide has the sequence X₁-X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 3), X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 4) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 5), wherein in any residue position combination thereof X₁ is independently βA, D-A, A or E; X₂ is independently P or A; X₃ is independently Y, F, W, V, L or H; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently any amino acid except P; X₉ is independently any amino acid except P; and X₁₁ is independently any amino acid except P. In other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 3), X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 4) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 5), wherein in any residue position combination thereof X₁ is independently βA, D-A, A or E; X₂ is independently P or A; X₃ is independently Y, F, W, V, L or H; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently R, T, N, D, S, Q, Y, K, A, G or E; X₉ is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X₁₁ is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 3), X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 4) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 5), wherein in any residue position combination thereof X₁ is independently βA, D-A, A or E; X₂ is independently P or A; X₃ is independently Y, F, W, V, L or H; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, W, R, L, D, Y; and X₁₁ is independently S, E, L, N, T, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 3), X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 4) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 5), wherein in any residue position combination thereof X₁ is independently βA, D-A, A or E; X₂ is independently P or A; X₃ is independently Y, F, W, V, L or H; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, D, Y; and X₁₁ is independently S, E, L, N, K, V, I or H. In other aspects of this embodiment, an APY cyclic

peptide has the sequence X_1 - X_2 - X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 3), X_2 - X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 4) or X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 5), wherein in any residue position combination thereof X_1 is independently βA , D-A, A or E; X_2 is independently P or A; X_3 is independently Y, F, W, V, L or H; X_5 is independently V or L; X_6 is independently Y, F, W or H; X_7 is independently R, T, or N; X_9 is independently S, E, T or V; and X_{11} is independently S, E, L or N.

[036] In aspects of this embodiment, an APY cyclic peptide has the sequence X_1 - X_2 - X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 3), X_2 - X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 4) or X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 5), wherein X_1 is independently βA , D-A, A or E; X_2 is independently P or A; X_3 is independently Y, F or W; X_5 is independently V or L; X_6 is independently Y, F or W; X_7 is independently any amino acid except P; X_9 is independently any amino acid except P; and X_{11} is independently any amino acid except P. In other aspects of this embodiment, an APY cyclic peptide has the sequence X_1 - X_2 - X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 3), X_2 - X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 4) or X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 5), wherein X_1 is independently βA , D-A, A or E; X_2 is independently P or A; X_3 is independently Y, F or W; X_5 is independently V or L; X_6 is independently Y, F or W; X_7 is independently R, T, N, D, S, Q, Y, K, A, G or E; X_9 is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X_{11} is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence X_1 - X_2 - X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 3), X_2 - X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 4) or X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 5), wherein X_1 is independently βA , D-A, A or E; X_2 is independently P or A; X_3 is independently Y, F or W; X_5 is independently V or L; X_6 is independently Y, F or W; X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, W, R, L, D, Y; and X_{11} is independently S, E, L, N, T, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence X_1 - X_2 - X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 3), X_2 - X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 4) or X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 5), wherein X_1 is independently βA , D-A, A or E; X_2 is independently P or A; X_3 is independently Y, F or W; X_5 is independently V or L; X_6 is independently Y, F or W; X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, D, Y; and X_{11} is independently S, E, L, N, K, V, I or H. In other aspects of this embodiment, an APY cyclic peptide has the sequence X_1 - X_2 - X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 3), X_2 - X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 4) or X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W - X_{11} - C_{12} (SEQ ID NO: 5), wherein X_1 is independently βA , D-A, A or E; X_2 is independently P or A; X_3 is independently Y, F or W; X_5 is independently V or L; X_6 is independently Y, F or W; X_7 is independently R, T, or N; X_9 is independently S, E, T or V; and X_{11} is independently S, E, L or N.

[037] In another embodiment, an APY cyclic peptide has the sequence X_1 - P_2 - X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W_{10} - X_{11} - C_{12} (SEQ ID NO: 6), X_1 - P_2 - X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W_{10} - X_{11} - C_{12} (SEQ ID NO: 7) or X_1 - P_2 - X_3 - C_4 - X_5 - X_6 - X_7 - βA_8 - X_9 - W_{10} - X_{11} - C_{12} (SEQ ID NO: 8), wherein X_1 is independently βA , D-A, A, E, G or Q; X_3 is independently Y, F, W, V, L or H; X_5 is independently V or L; X_6 is independently Y, F, W or H; X_7 is independently any amino acid except P; X_9 is independently any amino acid except P; and X_{11} is independently any amino acid except P. Residues C_4 and C_{12} of an APY cyclic peptide disclosed herein

form a disulfide bridge. In an aspect of this embodiment, residue C₁₂ is optionally amidated. In another aspect of this embodiment, the amino-terminal residue is optionally acetylated.

[038] In aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 6), P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 7) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 8), wherein X₁ is independently βA, D-A, A, E, G or Q; X₃ is independently Y, F, W, V, L or H; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently R, T, N, D, S, Q, Y, K, A, G or E; X₉ is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X₁₁ is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 6), P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 7) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 8), wherein X₁ is independently βA, D-A, A, E, G or Q; X₃ is independently Y, F, W, V, L or H; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, W, R, L, D, Y; and X₁₁ is independently S, E, L, N, T, K, V, I or H. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 6), P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 7) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 8), wherein X₁ is independently βA, D-A, A, E, G or Q; X₃ is independently Y, F, W, V, L or H; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, D, Y; and X₁₁ is independently S, E, L, N, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 6), P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 7) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 8), wherein X₁ is independently βA, D-A, A, E, G or Q; X₃ is independently Y, F, W, V, L or H; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently R, T, or N; X₉ is independently S, E, T or V; and X₁₁ is independently S, E, L or N.

[039] In aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 6), P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 7) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 8), wherein X₁ is independently βA, D-A, A or E; X₃ is independently Y, F or W; X₅ is independently V or L; X₆ is independently Y, F or W; X₇ is independently R, T, N, D, S, Q, Y, K, A, G or E; X₉ is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X₁₁ is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 6), P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 7) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 8), wherein X₁ is independently βA, D-A, A or E; X₃ is independently Y, F or W; X₅ is independently V or L; X₆ is independently Y, F or W; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, W, R, L, D, Y; and X₁₁ is independently S, E, L, N, T, K, V, I or H. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 6), P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 7) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 8), wherein X₁ is independently βA, D-A, A or E; X₃ is independently Y, F or W; X₅ is independently V or L; X₆ is independently Y, F or W; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, D, Y; and X₁₁ is independently S, E, L, N, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 6), P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 7) or X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 8), wherein X₁ is independently βA, D-A, A or E; X₃ is independently Y, F or W; X₅ is independently V or L; X₆ is independently Y, F or W; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, D, Y; and X₁₁ is independently S, E, L, N, K, V, I or H.

$\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 7) or $X_3-C_4-X_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 8), wherein X_1 is independently βA , D-A, A or E; X_3 is independently Y, F or W; X_5 is independently V or L; X_6 is independently Y, F or W; X_7 is independently R, T, or N; X_9 is independently S, E, T or V; and X_{11} is independently S, E, L or N.

[040] In another embodiment, an APY cyclic peptide has the sequence $X_1-X_2-X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 9), $X_2-X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 10) or $X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 11), wherein X_1 is independently Ahx, Ava, γ Abu, βA , Sar, D-A, A, E, G or Q; X_2 is independently P, A, G, Ahx, Ava, γ Abu, βA or Sar; X_3 is independently Y, F, W, V, L or H; X_6 is independently Y, F, W or H; X_7 is independently any amino acid except P; X_9 is independently any amino acid except P; and X_{11} is independently any amino acid except P. Residues C_4 and C_{12} of an APY cyclic peptide disclosed herein form a disulfide bridge. In an aspect of this embodiment, residue C_{12} is optionally amidated. In another aspect of this embodiment, the amino-terminal residue is optionally acetylated.

[041] In aspects of this embodiment, an APY cyclic peptide has the sequence $X_1-X_2-X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 9), $X_2-X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 10) or $X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 11), wherein X_1 is independently βA , D-A, A, E, G or Q; X_2 is independently P or A; X_3 is independently Y, F, W, V, L or H; X_6 is independently Y, F, W or H; X_7 is independently R, T, N, D, S, Q, Y, K, A, G or E; X_9 is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X_{11} is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In other aspects of this embodiment, an APY cyclic peptide has the sequence $X_1-X_2-X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 9), $X_2-X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 10) or $X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 11), wherein X_1 is independently βA , D-A, A, E, G or Q; X_2 is independently P or A; X_3 is independently Y, F, W, V, L or H; X_6 is independently Y, F, W or H; X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, W, R, L, D, Y; and X_{11} is independently S, E, L, N, T, K, V, I or H. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence $X_1-X_2-X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 9), $X_2-X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 10) or $X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 11), wherein X_1 is independently βA , D-A, A, E, G or Q; X_2 is independently P or A; X_3 is independently Y, F, W, V, L or H; X_6 is independently Y, F, W or H; X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, D, Y; and X_{11} is independently S, E, L, N, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence $X_1-X_2-X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 9), $X_2-X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 10) or $X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 11), wherein X_1 is independently βA , D-A, A, E, G or Q; X_2 is independently P or A; X_3 is independently Y, F, W, V, L or H; X_6 is independently Y, F, W or H; X_7 is independently R, T, or N; X_9 is independently S, E, T or V; and X_{11} is independently S, E, L or N.

[042] In aspects of this embodiment, an APY cyclic peptide has the sequence $X_1-X_2-X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 9), $X_2-X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 10) or $X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 11), wherein X_1 is independently βA , D-A, A or E; X_2 is independently P or A; X_3 is independently Y, F or W; X_6 is independently Y, F or W; X_7 is independently R, T, N, D, S, Q, Y, K, A, G or E; X_9 is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X_{11} is

independently S, E, L, N, V, I, H, K, M, D, W, T or G. In other aspects of this embodiment, an APY cyclic peptide has the sequence X_1 - X_2 - X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 9), X_2 - X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 10) or X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 11), wherein X_1 is independently βA, D-A, A or E; X_2 is independently P or A; X_3 is independently Y, F or W; X_6 is independently Y, F or W; X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, W, R, L, D, Y; and X_{11} is independently S, E, L, N, T, K, V, I or H. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence X_1 - X_2 - X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 9), X_2 - X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 10) or X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 11), wherein X_1 is independently βA, D-A, A or E; X_2 is independently P or A; X_3 is independently Y, F or W; X_6 is independently Y, F or W; X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, D, Y; and X_{11} is independently S, E, L, N, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence X_1 - X_2 - X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 9), X_2 - X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 10) or X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 11), wherein X_1 is independently βA, D-A, A or E; X_2 is independently P or A; X_3 is independently Y, F or W; X_6 is independently Y, F or W; X_7 is independently R, T, or N; X_9 is independently S, E, T or V; and X_{11} is independently S, E, L or N.

[043] In another embodiment, an APY cyclic peptide has the sequence X_1 -P₂- X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 12), P₂- X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 13) or X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 14), wherein X_1 is independently βA, D-A, A, E, G or Q; X_3 is independently Y, F, W, V, L or H; X_6 is independently Y, F, W or H; X_7 is independently any amino acid except P; X_9 is independently any amino acid except P; and X_{11} is independently any amino acid except P. Residues C₄ and C₁₂ of an APY cyclic peptide disclosed herein form a disulfide bridge. In an aspect of this embodiment, residue C₁₂ is optionally amidated. In another aspect of this embodiment, the amino-terminal residue is optionally acetylated.

[044] In aspects of this embodiment, an APY cyclic peptide has the sequence X_1 -P₂- X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 12), P₂- X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 13) or X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 14), wherein X_1 is independently βA, D-A, A, E, G or Q; X_3 is independently Y, F, W, V, L or H; X_6 is independently Y, F, W or H; X_7 is independently R, T, N, D, S, Q, Y, K, A, G or E; X_9 is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X_{11} is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In other aspects of this embodiment, an APY cyclic peptide has the sequence X_1 -P₂- $X_3-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 12), P₂- $X_3-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 13) or X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 14), wherein X_1 is independently βA, D-A, A, E, G or Q; X_3 is independently Y, F, W, V, L or H; X_6 is independently Y, F, W or H; X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, W, R, L, D, Y; and X_{11} is independently S, E, L, N, T, K, V, I or H. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence X_1 -P₂- $X_3-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 12), P₂- X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 13) or X_3 -C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 14), wherein X_1 is independently βA, D-A, A, E, G or Q; X_3 is independently Y, F, W, V, L or H; X_6 is independently Y, F, W or H; X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, D, Y; and X_{11} is independently S, E, L, N, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence X_1 -P₂-$$$

X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 12), P₂-X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 13) or X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 14), wherein X₁ is independently βA, D-A, A, E, G or Q; X₃ is independently Y, F, W, V, L or H; X₆ is independently Y, F, W or H; X₇ is independently R, T, or N; X₉ is independently S, E, T or V; and X₁₁ is independently S, E, L or N.

[045] In aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 12), P₂-X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 13) or X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 14), wherein X₁ is independently βA, D-A, A or E; X₃ is independently Y, F or W; X₆ is independently Y, F or W; X₇ is independently R, T, N, D, S, Q, Y, K, A, G or E; X₉ is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X₁₁ is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 12), P₂-X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 13) or X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 14), wherein X₁ is independently βA, D-A, A or E; X₃ is independently Y, F or W; X₆ is independently Y, F or W; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, W, R, L, D, Y; and X₁₁ is independently S, E, L, N, T, K, V, I or H. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 12), P₂-X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 13) or X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 14), wherein X₁ is independently βA, D-A, A or E; X₃ is independently Y, F or W; X₆ is independently Y, F or W; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, D, Y; and X₁₁ is independently S, E, L, N, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 12), P₂-X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 13) or X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 14), wherein X₁ is independently βA, D-A, A or E; X₃ is independently Y, F or W; X₆ is independently Y, F or W; X₇ is independently R, T, or N; X₉ is independently S, E, T or V; and X₁₁ is independently S, E, L or N.

[046] In another embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 15), P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 16), Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 17), wherein X₁ is independently βA, D-A, A, E, G or Q; X₆ is independently Y, F, W or H; X₇ is independently any amino acid except P; X₉ is independently any amino acid except P; and X₁₁ is independently any amino acid except P. Residues C₄ and C₁₂ of an APY cyclic peptide disclosed herein form a disulfide bridge. In an aspect of this embodiment, residue C₁₂ is optionally amidated. In another aspect of this embodiment, the amino-terminal residue is optionally acetylated.

[047] In aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 15), P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 16), Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 17), wherein X₁ is independently βA, D-A, A, E, G or Q; X₆ is independently Y, F, W or H; X₇ is independently R, T, N, D, S, Q, Y, K, A, G or E; X₉ is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X₁₁ is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 15), P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 16), Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 17), wherein X₁ is independently βA, D-A, A, E, G or Q; X₆ is

independently Y, F, W or H; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, W, R, L, D, Y; and X₁₁ is independently S, E, L, N, T, K, V, I or H. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 15), P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 16), Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 17), wherein X₁ is independently βA, D-A, A, E, G or Q; X₆ is independently Y, F, W or H; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, D, Y; and X₁₁ is independently S, E, L, N, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 15), P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 16), Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 17), wherein X₁ is independently βA, D-A, A, E, G or Q; X₆ is independently Y, F, W or H; X₇ is independently R, T, or N; X₉ is independently S, E, T or V; and X₁₁ is independently S, E, L or N.

[048] In aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 15), P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 16), Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 17), wherein X₁ is independently βA, D-A, A or E; X₆ is independently Y, F or W; X₇ is independently R, T, N, D, S, Q, Y, K, A, G or E; X₉ is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X₁₁ is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 15), P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 16), Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 17), wherein X₁ is independently βA, D-A, A or E; X₆ is independently Y, F or W; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, W, R, L, D, Y; and X₁₁ is independently S, E, L, N, T, K, V, I or H. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 15), P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 16), Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 17), wherein X₁ is independently βA, D-A, A or E; X₆ is independently Y, F or W; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, D, Y; and X₁₁ is independently S, E, L, N, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 15), P₂-Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 16), Y₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 17), wherein X₁ is independently βA, D-A, A or E; X₆ is independently Y, F or W; X₇ is independently R, T, or N; X₉ is independently S, E, T or V; and X₁₁ is independently S, E, L or N.

[049] In another embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 18), P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 19) or X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 20), wherein X₁ is independently βA, D-A, A, E, G or Q; X₃ is independently Y, F, W, V, L or H; X₇ is independently any amino acid except P; X₉ is independently any amino acid except P; and X₁₁ is independently any amino acid except P. Residues C₄ and C₁₂ of an APY cyclic peptide disclosed herein form a disulfide bridge. In an aspect of this embodiment, residue C₁₂ is optionally amidated. In another aspect of this embodiment, the amino-terminal residue is optionally acetylated.

[050] In aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 18), P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 19) or X₃-C₄-

V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 20), wherein X₁ is independently βA, D-A, A, E, G or Q; X₃ is independently Y, F, W, V, L or H; X₇ is independently R, T, N, D, S, Q, Y, K, A, G or E; X₉ is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X₁₁ is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 18), P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 19) or X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 20), wherein X₁ is independently βA, D-A, A, E, G or Q; X₃ is independently Y, F, W, V, L or H; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, W, R, L, D, Y; and X₁₁ is independently S, E, L, N, T, K, V, I or H. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 18), P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 19) or X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 20), wherein X₁ is independently βA, D-A, A, E, G or Q; X₃ is independently Y, F, W, V, L or H; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, D, Y; and X₁₁ is independently S, E, L, N, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 18), P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 19) or X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 20), wherein X₁ is independently βA, D-A, A, E, G or Q; X₃ is independently Y, F, W, V, L or H; X₇ is independently R, T, or N; X₉ is independently S, E, T or V; and X₁₁ is independently S, E, L or N.

[051] In aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 18), P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 19) or X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 20), wherein X₁ is independently βA, D-A, A or E; X₃ is independently Y, F or W; X₇ is independently R, T, N, D, S, Q, Y, K, A, G or E; X₉ is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X₁₁ is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 18), P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 19) or X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 20), wherein X₁ is independently βA, D-A, A or E; X₃ is independently Y, F or W; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, W, R, L, D, Y; and X₁₁ is independently S, E, L, N, T, K, V, I or H. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 18), P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 19) or X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 20), wherein X₁ is independently βA, D-A, A or E; X₃ is independently Y, F or W; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, D, Y; and X₁₁ is independently S, E, L, N, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 18), P₂-X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 19) or X₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 20), wherein X₁ is independently βA, D-A, A or E; X₃ is independently Y, F or W; X₇ is independently R, T, or N; X₉ is independently S, E, T or V; and X₁₁ is independently S, E, L or N.

[052] In another embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 21), P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 22) or Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 23), wherein X₁ is independently βA, D-A, A, E, G or Q; X₇ is independently any amino acid except P; X₉ is independently any amino acid except P; and X₁₁ is independently any amino acid except P. Residues C₄ and C₁₂ of an APY cyclic peptide disclosed herein

form a disulfide bridge. In an aspect of this embodiment, residue C₁₂ is optionally amidated. In another aspect of this embodiment, the amino-terminal residue is optionally acetylated.

[053] In aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 21), P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 22) or Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 23), wherein X₁ is independently βA, D-A, A, E, G or Q; X₇ is independently R, T, N, D, S, Q, Y, K, A, G or E; X₉ is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X₁₁ is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 21), P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 22) or Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 23), wherein X₁ is independently βA, D-A, A, E, G or Q; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, W, R, L, D, Y; and X₁₁ is independently S, E, L, N, T, K, V, I or H. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 21), P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 22) or Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 23), wherein X₁ is independently βA, D-A, A, E, G or Q; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, D, Y; and X₁₁ is independently S, E, L, N, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 21), P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 22) or Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 23), wherein X₁ is independently βA, D-A, A, E, G or Q; X₇ is independently R, T, or N; X₉ is independently S, E, T or V; and X₁₁ is independently S, E, L or N.

[054] In aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 21), P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 22) or Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 23), wherein X₁ is independently βA, D-A, A or E; X₇ is independently R, T, N, D, S, Q, Y, K, A, G or E; X₉ is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X₁₁ is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 21), P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 22) or Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 23), wherein X₁ is independently βA, D-A, A or E; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, W, R, L, D, Y; and X₁₁ is independently S, E, L, N, T, K, V, I or H. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 21), P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 22) or Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 23), wherein X₁ is independently βA, D-A, A or E; X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, D, Y; and X₁₁ is independently S, E, L, N, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 21), P₂-Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 22) or Y₃-C₄-V₅-Y₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 23), wherein X₁ is independently βA, D-A, A or E; X₇ is independently R, T, or N; X₉ is independently S, E, T or V; and X₁₁ is independently S, E, L or N.

[055] In another embodiment, an APY cyclic peptide has the sequence X₁-P₂-Y₃-C₄-V₅-Y₆-R₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 24), P₂-Y₃-C₄-V₅-Y₆-R₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 25) or Y₃-C₄-V₅-Y₆-R₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 26), wherein X₁ is independently βA, D-A, A or E; X₇ is independently R, T, or N; X₉ is independently S, E, T or V; and X₁₁ is independently S, E, L or N.

$\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 26), wherein X_1 is independently βA , D-A, A, E, G or Q; X_9 is independently any amino acid except P; and X_{11} is independently any amino acid except P. Residues C_4 and C_{12} of an APY cyclic peptide disclosed herein form a disulfide bridge. In an aspect of this embodiment, residue C_{12} is optionally amidated. In another aspect of this embodiment, the amino-terminal residue is optionally acetylated.

[056] In aspects of this embodiment, an APY cyclic peptide has the sequence $X_1-P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 24), $P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 25) or $Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 26), wherein X_1 is independently βA , D-A, A, E, G or Q; X_9 is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X_{11} is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In other aspects of this embodiment, an APY cyclic peptide has the sequence $X_1-P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 24), $P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 25) or $Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 26), wherein X_1 is independently βA , D-A, A, E, G or Q; X_9 is independently S, E, T, V, W, R, L, D, Y; and X_{11} is independently S, E, L, N, T, K, V, I or H. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence $X_1-P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 24), $P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 25) or $Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 26), wherein X_1 is independently βA , D-A, A, E, G or Q; X_9 is independently S, E, T, V, D, Y; and X_{11} is independently S, E, L, N, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence $X_1-P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 24), $P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 25) or $Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 26), wherein X_1 is independently βA , D-A, A, E, G or Q; X_9 is independently S, E, T or V; and X_{11} is independently S, E, L or N.

[057] In aspects of this embodiment, an APY cyclic peptide has the sequence $X_1-P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 24), $P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 25) or $Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 26), wherein X_1 is independently βA , D-A, A or E; X_9 is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X_{11} is independently S, E, L, N, V, I, H, K, M, D, W, T or G. In other aspects of this embodiment, an APY cyclic peptide has the sequence $X_1-P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 24), $P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 25) or $Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 26), wherein X_1 is independently βA , D-A, A or E; X_9 is independently S, E, T, V, W, R, L, D, Y; and X_{11} is independently S, E, L, N, T, K, V, I or H. In yet other aspects of this embodiment, an APY cyclic peptide has the sequence $X_1-P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 24), $P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 25) or $Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 26), wherein X_1 is independently βA , D-A, A or E; X_9 is independently S, E, T, V, D, Y; and X_{11} is independently S, E, L, N, K, V, I or H. In still other aspects of this embodiment, an APY cyclic peptide has the sequence $X_1-P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 24), $P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 25) or $Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 26), wherein X_1 is independently βA , D-A, A or E; X_9 is independently S, E, T or V; and X_{11} is independently S, E, L or N.

[058] In another embodiment, an APY cyclic peptide has the sequence APYCVYR β ASWSC (SEQ ID NO: 35), APYCVYR β ASWSC-am (SEQ ID NO: 36), APYCVYK β ASWSC-am (SEQ ID NO: 45),

β APYCVYR β ASWSC (SEQ ID NO: 46), β APYCVYR β ASWSC-am (SEQ ID NO: 47), β APYCVYK β ASWSC-am (SEQ ID NO: 48), β APYCVYR β AEWEC (SEQ ID NO: 49), β APYCVYR β AEWEC-am (SEQ ID NO: 50), D-APYCVYR β ASWSC (SEQ ID NO: 51), D-APYCVYR β ASWSC-am (SEQ ID NO: 52), APYCVWR β ASWSC (SEQ ID NO: 53), APYCVYT β AEWLC (SEQ ID NO: 54), APYCVYN β ATWNC (SEQ ID NO: 55), APYCVYR β AVWEC (SEQ ID NO: 56), APVCVWR β ASWSC (SEQ ID NO: 57), APLCVWR β ASWSC (SEQ ID NO: 58), APLCVYR β ASWSC (SEQ ID NO: 59), APWCVFR β ASWSC (SEQ ID NO: 60), APHCVFR β ASWSC (SEQ ID NO: 61), APFCLYT β ADWVC (SEQ ID NO: 62), APYCVYD β ATWIC (SEQ ID NO: 63), APYCVYS β ATWHC (SEQ ID NO: 64), APYCVYD β ASWNC (SEQ ID NO: 65), APYCVYQ β AYWKC (SEQ ID NO: 66), APYCVYR β ASWSC (SEQ ID NO: 67), EPYCVYR β ASWSC (SEQ ID NO: 68), APLCVYR β ASWSC (SEQ ID NO: 69), Ahx-YCVYR β ASWSC-am (SEQ ID NO: 91), Ava-YCVYR β ASWSC-am (SEQ ID NO: 92), γ Abu-YCVYR β ASWSC-am (SEQ ID NO: 93), β A-YCVYR β ASWSC-am (SEQ ID NO: 94), GYCVYR β ASWSC-am (SEQ ID NO: 95) or Sar1-YCVYR β ASWSC.am (SEQ ID NO: 96). In aspects of this embodiment, an APY cyclic peptide has the sequence APYCVYR β ASWSC-am (SEQ ID NO: 36), APYCVYK β ASWSC-am (SEQ ID NO: 45), β APYCVYR β ASWSC (SEQ ID NO: 46), β APYCVYR β ASWSC-am (SEQ ID NO: 47), β APYCVYR β AEWEC-am (SEQ ID NO: 50), D-APYCVYR β ASWSC-am (SEQ ID NO: 52), APYCVWR β ASWSC (SEQ ID NO: 53), APYCVYT β AEWLC (SEQ ID NO: 54), APYCVYN β ATWNC (SEQ ID NO: 55) or APYCVYR β AVWEC (SEQ ID NO: 56). In other aspects of this embodiment, an APY cyclic peptide has the sequence APYCVYR β ASWSC-am (SEQ ID NO: 36), β APYCVYR β ASWSC-am (SEQ ID NO: 47) or β APYCVYR β AEWEC-am (SEQ ID NO: 50). Other APY cyclic peptides useful to create the modified APY cyclic peptides disclosed herein are described in International Patent Application PCT/US2015/040649, which is hereby incorporated by reference in its entirety.

[059] Aspects of the present specification disclose, in part, multimers of an APY cyclic peptide disclosed herein. In aspects of this embodiment, an APY cyclic peptide multimer may be, e.g., an APY cyclic peptide dimer, an APY cyclic peptide trimer, an APY cyclic peptide tetramer, or an APY cyclic peptide pentamer. In aspects of this embodiment, an APY cyclic peptide multimer may be a homomultimer or a heteromultimer. For example, an APY cyclic peptide dimer may be composed of two copies of the same APY cyclic peptide or may be composed of two different APY cyclic peptides, each present once in the dimer. As another example, an APY cyclic peptide trimer may be composed of three copies of the same APY cyclic peptide or may be composed of two different APY cyclic peptides with one of the two peptides present in two copies and the other peptides present once, or may be composed of three different APY cyclic peptides, each present once in the trimer.

[060] In aspects of this embodiment, an APY cyclic peptide dimer may be a homodimer of APYCVYR β ASWSC-am (SEQ ID NO: 36), a homodimer of β APYCVYR β ASWSC-am (SEQ ID NO: 47), a homodimer of β APYCVYR β AEWEC-am (SEQ ID NO: 50), a homodimer of D-APYCVYR β ASWSC-am (SEQ ID NO: 52), a homodimer of APYCVWR β ASWSC (SEQ ID NO: 53), a homodimer of APYCVYT β AEWLC (SEQ ID NO: 54), a homodimer of APYCVYN β ATWNC (SEQ ID NO: 55) or a homodimer of APYCVYR β AVWEC (SEQ ID NO: 56). In other aspects of this embodiment, an APY cyclic peptide dimer may be a homodimer of APYCVYR β ASWSC-am (SEQ ID NO: 36), a homodimer of

β APYCVYR β ASWSC-am (SEQ ID NO: 47), a homodimer of β APYCVYR β AEWEC-am (SEQ ID NO: 50), or a homodimer of D-APYCVYR β ASWSC-am (SEQ ID NO: 52).

[061] In other aspects of this embodiment, an APY cyclic peptide dimer may be a heterodimer of any of the following APY cyclic peptides: APYCVYR β ASWSC-am (SEQ ID NO: 36), β APYCVYR β ASWSC-am (SEQ ID NO: 47), β APYCVYR β AEWEC-am (SEQ ID NO: 50), D-APYCVYR β ASWSC-am (SEQ ID NO: 52), APYCVWR β ASWSC (SEQ ID NO: 53), APYCVYT β AEWLC (SEQ ID NO: 54), APYCVYN β ATWNC (SEQ ID NO: 55) or APYCVYR β AVWEC (SEQ ID NO: 56). In other aspects of this embodiment, an APY cyclic peptide dimer may be a heterodimer of any of the following APY cyclic peptides: APYCVYR β ASWSC-am (SEQ ID NO: 36), β APYCVYR β ASWSC-am (SEQ ID NO: 47) β APYCVYR β AEWEC-am (SEQ ID NO: 50), or D-APYCVYR β ASWSC-am (SEQ ID NO: 52).

[062] Aspects of the present specification disclose, in part, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, that selectively binds to the ephrin-binding pocket in the EphA4 ligand binding domain. Selective binding includes binding properties such as, e.g., binding affinity and binding specificity. Binding affinity refers to the length of time a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, resides at the ephrin-binding pocket in the EphA4 ligand binding domain, and can be viewed as the strength with which a modified EphA4 antagonist binds to the ephrin-binding pocket. Binding affinity can be described by EphA4 antagonist's equilibrium dissociation constant (K_D), which is defined as the ratio K_d/K_a at equilibrium. Where K_a is the modified EphA4 antagonist's association rate constant and k_d is the modified EphA4 antagonist's dissociation rate constant. Binding affinity is determined by both the association and the dissociation and alone neither high association or low dissociation can ensure high affinity. The association rate constant (K_a), or on-rate constant (K_{on}), measures the number of binding events per unit time, or the propensity of the modified EphA4 antagonist and the ephrin-binding pocket in the EphA4 ligand binding domain to associate reversibly into its ligand-receptor complex. The association rate constant is expressed in $M^{-1} s^{-1}$, and is symbolized as follows: $[Ligand] \times [Receptor] \times K_{on}$. The larger the association rate constant, the more rapidly the modified EphA4 antagonist binds to the ephrin-binding pocket in the EphA4 ligand binding domain, or the higher the binding affinity between a modified EphA4 antagonist and EphA4. The dissociation rate constant (K_d), or off-rate constant (K_{off}), measures the number of dissociation events per unit time propensity of an ligand-receptor complex to separate (dissociate) reversibly into its component molecules, namely the modified EphA4 antagonist and EphA4. The dissociation rate constant is expressed in s^{-1} , and is symbolized as follows: $[Ligand + Receptor] \times K_{off}$. The smaller the dissociation rate constant, the more tightly bound the modified EphA4 antagonist is to the ephrin-binding pocket in the EphA4 ligand binding domain, or the higher the binding affinity between a modified EphA4 antagonist and EphA4. The equilibrium dissociation constant (K_D) measures the rate at which new ligand-receptor complexes formed equals the rate at which ligand-receptor complexes dissociate at equilibrium. The equilibrium dissociation constant is expressed in M, and is defined as $K_{off}/K_{on} = [Receptor] \times [Ligand] / [Receptor + Ligand]$, where $[Receptor]$ is the molar concentration of the receptor, $[Ligand]$ is the molar concentration of the ligand, and $[Receptor + Ligand]$ is the of molar concentration of the ligand-receptor complex, where all concentrations are of such components when the system is at equilibrium. The smaller the equilibrium dissociation constant, the more tightly bound the modified EphA4 antagonist is to the ephrin-binding

pocket in the EphA4 ligand binding domain, or the higher the binding affinity between a modified EphA4 antagonist and EphA4.

[063] Thus, in an embodiment, the binding affinity of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have an association rate constant for an EphA4 receptor of, e.g., less than $1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, $5 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, less than $5 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, less than $5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ or less than $1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$. In another embodiment, the binding affinity of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have an association rate constant for an EphA4 receptor of, e.g., more than $1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, more than $5 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, more than $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, more than $5 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, more than $1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, more than $5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ or more than $1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$. In other aspects, the binding affinity of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have an association rate constant for an EphA4 receptor of between $1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ to $1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ to $1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, $1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ to $1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ or $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ to $1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$.

[064] In another embodiment, the binding affinity of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have an association rate constant for an ephrin receptor other than an EphA4 receptor of, e.g., less than $1 \times 10^0 \text{ M}^{-1} \text{ s}^{-1}$, $5 \times 10^0 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$, less than $5 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, less than $5 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$, less than $5 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ or less than $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$. In another embodiment, the binding affinity of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have an association rate constant for an ephrin receptor other than an EphA4 receptor of, e.g., at most $1 \times 10^0 \text{ M}^{-1} \text{ s}^{-1}$, at most $5 \times 10^0 \text{ M}^{-1} \text{ s}^{-1}$, at most $1 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$, at most $5 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$, at most $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, at most $5 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, at most $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$, at most $5 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ or at most $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.

[065] In another embodiment, the binding affinity of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have a disassociation rate constant for an EphA4 receptor of, e.g., less than $1 \times 10^{-3} \text{ s}^{-1}$, $5 \times 10^{-3} \text{ s}^{-1}$, less than $1 \times 10^{-4} \text{ s}^{-1}$, less than $5 \times 10^{-4} \text{ s}^{-1}$ or less than $1 \times 10^{-5} \text{ s}^{-1}$. In other aspects of this embodiment, the binding affinity of an α -HIV antibody disclosed herein may have a disassociation rate constant for an EphA4 receptor of, e.g., less than $1.0 \times 10^{-4} \text{ s}^{-1}$, less than $2.0 \times 10^{-4} \text{ s}^{-1}$, less than $3.0 \times 10^{-4} \text{ s}^{-1}$, less than $4.0 \times 10^{-4} \text{ s}^{-1}$, less than $5.0 \times 10^{-4} \text{ s}^{-1}$, less than $6.0 \times 10^{-4} \text{ s}^{-1}$, less than $7.0 \times 10^{-4} \text{ s}^{-1}$, less than $8.0 \times 10^{-4} \text{ s}^{-1}$ or less than $9.0 \times 10^{-4} \text{ s}^{-1}$. In another embodiment, the binding affinity of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have a disassociation rate constant for an EphA4 receptor of, e.g., more than $1 \times 10^{-3} \text{ s}^{-1}$, more than $5 \times 10^{-3} \text{ s}^{-1}$, more than $1 \times 10^{-4} \text{ s}^{-1}$, more than $5 \times 10^{-4} \text{ s}^{-1}$ or more than $1 \times 10^{-5} \text{ s}^{-1}$. In other aspects of this embodiment, the binding affinity of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have a disassociation rate constant for an EphA4 receptor of, e.g., more than $1.0 \times 10^{-4} \text{ s}^{-1}$, more than $2.0 \times 10^{-4} \text{ s}^{-1}$, more than $3.0 \times 10^{-4} \text{ s}^{-1}$, more than $4.0 \times 10^{-4} \text{ s}^{-1}$, more than $5.0 \times 10^{-4} \text{ s}^{-1}$, more than $6.0 \times 10^{-4} \text{ s}^{-1}$, more than $7.0 \times 10^{-4} \text{ s}^{-1}$, more than $8.0 \times 10^{-4} \text{ s}^{-1}$ or more than $9.0 \times 10^{-4} \text{ s}^{-1}$. In other aspects, the binding affinity of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have a disassociation rate constant for an EphA4 receptor of between $1 \times 10^{-3} \text{ s}^{-1}$ to $1 \times 10^{-5} \text{ s}^{-1}$, $1 \times 10^{-3} \text{ s}^{-1}$ to $1 \times 10^{-4} \text{ s}^{-1}$ or $1 \times 10^{-4} \text{ s}^{-1}$ to $1 \times 10^{-5} \text{ s}^{-1}$.

[066] In another embodiment, the binding affinity of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have an equilibrium disassociation constant for an EphA4 receptor of less than 500 nM. In an aspect of this embodiment, the binding affinity of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have an equilibrium disassociation constant for an EphA4 receptor of, e.g., less than 500 nM, less than 450 nM, less than 400 nM, less than 350 nM, less than 300 nM, less than 250 nM, less than 200 nM, less than 150 nM, less than 100 nM, less than 75 nM, less than 50 nM, less than 25 nM, less than 20 nM, less than 15 nM, less than 10 nM, less than 5 nM, less than 1 nM, less than 0.5 nM, or less than 0.1 nM. In an aspect of this embodiment, the binding affinity of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have an equilibrium disassociation constant for an EphA4 receptor of, e.g., about 0.1 nM to about 10 nM, about 0.1 nM to about 25 nM, about 0.1 nM to about 75 nM, about 0.1 nM to about 100 nM, about 0.1 nM to about 125 nM, about 0.1 nM to about 150 nM, about 0.5 nM to about 10 nM, about 0.5 nM to about 25 nM, about 0.5 nM to about 75 nM, about 0.5 nM to about 100 nM, about 0.5 nM to about 125 nM, about 0.5 nM to about 150 nM, about 1 nM to about 10 nM, about 1 nM to about 25 nM, about 1 nM to about 75 nM, about 1 nM to about 100 nM, about 1 nM to about 125 nM, about 1 nM to about 150 nM, about 5 nM to about 10 nM, about 5 nM to about 25 nM, about 5 nM to about 75 nM, about 5 nM to about 100 nM, about 5 nM to about 125 nM, about 5 nM to about 150 nM, about 10 nM to about 25 nM, about 10 nM to about 50 nM, about 10 nM to about 75 nM, about 10 nM to about 100 nM, about 10 nM to about 125 nM, about 10 nM to about 150 nM, about 10 nM to about 175 nM or about 10 nM to about 200 nM.

[067] Binding specificity is the ability of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, to discriminate between a molecule containing the ephrin-binding pocket in the EphA4 ligand binding domain and a molecule that does not contain this ephrin-binding pocket. One way to measure binding specificity is to compare the K_{on} association rate of a modified EphA4 antagonist for a molecule containing the ephrin-binding pocket in the EphA4 ligand binding domain relative to the K_{on} association rate of the modified EphA4 antagonist for a molecule that does not contain this ephrin-binding pocket. For example, comparing the association rate constant (K_a) of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, that selectively binds to the ephrin-binding pocket in the EphA4 ligand binding domain relative to an ephrin-binding pocket to an Eph receptor other than EphA4. In aspects of this embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have an association rate constant (K_a) for an ephrin-binding pocket to an ephrin receptor other than an EphA4 receptor of, e.g., less than $1 \times 10^0 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ or less than $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$. In other aspects of this embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, have an association rate constant (K_a) for an ephrin-binding pocket to an ephrin receptor other than an EphA4 receptor of, e.g., at most $1 \times 10^0 \text{ M}^{-1} \text{ s}^{-1}$, at most $1 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$, at most $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, at most $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ or at most $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.

[068] In other aspects of this embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have an association rate constant (K_a) for the ephrin-binding pocket in the EphA4 ligand binding domain relative to an ephrin-binding pocket of an ephrin receptor other than an EphA4

receptor of, e.g., at least 2-fold more, at least 3-fold more, at least 4-fold more, at least 5-fold more, at least 6-fold more, at least 7-fold more, at least 8-fold more, or at least 9-fold more. In yet other aspects of this embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have an association rate constant (K_a) for the ephrin-binding pocket in the EphA4 ligand binding domain relative to an ephrin-binding pocket of an ephrin receptor other than an EphA4 receptor of, e.g., at least 10-fold more, at least 20-fold more, at least 30-fold more, at least 40-fold more, at least 50-fold more, at least 60-fold more, at least 70-fold more, at least 80-fold more, at least 90-fold more, at least 100-fold more, at least 200-fold more, at least 300-fold more, at least 400-fold more, at least 500-fold more, at least 600-fold more, at least 700-fold more, at least 800-fold more, at least 900-fold more, at least 1,000-fold more, at least 1,200-fold more, at least 1,400-fold more, at least 1,600-fold more, at least 1,800-fold more, at least 2,000-fold more, at least 2,500-fold more, at least 5,000-fold more, at least 7,500-fold more or at least 10,000-fold more. In aspects of this embodiment, an ephrin-binding pocket of an ephrin receptor other than an EphA4 receptor includes an EphA2 receptor, an EphA3 receptor, an EphA5 receptor, an EphA6 receptor, an EphA7 receptor, an EphA8 receptor, an EphB1 receptor, an EphB2 receptor, an EphB3 receptor, an EphB4 receptor, an EphB6 receptor, or any combination thereof.

[069] In other aspects of this embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have an association rate constant (K_a) for the ephrin-binding pocket in the EphA4 ligand binding domain relative to an ephrin-binding pocket of an ephrin receptor other than an EphA4 receptor of, e.g., at most 1-fold more, at most 2-fold more, at most 3-fold more, at most 4-fold more, at most 5-fold more, at most 6-fold more, at most 7-fold more, at most 8-fold more, or at most 9-fold more. In yet other aspects of this embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have an association rate constant (K_a) for the ephrin-binding pocket in the EphA4 ligand binding domain relative to an ephrin-binding pocket of an ephrin receptor other than an EphA4 receptor of, e.g., at most 10-fold more, at most 20-fold more, at most 30-fold more, at most 40-fold more, at most 50-fold more, at most 60-fold more, at most 70-fold more, at most 80-fold more, at most 90-fold more, at most 100-fold more, at most 200-fold more, at most 300-fold more, at most 400-fold more, at most 500-fold more, at most 600-fold more, at most 700-fold more, at most 800-fold more, at most 900-fold more, at most 1,000-fold more, at most 1,200-fold more, at most 1,400-fold more, at most 1,600-fold more, at most 1,800-fold more, at most 2,000-fold more, at most 2,500-fold more, at most 5,000-fold more, at most 7,500-fold more or at most 10,000-fold more. In aspects of this embodiment, an ephrin-binding pocket of an ephrin receptor other than an EphA4 receptor includes an EphA2 receptor, an EphA3 receptor, an EphA5 receptor, an EphA6 receptor, an EphA7 receptor, an EphA8 receptor, an EphB1 receptor, an EphB2 receptor, an EphB3 receptor, an EphB4 receptor, an EphB6 receptor, or any combination thereof.

[070] The binding specificity of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may also be characterized as a ratio that such a modified EphA4 antagonist can discriminate the ephrin-binding pocket in the EphA4 ligand binding domain relative to an ephrin-binding pocket of an ephrin receptor other than an EphA4 receptor. In aspects of this embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may have a binding specificity ratio for the ephrin-binding pocket in the EphA4 ligand binding domain relative to an ephrin-binding pocket of an ephrin

receptor other than an EphA4 receptor of, e.g., at least 2:1, at least 3:1, at least 4:1, at least 5:1, at least 64:1, at least 7:1, at least 8:1, at least 9:1, at least 10:1, at least 15:1, at least 20:1, at least 25:1, at least 30:1, at least 35:1, or at least 40:1. In aspects of this embodiment, an ephrin-binding pocket of an ephrin receptor other than an EphA4 receptor includes an EphA2 receptor, an EphA3 receptor, an EphA5 receptor, an EphA6 receptor, an EphA7 receptor, an EphA8 receptor, an EphB1 receptor, an EphB2 receptor, an EphB3 receptor, an EphB4 receptor, an EphB6 receptor, or any combination thereof.

[071] Aspects of the present specification disclose, in part, a modified EphA4 receptor antagonist. A modified EphA4 receptor antagonist disclosed herein is an APY cyclic peptide disclosed herein comprising a modification designed to increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide. Modification useful to increase binding affinity to EphA4, binding selectivity for EphA4, and/or physiological stability of an APY cyclic peptide disclosed herein include, without limitation, lipidation, PEGylation, polysialylation, a Blood-Brain Barrier (BBB) shuttle, hyperglycosylation, N-(2-hydroxypropyl) methacrylamide (HPMA) copolymers, and polyglutamic acid, poly(lactic acid) (PLA) polymers, poly(glycolic acid) (PGA) polymers and poly(D,L-lactic-coglycolic-acid) (PLGA) polymers.

[072] Aspects of the present specification disclose, in part, modification of an APY cyclic peptide disclosed herein by lipidation. Lipidation involves the formation of a stable covalent attachment of one or more lipid moieties to a peptide or polypeptide of interest.

[073] The presence of one or more lipid moieties can alter various physicochemical properties of a peptide or polypeptide including, without limitation, increasing the size and molecular weight of the peptide, changing the secondary structure of the peptide, providing low steric hindrance of intermolecular interactions of the peptide, increasing the hydrophobicity of the peptide, changing electrostatic binding properties of the peptide, forming micelle-like assemblies and masking antigenic sites on the peptide. Such modifications can change the pharmacokinetic and pharmacodynamic properties of the peptide conjugate while retaining its functionality as well as improve its metabolic stability, decrease its clearance rate, decrease its susceptibility to proteolysis, alter its self-assembling propensities, improve its membrane permeability, reduce its immunogenicity and antigenicity and/or improve its bioavailability relative to the non-lipidated peptide. The masking of potential antigenic sites by one or more lipid moieties also can decrease the generation of neutralizing antibodies against the peptide.

[074] Formation of a lipidated-conjugated peptide or polypeptide involves the acylation of a functional group present on a side chain of the peptide or polypeptide with a long-chain lipid. Covalent attachment of an activated lipid is generally made at the α or ϵ amino groups of lysine, a β -aspartic acid, a γ -glutamic acid, or any other amino acid have a free amino group; the N-terminal amino group of cysteine, histidine, arginine, aspartic acid, glutamic acid, serine, threonine, tyrosine; or the C-terminal carboxylic acid. In an aspect of this embodiment, a lipid can be conjugated to an appropriate amino acid present in an APY cyclic peptide disclosed herein. In another aspect of this embodiment, an additional peptide sequence is added to the C-terminal end of an APY cyclic peptide disclosed herein, the additional peptide sequence

having an amino acid appropriate to conjugate a lipid. In an aspect of this embodiment, the additional peptide sequence is a GGKG tetrapeptide (SEQ ID NO: 70). Reagents and methods of attaching a lipid to a peptide or polypeptide are described in Zhang and Bulaj, *Converting Peptides into Drug Leads by Lipidation*, Curr. Med. Chem. 19: 1602-1618 (2012), which is hereby incorporated by reference in its entirety.

[075] Typically, the lipid moiety used is a fatty acid, a lipid comprises a carboxylic acid with a long unbranched hydrocarbon chain which may be either saturated or unsaturated. Examples of fatty acids include, without limitation, hexanoic (caproic) acid (6:0), heptanoic (enanthic) acid (7:0), octanoic (caprylic) acid (8:0), nonanoic (pelargonic) acid (9:0), decanoic (capric) acid (10:0), undecanoic (undecylic) acid (11:0), dodecanoic (lauric) acid (12:0), tridecanoic (tridecylic) acid (13:0), tetradecanoic (myristic) acid (14:0), myristoleic acid (14:1), pentadecanoic (pentadecylic) acid (15:0), hexadecanoic (palmitic) acid (16:0), palmitoleic acid (16:1), sapienic acid (16:1), heptadecanoic (margaric) acid (17:0), octadecanoic (stearic) acid (18:0), oleic acid (18:1), elaidic acid (18:1), vaccenic acid (18:1), linoleic acid (18:2), linoelaidic acid (18:2), α -linolenic acid (18:3), γ -linolenic acid (18:3), stearidonic acid (18:4), nonadecylic acid (19:0), arachidic acid (20:0), eicosenoic acid (20:1), dihomo- γ -linolenic acid (20:3), mead acid (20:3), arachidonic acid (20:4), eicosapentaenoic acid (20:5), heneicosylic acid (21:0), behenic acid (22:0), erucic acid (22:1), docosahexaenoic acid (22:6), tricosylic acid (23:0), lignoceric acid (24:0), nervonic acid (24:1), pentacosylic acid (25:0), cerotic acid (26:0), heptacosylic acid (27:0), montanic acid (28:0), nonacosylic acid (29:0), melissic acid (30:0), henatriacontylic acid (31:0), lacceroic acid (32:0), psyllic acid (33:0), geddic acid (34:0), ceroplactic acid (35:0), and hexatriacontylic acid (36:0).

[076] In an embodiment, a lipid may be a pharmaceutically-acceptable saturated or unsaturated fatty acid. In aspects of this embodiment, a saturated or unsaturated fatty acid comprises, e.g., at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 22, at least 24, at least 26, at least 28, or at least 30 carbon atoms. In other aspects of this embodiment, a saturated or unsaturated fatty acid comprises, e.g., between 4 and 24 carbon atoms, between 5 and 24 carbon atoms, between 6 and 24 carbon atoms, between 7 and 24 carbon atoms, between 8 and 24 carbon atoms, between 9 and 24 carbon atoms, between 10 and 24 carbon atoms, between 11 and 24 carbon atoms, between 12 and 24 carbon atoms, between 13 and 24 carbon atoms, between 14 and 24 carbon atoms, between 15 and 24 carbon atoms, between 16 and 24 carbon atoms, between 4 and 22 carbon atoms, between 5 and 22 carbon atoms, between 6 and 22 carbon atoms, between 7 and 22 carbon atoms, between 8 and 22 carbon atoms, between 9 and 22 carbon atoms, between 10 and 22 carbon atoms, between 11 and 22 carbon atoms, between 12 and 22 carbon atoms, between 13 and 22 carbon atoms, between 14 and 22 carbon atoms, between 15 and 22 carbon atoms, between 16 and 22 carbon atoms, between 4 and 20 carbon atoms, between 5 and 20 carbon atoms, between 6 and 20 carbon atoms, between 7 and 20 carbon atoms, between 8 and 20 carbon atoms, between 9 and 20 carbon atoms, between 10 and 20 carbon atoms, between 11 and 20 carbon atoms, between 12 and 20 carbon atoms, between 13 and 20 carbon atoms, between 14 and 20 carbon atoms, between 15 and 20 carbon atoms, between 16 and 20 carbon atoms, between 4 and 18 carbon atoms, between 5 and 18 carbon atoms, between 6 and 18

carbon atoms, between 7 and 18 carbon atoms, between 8 and 18 carbon atoms, between 9 and 18 carbon atoms, between 10 and 18 carbon atoms, between 11 and 18 carbon atoms, between 12 and 18 carbon atoms, between 13 and 18 carbon atoms, between 14 and 18 carbon atoms, between 15 and 18 carbon atoms, between 16 and 18 carbon atoms, between 4 and 16 carbon atoms, between 5 and 16 carbon atoms, between 6 and 16 carbon atoms, between 7 and 16 carbon atoms, between 8 and 16 carbon atoms, between 9 and 16 carbon atoms, between 10 and 16 carbon atoms, between 11 and 16 carbon atoms, between 12 and 16 carbon atoms, between 13 and 16 carbon atoms, between 14 and 16 carbon atoms, between 4 and 14 carbon atoms, between 5 and 14 carbon atoms, between 6 and 14 carbon atoms, between 7 and 14 carbon atoms, between 8 and 14 carbon atoms, between 9 and 14 carbon atoms, between 10 and 14 carbon atoms, between 11 and 14 carbon atoms, between 12 and 14 carbon atoms, between 4 and 12 carbon atoms, between 5 and 12 carbon atoms, between 6 and 12 carbon atoms, between 7 and 12 carbon atoms, between 8 and 12 carbon atoms, between 9 and 12 carbon atoms, or between 10 and 12 carbon atoms. If unsaturated, the fatty acid may have, e.g., 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, or 6 or more double bonds.

[077] Aspects of the present specification disclose, in part, modification of an APY cyclic peptide disclosed herein by PEGylation. PEGylation involves the formation of a stable covalent attachment of one or more synthetic poly(ethylene glycol) (PEG) polymers to a peptide or polypeptide of interest. PEG polymers are typically biologically inert, non-immunogenic molecules that confers greater water solubility to peptides or polypeptides by forming a hydrophilic shell. PEG polymers are synthesized by the polymerization of ethylene oxide and are commercially available over a wide range of molecular weights from 100 g/mol to 10,000,000 g/mol. PEG polymers can have a linear or branched structure. Branched PEG polymers can increase the size of the total conjugate without resultant increase in number of attachment sites and have been shown to improve stability in response to changes in pH, proteolytic digestion, and temperature change as compared to linear PEG polymers. Depending on how one chooses to define the constituent monomer (as ethylene glycol, ethylene oxide or oxyethylene), PEG polymers are also known as polyethylene oxide (PEO) polymers and polyoxyethylene (POE) polymers.

[078] The presence of one or more PEG polymers can alter various physicochemical properties of a peptide or polypeptide including, without limitation, increasing the size and molecular weight of the peptide, changing the secondary structure of the peptide, providing low steric hindrance of intermolecular interactions of the peptide, increasing the hydrophilicity of the peptide, increasing the solubility of the peptide, changing electrostatic binding properties of the peptide and masking antigenic sites on the peptide. Such modifications can also change the pharmacokinetic and pharmacodynamic properties of the peptide conjugate while retaining its functionality as well as improve its metabolic stability, decrease its clearance rate, decrease its susceptibility to proteolysis, alter its distribution, reduce its uptake by macrophages, alter its self-assembling propensities, reduce its immunogenicity and antigenicity and/or improve its bioavailability relative to the non-PEGylated peptide. The masking of potential antigenic sites by one or more PEG polymers also can decrease the generation of neutralizing antibodies against the peptide.

[079] Formation of a PEG-conjugated peptide or polypeptide involves the activation of PEG polymers by preparing derivatives with functional groups at one or both of the terminal ends of the polymers. PEG polymer derivatives with functional groups at both terminal ends can be homobifunctional (identical reactive groups at either end) and heterobifunctional (different reactive groups at either end). PEG polymers can be an oxidized, reduced, aminated and/or hydrazide derivative. Useful functional groups include, without limitation, amine reactive PEG polymers activate by, e.g., the presence of an N-hydroxy-succinimide (NHS) ester that react with amine groups; and sulfhydryl-reactive PEG polymers activate by, e.g., the presence of a maleimide group that react sulfhydryl groups. Covalent attachment of an activated PEG polymer is generally made at the α or ϵ amino groups of lysine, a β -aspartic acid, a γ -glutamic acid, or any other amino acid have a free amino group; the N-terminal amino group of cysteine, histidine, arginine, aspartic acid, glutamic acid, serine, threonine, tyrosine; or the C-terminal carboxylic acid. Among these amino acids, the most common choices for PEGylation are lysine and proteins N-terminal amino group. Activated PEG polymer derivatives useful to modify an APY peptide disclosed herein are commercially available.

[080] The exact molecular weight of a PEG polymer used to conjugate to a peptide or polypeptide may depend on the purpose of the PEGylation. In aspects of this embodiment, the number of monomers comprising an activated PEG polymers useful to modify an APY peptide disclosed herein may be, e.g., about 4 monomers, about 5 monomers, about 6 monomers, about 7 monomers, about 8 monomers, about 9 monomers, about 10 monomers, about 11 monomers, about 12 monomers, about 13 monomers, about 14 monomers, about 15 monomers, about 16 monomers, about 17 monomers, about 18 monomers, about 19 monomers, about 20 monomers, about 21 monomers, about 22 monomers, about 23 monomers, about 24 monomers, about 25 monomers, about 26 monomers, about 27 monomers, about 28 monomers, about 29 monomers or about 30 monomers. In other aspects of this embodiment, the number of monomers comprising an activated PEG polymers useful to modify an APY peptide disclosed herein may be, e.g., at least 4 monomers, at least 5 monomers, at least 6 monomers, at least 7 monomers, at least 8 monomers, at least 9 monomers, at least 10 monomers, at least 11 monomers, at least 12 monomers, at least 13 monomers, at least 14 monomers, at least 15 monomers, at least 16 monomers, at least 17 monomers, at least 18 monomers, at least 19 monomers, at least 20 monomers, at least 21 monomers, at least 22 monomers, at least 23 monomers, at least 24 monomers, at least at least 25 monomers, at least 26 monomers, at least 27 monomers, at least 28 monomers, at least 29 monomers or at least 30 monomers. In yet other aspects of this embodiment, the number of monomers comprising an activated PEG polymers useful to modify an APY peptide disclosed herein may be, e.g., at most 4 monomers, at most 5 monomers, at most 6 monomers, at most 7 monomers, at most 8 monomers, at most 9 monomers, at most 10 monomers, at most 11 monomers, at most 12 monomers, at most 13 monomers, at most 14 monomers, at most 15 monomers, at most 16 monomers, at most 17 monomers, at most 18 monomers, at most 19 monomers, at most 20 monomers, at most 21 monomers, at most 22 monomers, at most 23 monomers, at most 24 monomers, at most at least 25 monomers, at most 26 monomers, at most 27 monomers, at most 28 monomers, at most 29 monomers or at most 30 monomers.

[081] In still other aspects of this embodiment, the number of monomers comprising an activated PEG polymers useful to modify an APY peptide disclosed herein may be, *e.g.*, about 4 to about 8 monomers, about 4 to about 12 monomers, about 4 to about 16 monomers, about 4 to about 20 monomers, about 4 to about 24 monomers, about 4 to about 28 monomers, about 4 to about 32 monomers, about 6 to about 8 monomers, about 6 to about 12 monomers, about 6 to about 16 monomers, about 6 to about 20 monomers, about 6 to about 24 monomers, about 6 to about 28 monomers, about 6 to about 32 monomers, about 8 to about 12 monomers, about 8 to about 16 monomers, about 8 to about 20 monomers, about 8 to about 24 monomers, about 8 to about 28 monomers, about 8 to about 32 monomers, about 10 to about 12 monomers, about 10 to about 16 monomers, about 10 to about 20 monomers, about 10 to about 24 monomers, about 10 to about 28 monomers, about 10 to about 32 monomers, about 12 to about 16 monomers, about 12 to about 20 monomers, about 12 to about 24 monomers, about 12 to about 28 monomers, about 12 to about 32 monomers, about 14 to about 16 monomers, about 14 to about 20 monomers, about 14 to about 24 monomers, about 14 to about 28 monomers, about 14 to about 32 monomers, about 16 to about 20 monomers, about 16 to about 24 monomers, about 16 to about 28 monomers, about 16 to about 32 monomers, about 18 to about 20 monomers, about 18 to about 24 monomers, about 18 to about 28 monomers, about 18 to about 32 monomers, about 20 to about 24 monomers, about 20 to about 28 monomers, about 20 to about 32 monomers, about 22 to about 24 monomers, about 22 to about 28 monomers, about 22 to about 32 monomers, about 24 to about 28 monomers, about 24 to about 32 monomers, about 26 to about 28 monomers, about 26 to about 32 monomers, about 28 to about 32 monomers or about 30 to about 32 monomers.

[082] In aspects of this embodiment, the molecular weight of the activated PEG polymer derivative may be, *e.g.*, about 20 kDa, about 25 kDa, about 30 kDa, about 35 kDa, about 40 kDa, about 45 kDa, about 50 kDa, about 55 kDa, about 60 kDa, about 65 kDa, about 70 kDa, about 75 kDa, about 80 kDa, about 85 kDa, about 90 kDa, about 95 kDa, or about 100 kDa. In other aspects of this embodiment, the molecular weight of the activated PEG polymer derivative may be, *e.g.*, at least 20 kDa, at least 25 kDa, at least 30 kDa, at least 35 kDa, at least 40 kDa, at least 45 kDa, at least 50 kDa, at least 55 kDa, at least 60 kDa, at least 65 kDa, at least 70 kDa, at least 75 kDa, at least 80 kDa, at least 85 kDa, at least 90 kDa, at least 95 kDa, or at least 100 kDa. In yet other aspects of this embodiment, the molecular weight of the activated PEG polymer derivative may be, *e.g.*, at most 20 kDa, at most 25 kDa, at most 30 kDa, at most 35 kDa, at most 40 kDa, at most 45 kDa, at most 50 kDa, at most 55 kDa, at most 60 kDa, at most 65 kDa, at most 70 kDa, at most 75 kDa, at most 80 kDa, at most 85 kDa, at most 90 kDa, at most 95 kDa, or at most 100 kDa. In still other aspects of this embodiment, the molecular weight of the activated PEG polymer derivative may be, *e.g.*, about 20 kDa to about 30 kDa, about 20 kDa to about 40 kDa, about 20 kDa to about 50 kDa, about 20 kDa to about 60 kDa, about 20 kDa to about 70 kDa, about 20 kDa to about 80 kDa, about 20 kDa to about 90 kDa, about 20 kDa to about 100 kDa, about 30 kDa to about 40 kDa, about 30 kDa to about 50 kDa, about 30 kDa to about 60 kDa, about 30 kDa to about 70 kDa, about 30 kDa to about 80 kDa, about 30 kDa to about 90 kDa, about 30 kDa to about 100 kDa, about 40 kDa to about 50 kDa, about 40 kDa to about 60 kDa, about 40 kDa to about 70 kDa, about 40 kDa to about 80 kDa, about 40 kDa to about 90 kDa, about 40 kDa to about 100 kDa, about 50 kDa to about 60 kDa,

about 50 kDa to about 70 kDa, about 50 kDa to about 80 kDa, about 50 kDa to about 90 kDa, about 50 kDa to about 100 kDa, about 60 kDa to about 70 kDa, about 60 kDa to about 80 kDa, about 60 kDa to about 90 kDa, about 60 kDa to about 100 kDa, about 70 kDa to about 80 kDa, about 70 kDa to about 90 kDa, about 70 kDa to about 100 kDa, about 80 kDa to about 90 kDa, about 80 kDa to about 100 kDa, or about 90 kDa to about 100 kDa.

[083] In aspects of this embodiment, the molecular weight of the PEG-conjugated peptide or polypeptide may be, *e.g.*, about 20 kDa, about 25 kDa, about 30 kDa, about 35 kDa, about 40 kDa, about 45 kDa, about 50 kDa, about 55 kDa, about 60 kDa, about 65 kDa, about 70 kDa, about 75 kDa, about 80 kDa, about 85 kDa, about 90 kDa, about 95 kDa, or about 100 kDa. In other aspects of this embodiment, the molecular weight of the PEG-conjugated peptide or polypeptide may be, *e.g.*, at least 20 kDa, at least 25 kDa, at least 30 kDa, at least 35 kDa, at least 40 kDa, at least 45 kDa, at least 50 kDa, at least 55 kDa, at least 60 kDa, at least 65 kDa, at least 70 kDa, at least 75 kDa, at least 80 kDa, at least 85 kDa, at least 90 kDa, at least 95 kDa, or at least 100 kDa. In yet other aspects of this embodiment, the molecular weight of the PEG-conjugated peptide or polypeptide may be, *e.g.*, at most 20 kDa, at most 25 kDa, at most 30 kDa, at most 35 kDa, at most 40 kDa, at most 45 kDa, at most 50 kDa, at most 55 kDa, at most 60 kDa, at most 65 kDa, at most 70 kDa, at most 75 kDa, at most 80 kDa, at most 85 kDa, at most 90 kDa, at most 95 kDa, or at most 100 kDa. In still other aspects of this embodiment, the molecular weight of the PEG-conjugated peptide or polypeptide may be, *e.g.*, about 20 kDa to about 30 kDa, about 20 kDa to about 40 kDa, about 20 kDa to about 50 kDa, about 20 kDa to about 60 kDa, about 20 kDa to about 70 kDa, about 20 kDa to about 80 kDa, about 20 kDa to about 90 kDa, about 20 kDa to about 100 kDa, about 30 kDa to about 40 kDa, about 30 kDa to about 50 kDa, about 30 kDa to about 60 kDa, about 30 kDa to about 70 kDa, about 30 kDa to about 80 kDa, about 30 kDa to about 90 kDa, about 30 kDa to about 100 kDa, about 40 kDa to about 50 kDa, about 40 kDa to about 60 kDa, about 40 kDa to about 70 kDa, about 40 kDa to about 80 kDa, about 40 kDa to about 90 kDa, about 40 kDa to about 100 kDa, about 50 kDa to about 60 kDa, about 50 kDa to about 70 kDa, about 50 kDa to about 80 kDa, about 50 kDa to about 90 kDa, about 50 kDa to about 100 kDa, about 60 kDa to about 70 kDa, about 60 kDa to about 80 kDa, about 60 kDa to about 90 kDa, about 60 kDa to about 100 kDa, about 70 kDa to about 80 kDa, about 70 kDa to about 90 kDa, about 70 kDa to about 100 kDa, about 80 kDa to about 90 kDa, about 80 kDa to about 100 kDa, or about 90 kDa to about 100 kDa.

[084] Aspects of the present specification disclose, in part, modification of an APY cyclic peptide disclosed herein by polysialylation. Polysialylation involves the formation of a stable covalent attachment of one or more polysialic acid (PSA) polymers to a peptide or polypeptide of interest. Having no known receptors in humans, PSA polymers are biodegradable, biologically inert, non-immunogenic molecules that confers greater water solubility and lower viscosity to peptides or polypeptides by forming a “watery cloud”. Similar to the fixed aqueous hydrophilic coat associated with PEG-modified compounds, the “watery cloud” is a protective envelope of water surrounding the PSA polymers which prevents their interactions with cells and proteins. PSA polymers are linear polysaccharides consisting of α -(2,8) and/or α -(2,9)-linked sialic acids (N-acetyl neuraminic acid; (Neu5Ac) monomers. Naturally occurring PSA polymers are produced by *Escherichia coli*, *Neisseria meningitides*, *Moraxella nonliquefaciens*,

Pasteurella haemolytica and *Mannheimia haemolytica*. PSA polymers are commercially available over various degrees of polymerization, such as, e.g., from 2-80 sialic acid monomers. PSA polymers exist as homopolymeric forms, e.g., α -(2,8)-linked PSA polymers or α -(2,9)-linked PSA polymers, or as heteropolymeric forms, e.g., PSA polymers composed of alternating α -(2,8) and α -(2,9)-linked sialic acid monomers. The α -(2,8)-linked PSA polymer is also known as colominic acid (CA). In addition, PSA copolymeric forms exist, e.g., PSA copolymers composed of alternating sialic acid monomers with other neuraminic acid monomers such as N-acetyl neuraminic acid hydroxyalkyl (Neu5Gc) or 3-deoxy-d-glycero-d-galacto-nonyl ketose (KDN).

[085] The presence of one or more PSA polymers can alter various physicochemical properties of a peptide or polypeptide including, without limitation, increasing the size and molecular weight of the peptide, changing the secondary structure of the peptide, providing low steric hindrance of intermolecular interactions of the peptide, increasing the hydrophilicity of the peptide, increasing the solubility of the peptide, changing electrostatic binding properties of the peptide and masking antigenic sites on the peptide. Such modifications can also change the pharmacokinetic and pharmacodynamic properties of the peptide conjugate while retaining its functionality as well as improve its metabolic stability, prolong its physiological half-life in circulation, decrease its clearance rate, decrease its susceptibility to proteolysis, alter its distribution, reduce its uptake by macrophages and phagocytes, alter its self-assembling propensities, reduce its immunogenicity and antigenicity and/or improve its bioavailability relative to the non-polysialated peptide. The masking of potential antigenic sites by one or more PSA polymers also can decrease the generation of neutralizing antibodies against the peptide. In addition, PSA polymers are endogenous substances in humans and can be completely degraded non-toxic SA by neuraminidase.

[086] Formation of a PSA-conjugated peptide or polypeptide involves the activation of PSA polymers by preparing derivatives with functional groups at one or both of the terminal ends of the polymers. PSA polymer derivatives with functional groups at both terminal ends can be homobifunctional (identical reactive groups at either end) and heterobifunctional (different reactive groups at either end). PSA polymers can be an oxidized, reduced, aminated and/or hydrazide derivative. Useful functional groups include, without limitation, amine reactive PSA polymers activate by, e.g., the presence of an N-hydroxy-succinimide (NHS) ester that react with amine groups; the presence of an aldehyde group that react with amine groups; and sulfhydryl-reactive PSA polymers activate by, e.g., the presence of a maleimide group that react sulfhydryl groups. Covalent attachment of an activated PSA polymer is generally made at the α or ϵ amino groups of lysine, a β -aspartic acid, a γ -glutamic acid, or any other amino acid have a free amino group; the N-terminal amino group of cysteine, histidine, arginine, aspartic acid, glutamic acid, serine, threonine, tyrosine; or the C-terminal carboxylic acid. Among these amino acids, the most common choices for polysialylation are lysine and proteins N-terminal amino group. Methods for making activated PSA polymers useful to modify an APY peptide disclosed herein are described in, e.g., U.S. Patent 5,846,951, U.S. Patent 7,691,826, U.S. Patent 7,807,824, U.S. Patent 7,875,708, U.S. Patent 8,217,154, U.S. Patent 8,394,921, each of which is hereby incorporated by reference in its entirety.

[087] The exact molecular weight of an activated PSA polymer derivative used to conjugate to a peptide or polypeptide may depend on the purpose of the polysialylation. In aspects of this embodiment, the number of monomers comprising an activated PSA polymers useful to modify an APY peptide disclosed herein may be, *e.g.*, about 5 monomers, about 10 monomers, about 15 monomers, about 20 monomers, about 25 monomers, about 30 monomers, about 35 monomers, about 40 monomers, about 45 monomers, about 50 monomers, about 55 monomers, about 60 monomers, about 65 monomers, about 70 monomers, about 75 monomers, about 80 monomers, about 85 monomers, about 90 monomers, about 95 monomers, or about 100 monomers. In other aspects of this embodiment, the number of monomers comprising an activated PSA polymers useful to modify an APY peptide disclosed herein may be, *e.g.*, at least 5 monomers, at least 10 monomers, at least 15 monomers, at least 20 monomers, at least 25 monomers, at least 30 monomers, at least 35 monomers, at least 40 monomers, at least 45 monomers, at least 50 monomers, at least 55 monomers, at least 60 monomers, at least 65 monomers, at least 70 monomers, at least 75 monomers, at least 80 monomers, at least 85 monomers, at least 90 monomers, at least 95 monomers, or at least 100 monomers. In yet other aspects of this embodiment, the number of monomers comprising an activated PSA polymers useful to modify an APY peptide disclosed herein may be, *e.g.*, at most 5 monomers, at most 10 monomers, at most 15 monomers, at most 20 monomers, at most 25 monomers, at most 30 monomers, at most 35 monomers, at most 40 monomers, at most 45 monomers, at most 50 monomers, at most 55 monomers, at most 60 monomers, at most 65 monomers, at most 70 monomers, at most 75 monomers, at most 80 monomers, at most 85 monomers, at most 90 monomers, at most 95 monomers, or at most 100 monomers.

[088] In still other aspects of this embodiment, the number of monomers comprising an activated PSA polymers useful to modify an APY peptide disclosed herein may be, *e.g.*, about 5 to about 15 monomers, about 5 to about 20 monomers, about 5 to about 25 monomers, about 5 to about 30 monomers, about 5 to about 35 monomers, about 5 to about 40 monomers, about 5 to about 45 monomers, about 5 to about 50 monomers, about 5 to about 55 monomers, about 5 to about 60 monomers, about 5 to about 65 monomers, about 5 to about 70 monomers, about 5 to about 75 monomers, about 5 to about 80 monomers, about 5 to about 85 monomers, about 5 to about 90 monomers, about 5 to about 95 monomers, about 5 to about 100 monomers, about 10 to about 20 monomers, about 10 to about 25 monomers, about 10 to about 30 monomers, about 10 to about 35 monomers, about 10 to about 40 monomers, about 10 to about 45 monomers, about 10 to about 50 monomers, about 10 to about 55 monomers, about 10 to about 60 monomers, about 10 to about 65 monomers, about 10 to about 70 monomers, about 10 to about 75 monomers, about 10 to about 80 monomers, about 10 to about 85 monomers, about 10 to about 90 monomers, about 10 to about 95 monomers, about 10 to about 100 monomers, about 15 to about 20 monomers, about 15 to about 25 monomers, about 15 to about 30 monomers, about 15 to about 35 monomers, about 15 to about 40 monomers, about 15 to about 45 monomers, about 15 to about 50 monomers, about 15 to about 55 monomers, about 15 to about 60 monomers, about 15 to about 65 monomers, about 15 to about 70 monomers, about 15 to about 75 monomers, about 15 to about 80 monomers, about 15 to about 85 monomers, about 15 to about 90 monomers, about 15 to about 95 monomers, about 15 to about 100 monomers, about 20 to about 30 monomers, about 20 to about 35 monomers, about 20 to about 40 monomers, about 20 to about 45

[illegible]

monomers, about 80 to about 100 monomers, about 85 to about 90 monomers, about 85 to about 95 monomers, about 85 to about 100 monomers, about 90 to about 95 monomers, about 90 to about 100 monomers, or about 95 to about 100 monomers.

[089] In aspects of this embodiment, the molecular weight of the activated PSA polymer derivative may be, *e.g.*, about 20 kDa, about 25 kDa, about 30 kDa, about 35 kDa, about 40 kDa, about 45 kDa, about 50 kDa, about 55 kDa, about 60 kDa, about 65 kDa, about 70 kDa, about 75 kDa, about 80 kDa, about 85 kDa, about 90 kDa, about 95 kDa, or about 100 kDa. In other aspects of this embodiment, the molecular weight of the activated PSA polymer derivative may be, *e.g.*, at least 20 kDa, at least 25 kDa, at least 30 kDa, at least 35 kDa, at least 40 kDa, at least 45 kDa, at least 50 kDa, at least 55 kDa, at least 60 kDa, at least 65 kDa, at least 70 kDa, at least 75 kDa, at least 80 kDa, at least 85 kDa, at least 90 kDa, at least 95 kDa, or at least 100 kDa. In yet other aspects of this embodiment, the molecular weight of the activated PSA polymer derivative may be, *e.g.*, at most 20 kDa, at most 25 kDa, at most 30 kDa, at most 35 kDa, at most 40 kDa, at most 45 kDa, at most 50 kDa, at most 55 kDa, at most 60 kDa, at most 65 kDa, at most 70 kDa, at most 75 kDa, at most 80 kDa, at most 85 kDa, at most 90 kDa, at most 95 kDa, or at most 100 kDa. In still other aspects of this embodiment, the molecular weight of the activated PSA polymer derivative may be, *e.g.*, about 20 kDa to about 30 kDa, about 20 kDa to about 40 kDa, about 20 kDa to about 50 kDa, about 20 kDa to about 60 kDa, about 20 kDa to about 70 kDa, about 20 kDa to about 80 kDa, about 20 kDa to about 90 kDa, about 20 kDa to about 100 kDa, about 30 kDa to about 40 kDa, about 30 kDa to about 50 kDa, about 30 kDa to about 60 kDa, about 30 kDa to about 70 kDa, about 30 kDa to about 80 kDa, about 30 kDa to about 90 kDa, about 30 kDa to about 100 kDa, about 40 kDa to about 50 kDa, about 40 kDa to about 60 kDa, about 40 kDa to about 70 kDa, about 40 kDa to about 80 kDa, about 40 kDa to about 90 kDa, about 40 kDa to about 100 kDa, about 50 kDa to about 60 kDa, about 50 kDa to about 70 kDa, about 50 kDa to about 80 kDa, about 50 kDa to about 90 kDa, about 50 kDa to about 100 kDa, about 60 kDa to about 70 kDa, about 60 kDa to about 80 kDa, about 60 kDa to about 90 kDa, about 60 kDa to about 100 kDa, about 70 kDa to about 80 kDa, about 70 kDa to about 90 kDa, about 70 kDa to about 100 kDa, about 80 kDa to about 90 kDa, about 80 kDa to about 100 kDa, or about 90 kDa to about 100 kDa.

[090] In aspects of this embodiment, the molecular weight of the PSA-conjugated peptide or polypeptide may be, *e.g.*, about 20 kDa, about 25 kDa, about 30 kDa, about 35 kDa, about 40 kDa, about 45 kDa, about 50 kDa, about 55 kDa, about 60 kDa, about 65 kDa, about 70 kDa, about 75 kDa, about 80 kDa, about 85 kDa, about 90 kDa, about 95 kDa, or about 100 kDa. In other aspects of this embodiment, the molecular weight of the PSA-conjugated peptide or polypeptide may be, *e.g.*, at least 20 kDa, at least 25 kDa, at least 30 kDa, at least 35 kDa, at least 40 kDa, at least 45 kDa, at least 50 kDa, at least 55 kDa, at least 60 kDa, at least 65 kDa, at least 70 kDa, at least 75 kDa, at least 80 kDa, at least 85 kDa, at least 90 kDa, at least 95 kDa, or at least 100 kDa. In yet other aspects of this embodiment, the molecular weight of the PSA-conjugated peptide or polypeptide may be, *e.g.*, at most 20 kDa, at most 25 kDa, at most 30 kDa, at most 35 kDa, at most 40 kDa, at most 45 kDa, at most 50 kDa, at most 55 kDa, at most 60 kDa, at most 65 kDa, at most 70 kDa, at most 75 kDa, at most 80 kDa, at most 85 kDa, at most 90 kDa, at most 95 kDa, or at most 100 kDa. In still other aspects of this embodiment, the molecular weight

of the PSA-conjugated peptide or polypeptide may be, e.g., about 20 kDa to about 30 kDa, about 20 kDa to about 40 kDa, about 20 kDa to about 50 kDa, about 20 kDa to about 60 kDa, about 20 kDa to about 70 kDa, about 20 kDa to about 80 kDa, about 20 kDa to about 90 kDa, about 20 kDa to about 100 kDa, about 30 kDa to about 40 kDa, about 30 kDa to about 50 kDa, about 30 kDa to about 60 kDa, about 30 kDa to about 70 kDa, about 30 kDa to about 80 kDa, about 30 kDa to about 90 kDa, about 30 kDa to about 100 kDa, about 40 kDa to about 50 kDa, about 40 kDa to about 60 kDa, about 40 kDa to about 70 kDa, about 40 kDa to about 80 kDa, about 40 kDa to about 90 kDa, about 40 kDa to about 100 kDa, about 50 kDa to about 60 kDa, about 50 kDa to about 70 kDa, about 50 kDa to about 80 kDa, about 50 kDa to about 90 kDa, about 50 kDa to about 100 kDa, about 60 kDa to about 70 kDa, about 60 kDa to about 80 kDa, about 60 kDa to about 90 kDa, about 60 kDa to about 100 kDa, about 70 kDa to about 80 kDa, about 70 kDa to about 90 kDa, about 70 kDa to about 100 kDa, about 80 kDa to about 90 kDa, about 80 kDa to about 100 kDa, or about 90 kDa to about 100 kDa.

[091] Aspects of the present specification disclose, in part, modification of an APY cyclic peptide disclosed herein by using a blood-brain barrier (BBB) shuttle. In one embodiment, an APY cyclic peptide disclosed herein may be conjugated to an antibody useful to mediated transferrin receptor (TfR) uptake and transcytosis across the blood-brain barrier. In one aspect of this embodiment, construction of an anti-TfR-conjugated APY cyclic peptide involves the fusing one (sFab) anti-TfR Fab fragment to the C terminus of a peptide or polypeptide. Reagents and methods for making such an anti-TfR-APY cyclic peptide conjugate are described in Niewoehner, et al., *Increased Brain Penetration and Potency of a Therapeutic Antibody Using a Monovalent Molecular Shuttle*, Neuron 81: 49-60 (2014) and Prades, et al., *Applying the Retro-Enantio Approach to Obtain a Peptide Capable of Overcoming the Blood-Brain Barrier*, Angew Chem. Int. Ed. Engl. 54(13): 3967-3972 (2015), each of which is hereby incorporated by reference in its entirety.

[092] In another embodiment, an APY cyclic peptide disclosed herein may be conjugated to phenylproline tetrapeptides (FP)₄. The phenylproline tetrapeptide facilitates passive diffusion that enables an APY cyclic peptide to transport across the blood-brain barrier. In one aspect, of this embodiment, construction of an (FP)₄-conjugated APY cyclic peptide involves the chemical synthesis of an APY cyclic peptide disclosed herein with the addition of the phenylproline tetrapeptide at the C-terminus. Reagents and methods for making such a (FP)₄-conjugated APY cyclic peptide conjugate are described in Arranz-Gibert, et al., *Lipid Bilayer Crossing – The Gate of Symmetry. Water-Soluble Phenylproline-Based Blood-Brain Barrier Shuttles*, J. Am. Chem. Soc. 137(23): 7357-7364 (2015), which is hereby incorporated by reference in its entirety.

[093] Aspects of the present specification disclose, in part, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, that exhibits physiological stability. Physiological stability includes properties such as, e.g., biological half-life and plasma half-life. A biological half-life is the time required for one half of the total amount of a particular substance in a biological system to be degraded or eliminated by biological processes such as, e.g., through the kidney, liver and excretion functions when the rate of removal is nearly exponential. Typically, a biological half-life is measured by assaying a pharmacologic and/or physiologic property of the substance. A plasma half-life is the time required for

one half of the total concentration of a particular substance in a biological system to reach its steady-state value in blood plasma. The relationship between the biological and plasma half-lives of a substance can be complex, due to factors including accumulation in tissues, active metabolites, and receptor interactions.

[094] In an embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may exhibit a therapeutically effective biological half-life. In aspects of this embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may exhibit a biological half-life of, *e.g.*, about 12 hours, about 18 hours, about 24 hours, about 30 hours, about 36 hours, about 42 hours, about 48 hours, about 54 hours, about 60 hours, about 66 hours, about 72 hours, about 78 hours, about 84 hours, about 90 hours or about 96 hours. In other aspects of this embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may exhibit a biological half-life of, *e.g.*, at least 12 hours, at least 18 hours, at least 24 hours, at least 30 hours, at least 36 hours, at least 42 hours, at least 48 hours, at least 54 hours, at least 60 hours, at least 66 hours, at least 72 hours, at least 78 hours, at least 84 hours, at least 90 hours or at least 96 hours. In yet other aspects of this embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may exhibit a biological half-life of, *e.g.*, at most 12 hours, at most 18 hours, at most 24 hours, at most 30 hours, at most 36 hours, at most 42 hours, at most 48 hours, at most 54 hours, at most 60 hours, at most 66 hours, at most 72 hours, at most 78 hours, at most 84 hours, at most 90 hours or at most 96 hours. In still other aspects of this embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may exhibit a biological half-life of, *e.g.*, about 12 hours to about 24 hours, about 12 hours to about 36 hours, about 12 hours to about 48 hours, about 12 hours to about 60 hours, about 12 hours to about 72 hours, about 12 hours to about 84 hours, about 12 hours to about 96 hours, about 24 hours to about 36 hours, about 24 hours to about 48 hours, about 24 hours to about 60 hours, about 24 hours to about 72 hours, about 24 hours to about 84 hours, about 24 hours to about 96 hours, about 36 hours to about 48 hours, about 36 hours to about 60 hours, about 36 hours to about 72 hours, about 36 hours to about 84 hours, about 36 hours to about 96 hours, about 48 hours to about 60 hours, about 48 hours to about 72 hours, about 48 hours to about 84 hours, about 48 hours to about 96 hours, about 60 hours to about 72 hours, about 60 hours to about 84 hours, about 60 hours to about 96 hours, about 72 hours to about 84 hours, about 72 hours to about 96 hours or about 84 hours to about 96 hours.

[095] In another embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may exhibit a therapeutically effective plasma half-life. In aspects of this embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may exhibit a plasma half-life of, *e.g.*, about 12 hours, about 18 hours, about 24 hours, about 30 hours, about 36 hours, about 42 hours, about 48 hours, about 54 hours, about 60 hours, about 66 hours, about 72 hours, about 78 hours, about 84 hours, about 90 hours or about 96 hours. In other aspects of this embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may exhibit a plasma half-life of, *e.g.*, at least 12 hours, at least 18 hours, at least 24 hours, at least 30 hours, at least 36 hours, at least 42 hours, at least 48 hours, at least 54 hours, at least 60 hours, at least 66 hours, at least 72 hours, at least 78 hours, at least 84 hours, at least 90 hours or at least 96 hours. In yet other aspects of this embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may exhibit a plasma half-life of, *e.g.*, at

most 12 hours, at most 18 hours, at most 24 hours, at most 30 hours, at most 36 hours, at most 42 hours, at most 48 hours, at most 54 hours, at most 60 hours, at most 66 hours, at most 72 hours, at most 78 hours, at most 84 hours, at most 90 hours or at most 96 hours. In still other aspects of this embodiment, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, may exhibit a plasma half-life of, e.g., about 12 hours to about 24 hours, about 12 hours to about 36 hours, about 12 hours to about 48 hours, about 12 hours to about 60 hours, about 12 hours to about 72 hours, about 12 hours to about 84 hours, about 12 hours to about 96 hours, about 24 hours to about 36 hours, about 24 hours to about 48 hours, about 24 hours to about 60 hours, about 24 hours to about 72 hours, about 24 hours to about 84 hours, about 24 hours to about 96 hours, about 36 hours to about 48 hours, about 36 hours to about 60 hours, about 36 hours to about 72 hours, about 36 hours to about 84 hours, about 36 hours to about 96 hours, about 48 hours to about 60 hours, about 48 hours to about 72 hours, about 48 hours to about 84 hours, about 48 hours to about 96 hours, about 60 hours to about 72 hours, about 60 hours to about 84 hours, about 60 hours to about 96 hours, about 72 hours to about 84 hours, about 72 hours to about 96 hours or about 84 hours to about 96 hours.

[096] Aspects of the present specification disclose, in part, a pharmaceutical composition. As used herein, the term “pharmaceutical composition” is synonymous with “therapeutic composition” or “pharmaceutically acceptable therapeutic composition” and refers to a composition comprising a therapeutically effective concentration of an active ingredient, such as, e.g., a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein. A pharmaceutical composition disclosed herein may comprise a single EphA4 antagonist, like an APY cyclic peptide disclosed herein. Alternatively, a pharmaceutical composition disclosed herein may comprise a plurality of EphA4 antagonists, like the APY cyclic peptides disclosed herein. In aspects of this embodiment, pharmaceutical composition disclosed herein may comprise about one, about two, about three, about four, or about five EphA4 antagonists, like the APY cyclic peptides disclosed herein. In other aspects of this embodiment, pharmaceutical composition disclosed herein may comprise one or more, two or more, three or more, four or more or five or more EphA4 antagonists, like the APY cyclic peptides disclosed herein. In yet other aspects of this embodiment, pharmaceutical composition disclosed herein may comprise at most one, at most two, at most three, at most four, or at most five EphA4 antagonists, like the APY cyclic peptides disclosed herein. In still other aspects of this embodiment, pharmaceutical composition disclosed herein may comprise about one to about two, about one to about three, about one to about four, about one to about five, about two to about three, about two to about four, about two to about five, about three to about four, about three to about five or about four to about five, EphA4 antagonists, like the APY cyclic peptides disclosed herein.

[097] The amount of EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a pharmaceutical composition is an amount sufficient to elicit an appropriate therapeutic response in the individual. Typically, this amount is also one that does not cause significant adverse side effects. Such amount will vary depending on which specific EphA4 antagonist(s), like an APY cyclic peptide disclosed herein, are employed. An optimal amount for a particular pharmaceutical composition can be ascertained by standard studies involving observation of antibody titers and other responses in individuals.

[098] Generally, an effective and safe amount of EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a pharmaceutical composition varies from about 1 ng to 1,000 µg. In aspects of this embodiment, an amount of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a therapeutic composition may be, *e.g.*, about 1 ng, about 2 ng, about 3 ng, about 4 ng, about 5 ng, about 6 ng, about 7 ng, about 8 ng, about 9 ng, about 10 ng, about 15 ng, about 20 ng, about 25 ng, about 30 ng, about 35 ng, about 40 ng, about 45 ng, about 50 ng, about 55 ng, about 60 ng, about 65 ng, about 70 ng, about 75 ng, about 80 ng, about 85 ng, about 90 ng, about 95 ng, about 100 ng, about 110 ng, about 120 ng, about 130 ng, about 140 ng, about 150 ng, about 160 ng, about 170 ng, about 180 ng, about 190 ng, about 200 ng, about 210 ng, about 220 ng, about 230 ng, about 240 ng, about 250 ng, 260 ng, about 270 ng, about 280 ng, about 290 ng, about 300 ng, about 310 ng, about 320 ng, about 330 ng, about 340 ng, about 350 ng, 360 ng, about 370 ng, about 380 ng, about 390 ng, about 400 ng, about 410 ng, about 420 ng, about 430 ng, about 440 ng, about 450 ng, 460 ng, about 470 ng, about 480 ng, about 490 ng, about 500 ng, about 510 ng, about 520 ng, about 530 ng, about 540 ng, about 550 ng, 560 ng, about 570 ng, about 580 ng, about 590 ng, about 600 ng, about 610 ng, about 620 ng, about 630 ng, about 640 ng, about 650 ng, 660 ng, about 670 ng, about 680 ng, about 690 ng, about 700 ng, about 710 ng, about 720 ng, about 730 ng, about 740 ng, about 750 ng, 760 ng, about 770 ng, about 780 ng, about 790 ng, about 800 ng, about 810 ng, about 820 ng, about 830 ng, about 840 ng, about 850 ng, 860 ng, about 870 ng, about 880 ng, about 890 ng, about 900 ng, about 910 ng, about 920 ng, about 930 ng, about 940 ng, about 950 ng, 960 ng, about 970 ng, about 980 ng, about 990 ng, or about 1,000 ng.

[099] In other aspects of this embodiment, an amount of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a pharmaceutical composition may be, *e.g.*, at least 1 ng, at least 2 ng, at least 3 ng, at least 4 ng, at least 5 ng, at least 6 ng, at least 7 ng, at least 8 ng, at least 9 ng, at least 10 ng, at least 15 ng, at least 20 ng, at least 25 ng, at least 30 ng, at least 35 ng, at least 40 ng, at least 45 ng, at least 50 ng, at least 55 ng, at least 60 ng, at least 65 ng, at least 70 ng, at least 75 ng, at least 80 ng, at least 85 ng, at least 90 ng, at least 95 ng, at least 100 ng, at least 110 ng, at least 120 ng, at least 130 ng, at least 140 ng, at least 150 ng, at least 160 ng, at least 170 ng, at least 180 ng, at least 190 ng, at least 200 ng, at least 210 ng, at least 220 ng, at least 230 ng, at least 240 ng, at least 250 ng, 260 ng, at least 270 ng, at least 280 ng, at least 290 ng, at least 300 ng, at least 310 ng, at least 320 ng, at least 330 ng, at least 340 ng, at least 350 ng, 360 ng, at least 370 ng, at least 380 ng, at least 390 ng, at least 400 ng, at least 410 ng, at least 420 ng, at least 430 ng, at least 440 ng, at least 450 ng, 460 ng, at least 470 ng, at least 480 ng, at least 490 ng, at least 500 ng, at least 510 ng, at least 520 ng, at least 530 ng, at least 540 ng, at least 550 ng, 560 ng, at least 570 ng, at least 580 ng, at least 590 ng, at least 600 ng, at least 610 ng, at least 620 ng, at least 630 ng, at least 640 ng, at least 650 ng, 660 ng, at least 670 ng, at least 680 ng, at least 690 ng, at least 700 ng, at least 710 ng, at least 720 ng, at least 730 ng, at least 740 ng, at least 750 ng, 760 ng, at least 770 ng, at least 780 ng, at least 790 ng, at least 800 ng, at least 810 ng, at least 820 ng, at least 830 ng, at least 840 ng, at least 850 ng, 860 ng, at least 870 ng, at least 880 ng, at least 890 ng, at least 900 ng, at least 910 ng, at least 920 ng, at least 930 ng, at least 940 ng, at least 950 ng, 960 ng, at least 970 ng, at least 980 ng, at least 990 ng, or at least 1,000 ng.

[0100] In yet other aspects of this embodiment, an amount of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a pharmaceutical composition may be, *e.g.*, at most 1 ng, at most 2 ng, at most 3 ng, at most 4 ng, at most 5 ng, at most 6 ng, at most 7 ng, at most 8 ng, at most 9 ng, at most 10 ng, at most 15 ng, at most 20 ng, at most 25 ng, at most 30 ng, at most 35 ng, at most 40 ng, at most 45 ng, at most 50 ng, at most 55 ng, at most 60 ng, at most 65 ng, at most 70 ng, at most 75 ng, at most 80 ng, at most 85 ng, at most 90 ng, at most 95 ng, at most 100 ng, at most 110 ng, at most 120 ng, at most 130 ng, at most 140 ng, at most 150 ng, at most 160 ng, at most 170 ng, at most 180 ng, at most 190 ng, at most 200 ng, at most 210 ng, at most 220 ng, at most 230 ng, at most 240 ng, at most 250 ng, 260 ng, at most 270 ng, at most 280 ng, at most 290 ng, at most 300 ng, at most 310 ng, at most 320 ng, at most 330 ng, at most 340 ng, at most 350 ng, 360 ng, at most 370 ng, at most 380 ng, at most 390 ng, at most 400 ng, at most 410 ng, at most 420 ng, at most 430 ng, at most 440 ng, at most 450 ng, 460 ng, at most 470 ng, at most 480 ng, at most 490 ng, at most 500 ng, at most 510 ng, at most 520 ng, at most 530 ng, at most 540 ng, at most 550 ng, 560 ng, at most 570 ng, at most 580 ng, at most 590 ng, at most 600 ng, at most 610 ng, at most 620 ng, at most 630 ng, at most 640 ng, at most 650 ng, 660 ng, at most 670 ng, at most 680 ng, at most 690 ng, at most 700 ng, at most 710 ng, at most 720 ng, at most 730 ng, at most 740 ng, at most 750 ng, 760 ng, at most 770 ng, at most 780 ng, at most 790 ng, at most 800 ng, at most 810 ng, at most 820 ng, at most 830 ng, at most 840 ng, at most 850 ng, 860 ng, at most 870 ng, at most 880 ng, at most 890 ng, at most 900 ng, at most 910 ng, at most 920 ng, at most 930 ng, at most 940 ng, at most 950 ng, 960 ng, at most 970 ng, at most 980 ng, at most 990 ng, or at most 1,000 ng.

[0101] In still other aspects of this embodiment, an amount of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a pharmaceutical composition may be in the range of, *e.g.*, about 1 ng to about 10 ng, about 1 ng to about 20 ng, about 1 ng to about 30 ng, about 1 ng to about 40 ng, about 1 ng to about 50 ng, about 1 ng to about 60 ng, about 1 ng to about 70 ng, about 1 ng to about 80 ng, about 1 ng to about 90 ng, about 1 ng to about 100 ng, about 1 ng to about 110 ng, about 1 ng to about 120 ng, about 1 ng to about 130 ng, about 1 ng to about 140 ng, about 1 ng to about 150 ng, about 5 ng to about 10 ng, about 5 ng to about 20 ng, about 5 ng to about 30 ng, about 5 ng to about 40 ng, about 5 ng to about 50 ng, about 5 ng to about 60 ng, about 5 ng to about 70 ng, about 5 ng to about 80 ng, about 5 ng to about 90 ng, about 5 ng to about 100 ng, about 5 ng to about 110 ng, about 5 ng to about 120 ng, about 5 ng to about 130 ng, about 5 ng to about 140 ng, about 5 ng to about 150 ng, about 10 ng to about 20 ng, about 10 ng to about 30 ng, about 10 ng to about 40 ng, about 10 ng to about 50 ng, about 10 ng to about 60 ng, about 10 ng to about 70 ng, about 10 ng to about 80 ng, about 10 ng to about 90 ng, about 10 ng to about 100 ng, about 10 ng to about 110 ng, about 10 ng to about 120 ng, about 10 ng to about 130 ng, about 10 ng to about 140 ng, about 10 ng to about 150 ng, about 10 ng to about 175 ng, about 10 ng to about 200 ng, about 10 ng to about 225 ng, about 10 ng to about 250 ng, about 25 ng to about 50 ng, about 25 ng to about 75 ng, about 25 ng to about 100 ng, about 25 ng to about 125 ng, about 25 ng to about 150 ng, about 25 ng to about 175 ng, about 25 ng to about 200 ng, about 25 ng to about 225 ng, about 25 ng to about 250 ng, about 50 ng to about 75 ng, about 50 ng to about 100 ng, about 50 ng to about 125 ng, about 50 ng to about 150 ng, about 50 ng to about 175 ng,

about 50 ng to about 200 ng, about 50 ng to about 225 ng, about 50 ng to about 250 ng, about 75 ng to about 100 ng, about 75 ng to about 125 ng, about 75 ng to about 150 ng, about 75 ng to about 175 ng, about 75 ng to about 200 ng, about 75 ng to about 225 ng, or about 75 ng to about 250 ng.

[0102] In still other aspects of this embodiment, an amount of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a pharmaceutical composition may be in the range of, *e.g.*, about 100 ng to about 125 ng, about 100 ng to about 150 ng, about 100 ng to about 175 ng, about 100 ng to about 200 ng, about 100 ng to about 225 ng, about 100 ng to about 250 ng, about 100 ng to about 275 ng, about 100 ng to about 300 ng, about 100 ng to about 325 ng, about 100 ng to about 350 ng, about 100 ng to about 375 ng, about 100 ng to about 400 ng, about 100 ng to about 425 ng, about 100 ng to about 450 ng, about 100 ng to about 475 ng, about 100 ng to about 500 ng, about 100 ng to about 525 ng, about 100 ng to about 550 ng, about 100 ng to about 575 ng, about 100 ng to about 600 ng, about 125 ng to about 150 ng, about 125 ng to about 175 ng, about 125 ng to about 200 ng, about 125 ng to about 225 ng, about 125 ng to about 250 ng, about 125 ng to about 275 ng, about 125 ng to about 300 ng, about 125 ng to about 325 ng, about 125 ng to about 350 ng, about 125 ng to about 375 ng, about 125 ng to about 400 ng, about 125 ng to about 425 ng, about 125 ng to about 450 ng, about 125 ng to about 475 ng, about 125 ng to about 500 ng, about 125 ng to about 525 ng, about 125 ng to about 550 ng, about 125 ng to about 575 ng, about 125 ng to about 600 ng, about 150 ng to about 175 ng, about 150 ng to about 200 ng, about 150 ng to about 225 ng, about 150 ng to about 250 ng, about 150 ng to about 275 ng, about 150 ng to about 300 ng, about 150 ng to about 325 ng, about 150 ng to about 350 ng, about 150 ng to about 375 ng, about 150 ng to about 400 ng, about 150 ng to about 425 ng, about 150 ng to about 450 ng, about 150 ng to about 475 ng, about 150 ng to about 500 ng, about 150 ng to about 525 ng, about 150 ng to about 550 ng, about 150 ng to about 575 ng, about 150 ng to about 600 ng, about 200 ng to about 225 ng, about 200 ng to about 250 ng, about 200 ng to about 275 ng, about 200 ng to about 300 ng, about 200 ng to about 325 ng, about 200 ng to about 350 ng, about 200 ng to about 375 ng, about 200 ng to about 400 ng, about 200 ng to about 425 ng, about 200 ng to about 450 ng, about 200 ng to about 475 ng, about 200 ng to about 500 ng, about 200 ng to about 525 ng, about 200 ng to about 550 ng, about 200 ng to about 575 ng, about 200 ng to about 600 ng, about 200 ng to about 625 ng, about 200 ng to about 650 ng, about 200 ng to about 675 ng, about 200 ng to about 700 ng, about 200 ng to about 725 ng, about 200 ng to about 750 ng, about 200 ng to about 775 ng, about 200 ng to about 800 ng, about 200 ng to about 825 ng, about 200 ng to about 850 ng, about 200 ng to about 875 ng, about 200 ng to about 900 ng, about 200 ng to about 925 ng, about 200 ng to about 950 ng, about 200 ng to about 975 ng, or about 200 ng to about 1,000 ng.

[0103] In still other aspects of this embodiment, an amount of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a pharmaceutical composition may be in the range of, *e.g.*, about 250 ng to about 275 ng, about 250 ng to about 300 ng, about 250 ng to about 325 ng, about 250 ng to about 350 ng, about 250 ng to about 375 ng, about 250 ng to about 400 ng, about 250 ng to about 425 ng, about 250 ng to about 450 ng, about 250 ng to about 475 ng, about 250 ng to about 500 ng, about 250 ng to about 525 ng, about 250 ng to about 550 ng, about 250 ng to about 575 ng, about 250 ng to about 600 ng, about 250 ng to about 625 ng, about 250 ng to about 650 ng, about 250 ng to about 675

ng, about 250 ng to about 700 ng, about 250 ng to about 725 ng, about 250 ng to about 750 ng, about 250 ng to about 775 ng, about 250 ng to about 800 ng, about 250 ng to about 825 ng, about 250 ng to about 850 ng, about 250 ng to about 875 ng, about 250 ng to about 900 ng, about 250 ng to about 925 ng, about 250 ng to about 950 ng, about 250 ng to about 975 ng, about 250 ng to about 1,000 ng, about 300 ng to about 325 ng, about 300 ng to about 350 ng, about 300 ng to about 375 ng, about 300 ng to about 400 ng, about 300 ng to about 425 ng, about 300 ng to about 450 ng, about 300 ng to about 475 ng, about 300 ng to about 500 ng, about 300 ng to about 525 ng, about 300 ng to about 550 ng, about 300 ng to about 575 ng, about 300 ng to about 600 ng, about 300 ng to about 625 ng, about 300 ng to about 650 ng, about 300 ng to about 675 ng, about 300 ng to about 700 ng, about 300 ng to about 725 ng, about 300 ng to about 750 ng, about 300 ng to about 775 ng, about 300 ng to about 800 ng, about 300 ng to about 825 ng, about 300 ng to about 850 ng, about 300 ng to about 875 ng, about 300 ng to about 900 ng, about 300 ng to about 925 ng, about 300 ng to about 950 ng, about 300 ng to about 975 ng, about 300 ng to about 1,000 ng, about 400 ng to about 425 ng, about 400 ng to about 450 ng, about 400 ng to about 475 ng, about 400 ng to about 500 ng, about 400 ng to about 525 ng, about 400 ng to about 550 ng, about 400 ng to about 575 ng, about 400 ng to about 600 ng, about 400 ng to about 625 ng, about 400 ng to about 650 ng, about 400 ng to about 675 ng, about 400 ng to about 700 ng, about 400 ng to about 725 ng, about 400 ng to about 750 ng, about 400 ng to about 775 ng, about 400 ng to about 800 ng, about 400 ng to about 825 ng, about 400 ng to about 850 ng, about 400 ng to about 875 ng, about 400 ng to about 900 ng, about 400 ng to about 925 ng, about 400 ng to about 950 ng, about 400 ng to about 975 ng, or about 400 ng to about 1,000 ng.

[0104] In still other aspects of this embodiment, an amount of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a pharmaceutical composition may be in the range of, *e.g.*, about 500 ng to about 525 ng, about 500 ng to about 550 ng, about 500 ng to about 575 ng, about 500 ng to about 600 ng, about 500 ng to about 625 ng, about 500 ng to about 650 ng, about 500 ng to about 675 ng, about 500 ng to about 700 ng, about 500 ng to about 725 ng, about 500 ng to about 750 ng, about 500 ng to about 775 ng, about 500 ng to about 800 ng, about 500 ng to about 825 ng, about 500 ng to about 850 ng, about 500 ng to about 875 ng, about 500 ng to about 900 ng, about 500 ng to about 925 ng, about 500 ng to about 950 ng, about 500 ng to about 975 ng, about 500 ng to about 1,000 ng, about 600 ng to about 625 ng, about 600 ng to about 650 ng, about 600 ng to about 675 ng, about 600 ng to about 700 ng, about 600 ng to about 725 ng, about 600 ng to about 750 ng, about 600 ng to about 775 ng, about 600 ng to about 800 ng, about 600 ng to about 825 ng, about 600 ng to about 850 ng, about 600 ng to about 875 ng, about 600 ng to about 900 ng, about 600 ng to about 925 ng, about 600 ng to about 950 ng, about 600 ng to about 975 ng, about 600 ng to about 1,000 ng, about 700 ng to about 725 ng, about 700 ng to about 750 ng, about 700 ng to about 775 ng, about 700 ng to about 800 ng, about 700 ng to about 825 ng, about 700 ng to about 850 ng, about 700 ng to about 875 ng, about 700 ng to about 900 ng, about 700 ng to about 925 ng, about 700 ng to about 950 ng, about 700 ng to about 975 ng, about 700 ng to about 1,000 ng, about 800 ng to about 825 ng, about 800 ng to about 850 ng, about 800 ng to about 875 ng, about 800 ng to about 900 ng, about 800 ng to about 925 ng, about 800 ng to about 950 ng, about 800 ng to about 975 ng, or about 800 ng to about 1,000 ng.

[0105] In aspects of this embodiment, an amount of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a pharmaceutical composition may be, *e.g.*, about 1 µg, about 2 µg, about 3 µg, about 4 µg, about 5 µg, about 6 µg, about 7 µg, about 8 µg, about 9 µg, about 10 µg, about 15 µg, about 20 µg, about 25 µg, about 30 µg, about 35 µg, about 40 µg, about 45 µg, about 50 µg, about 55 µg, about 60 µg, about 65 µg, about 70 µg, about 75 µg, about 80 µg, about 85 µg, about 90 µg, about 95 µg, about 100 µg, about 110 µg, about 120 µg, about 130 µg, about 140 µg, about 150 µg, about 160 µg, about 170 µg, about 180 µg, about 190 µg, about 200 µg, about 210 µg, about 220 µg, about 230 µg, about 240 µg, about 250 µg, 260 µg, about 270 µg, about 280 µg, about 290 µg, about 300 µg, about 310 µg, about 320 µg, about 330 µg, about 340 µg, about 350 µg, 360 µg, about 370 µg, about 380 µg, about 390 µg, about 400 µg, about 410 µg, about 420 µg, about 430 µg, about 440 µg, about 450 µg, 460 µg, about 470 µg, about 480 µg, about 490 µg, about 500 µg, about 510 µg, about 520 µg, about 530 µg, about 540 µg, about 550 µg, 560 µg, about 570 µg, about 580 µg, about 590 µg, about 600 µg, about 610 µg, about 620 µg, about 630 µg, about 640 µg, about 650 µg, 660 µg, about 670 µg, about 680 µg, about 690 µg, about 700 µg, about 710 µg, about 720 µg, about 730 µg, about 740 µg, about 750 µg, 760 µg, about 770 µg, about 780 µg, about 790 µg, about 800 µg, about 810 µg, about 820 µg, about 830 µg, about 840 µg, about 850 µg, 860 µg, about 870 µg, about 880 µg, about 890 µg, about 900 µg, about 910 µg, about 920 µg, about 930 µg, about 940 µg, about 950 µg, 960 µg, about 970 µg, about 980 µg, about 990 µg, or about 1,000 µg.

[0106] In other aspects of this embodiment, an amount of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a pharmaceutical composition may be, *e.g.*, at least 1 µg, at least 2 µg, at least 3 µg, at least 4 µg, at least 5 µg, at least 6 µg, at least 7 µg, at least 8 µg, at least 9 µg, at least 10 µg, at least 15 µg, at least 20 µg, at least 25 µg, at least 30 µg, at least 35 µg, at least 40 µg, at least 45 µg, at least 50 µg, at least 55 µg, at least 60 µg, at least 65 µg, at least 70 µg, at least 75 µg, at least 80 µg, at least 85 µg, at least 90 µg, at least 95 µg, at least 100 µg, at least 110 µg, at least 120 µg, at least 130 µg, at least 140 µg, at least 150 µg, at least 160 µg, at least 170 µg, at least 180 µg, at least 190 µg, at least 200 µg, at least 210 µg, at least 220 µg, at least 230 µg, at least 240 µg, at least 250 µg, 260 µg, at least 270 µg, at least 280 µg, at least 290 µg, at least 300 µg, at least 310 µg, at least 320 µg, at least 330 µg, at least 340 µg, at least 350 µg, 360 µg, at least 370 µg, at least 380 µg, at least 390 µg, at least 400 µg, at least 410 µg, at least 420 µg, at least 430 µg, at least 440 µg, at least 450 µg, 460 µg, at least 470 µg, at least 480 µg, at least 490 µg, at least 500 µg, at least 510 µg, at least 520 µg, at least 530 µg, at least 540 µg, at least 550 µg, 560 µg, at least 570 µg, at least 580 µg, at least 590 µg, at least 600 µg, at least 610 µg, at least 620 µg, at least 630 µg, at least 640 µg, at least 650 µg, 660 µg, at least 670 µg, at least 680 µg, at least 690 µg, at least 700 µg, at least 710 µg, at least 720 µg, at least 730 µg, at least 740 µg, at least 750 µg, 760 µg, at least 770 µg, at least 780 µg, at least 790 µg, at least 800 µg, at least 810 µg, at least 820 µg, at least 830 µg, at least 840 µg, at least 850 µg, 860 µg, at least 870 µg, at least 880 µg, at least 890 µg, at least 900 µg, at least 910 µg, at least 920 µg, at least 930 µg, at least 940 µg, at least 950 µg, 960 µg, at least 970 µg, at least 980 µg, at least 990 µg, or at least 1,000 µg.

[0107] In yet other aspects of this embodiment, an amount of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a pharmaceutical composition may be, *e.g.*, at most 1 µg, at most 2 µg, at most 3 µg, at most 4 µg, at most 5 µg, at most 6 µg, at most 7 µg, at most 8 µg, at most 9 µg, at most 10 µg, at most 15 µg, at most 20 µg, at most 25 µg, at most 30 µg, at most 35 µg, at most 40 µg, at most 45 µg, at most 50 µg, at most 55 µg, at most 60 µg, at most 65 µg, at most 70 µg, at most 75 µg, at most 80 µg, at most 85 µg, at most 90 µg, at most 95 µg, at most 100 µg, at most 110 µg, at most 120 µg, at most 130 µg, at most 140 µg, at most 150 µg, at most 160 µg, at most 170 µg, at most 180 µg, at most 190 µg, at most 200 µg, at most 210 µg, at most 220 µg, at most 230 µg, at most 240 µg, at most 250 µg, 260 µg, at most 270 µg, at most 280 µg, at most 290 µg, at most 300 µg, at most 310 µg, at most 320 µg, at most 330 µg, at most 340 µg, at most 350 µg, 360 µg, at most 370 µg, at most 380 µg, at most 390 µg, at most 400 µg, at most 410 µg, at most 420 µg, at most 430 µg, at most 440 µg, at most 450 µg, 460 µg, at most 470 µg, at most 480 µg, at most 490 µg, at most 500 µg, at most 510 µg, at most 520 µg, at most 530 µg, at most 540 µg, at most 550 µg, 560 µg, at most 570 µg, at most 580 µg, at most 590 µg, at most 600 µg, at most 610 µg, at most 620 µg, at most 630 µg, at most 640 µg, at most 650 µg, 660 µg, at most 670 µg, at most 680 µg, at most 690 µg, at most 700 µg, at most 710 µg, at most 720 µg, at most 730 µg, at most 740 µg, at most 750 µg, 760 µg, at most 770 µg, at most 780 µg, at most 790 µg, at most 800 µg, at most 810 µg, at most 820 µg, at most 830 µg, at most 840 µg, at most 850 µg, 860 µg, at most 870 µg, at most 880 µg, at most 890 µg, at most 900 µg, at most 910 µg, at most 920 µg, at most 930 µg, at most 940 µg, at most 950 µg, 960 µg, at most 970 µg, at most 980 µg, at most 990 µg, or at most 1,000 µg.

[0108] In still other aspects of this embodiment, an amount of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a pharmaceutical composition may be in the range of, *e.g.*, about 1 µg to about 10 µg, about 1 µg to about 20 µg, about 1 µg to about 30 µg, about 1 µg to about 40 µg, about 1 µg to about 50 µg, about 1 µg to about 60 µg, about 1 µg to about 70 µg, about 1 µg to about 80 µg, about 1 µg to about 90 µg, about 1 µg to about 100 µg, about 1 µg to about 110 µg, about 1 µg to about 120 µg, about 1 µg to about 130 µg, about 1 µg to about 140 µg, about 1 µg to about 150 µg, about 5 µg to about 10 µg, about 5 µg to about 20 µg, about 5 µg to about 30 µg, about 5 µg to about 40 µg, about 5 µg to about 50 µg, about 5 µg to about 60 µg, about 5 µg to about 70 µg, about 5 µg to about 80 µg, about 5 µg to about 90 µg, about 5 µg to about 100 µg, about 5 µg to about 110 µg, about 5 µg to about 120 µg, about 5 µg to about 130 µg, about 5 µg to about 140 µg, about 5 µg to about 150 µg, about 10 µg to about 20 µg, about 10 µg to about 30 µg, about 10 µg to about 40 µg, about 10 µg to about 50 µg, about 10 µg to about 60 µg, about 10 µg to about 70 µg, about 10 µg to about 80 µg, about 10 µg to about 90 µg, about 10 µg to about 100 µg, about 10 µg to about 110 µg, about 10 µg to about 120 µg, about 10 µg to about 130 µg, about 10 µg to about 140 µg, about 10 µg to about 150 µg, about 10 µg to about 175 µg, about 10 µg to about 200 µg, about 10 µg to about 225 µg, about 10 µg to about 250 µg, about 25 µg to about 50 µg, about 25 µg to about 75 µg, about 25 µg to about 100 µg, about 25 µg to about 125 µg, about 25 µg to about 150 µg, about 25 µg to about 175 µg, about 25 µg to about 200 µg, about 25 µg to about 225 µg, about 25 µg to about 250 µg, about 50 µg to about 75 µg, about 50 µg to about 100 µg, about 50 µg to about 125 µg, about 50 µg to about 150 µg, about 50 µg to about 175 µg, about 50 µg to about 200 µg, about 50 µg to about 225 µg, about 50 µg to about 250 µg, about 75 µg to

about 100 µg, about 75 µg to about 125 µg, about 75 µg to about 150 µg, about 75 µg to about 175 µg, about 75 µg to about 200 µg, about 75 µg to about 225 µg, or about 75 µg to about 250 µg.

[0109] In still other aspects of this embodiment, an amount of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a pharmaceutical composition may be in the range of, *e.g.*, about 100 µg to about 125 µg, about 100 µg to about 150 µg, about 100 µg to about 175 µg, about 100 µg to about 200 µg, about 100 µg to about 225 µg, about 100 µg to about 250 µg, about 100 µg to about 275 µg, about 100 µg to about 300 µg, about 100 µg to about 325 µg, about 100 µg to about 350 µg, about 100 µg to about 375 µg, about 100 µg to about 400 µg, about 100 µg to about 425 µg, about 100 µg to about 450 µg, about 100 µg to about 475 µg, about 100 µg to about 500 µg, about 100 µg to about 525 µg, about 100 µg to about 550 µg, about 100 µg to about 575 µg, about 100 µg to about 600 µg, about 125 µg to about 150 µg, about 125 µg to about 175 µg, about 125 µg to about 200 µg, about 125 µg to about 225 µg, about 125 µg to about 250 µg, about 125 µg to about 275 µg, about 125 µg to about 300 µg, about 125 µg to about 325 µg, about 125 µg to about 350 µg, about 125 µg to about 375 µg, about 125 µg to about 400 µg, about 125 µg to about 425 µg, about 125 µg to about 450 µg, about 125 µg to about 475 µg, about 125 µg to about 500 µg, about 125 µg to about 525 µg, about 125 µg to about 550 µg, about 125 µg to about 575 µg, about 125 µg to about 600 µg, about 150 µg to about 175 µg, about 150 µg to about 200 µg, about 150 µg to about 225 µg, about 150 µg to about 250 µg, about 150 µg to about 275 µg, about 150 µg to about 300 µg, about 150 µg to about 325 µg, about 150 µg to about 350 µg, about 150 µg to about 375 µg, about 150 µg to about 400 µg, about 150 µg to about 425 µg, about 150 µg to about 450 µg, about 150 µg to about 475 µg, about 150 µg to about 500 µg, about 150 µg to about 525 µg, about 150 µg to about 550 µg, about 150 µg to about 575 µg, about 150 µg to about 600 µg, about 200 µg to about 225 µg, about 200 µg to about 250 µg, about 200 µg to about 275 µg, about 200 µg to about 300 µg, about 200 µg to about 325 µg, about 200 µg to about 350 µg, about 200 µg to about 375 µg, about 200 µg to about 400 µg, about 200 µg to about 425 µg, about 200 µg to about 450 µg, about 200 µg to about 475 µg, about 200 µg to about 500 µg, about 200 µg to about 525 µg, about 200 µg to about 550 µg, about 200 µg to about 575 µg, about 200 µg to about 600 µg, about 200 µg to about 625 µg, about 200 µg to about 650 µg, about 200 µg to about 675 µg, about 200 µg to about 700 µg, about 200 µg to about 725 µg, about 200 µg to about 750 µg, about 200 µg to about 775 µg, about 200 µg to about 800 µg, about 200 µg to about 825 µg, about 200 µg to about 850 µg, about 200 µg to about 875 µg, about 200 µg to about 900 µg, about 200 µg to about 925 µg, about 200 µg to about 950 µg, about 200 µg to about 975 µg, or about 200 µg to about 1,000 µg.

[0110] In still other aspects of this embodiment, an amount of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a pharmaceutical composition may be in the range of, *e.g.*, about 250 µg to about 275 µg, about 250 µg to about 300 µg, about 250 µg to about 325 µg, about 250 µg to about 350 µg, about 250 µg to about 375 µg, about 250 µg to about 400 µg, about 250 µg to about 425 µg, about 250 µg to about 450 µg, about 250 µg to about 475 µg, about 250 µg to about 500 µg, about 250 µg to about 525 µg, about 250 µg to about 550 µg, about 250 µg to about 575 µg, about 250 µg to about 600 µg, about 250 µg to about 625 µg, about 250 µg to about 650 µg, about 250 µg to about 675 µg, about 250 µg to about 700 µg, about 250 µg to about 725 µg, about 250 µg to about 750 µg,

about 250 µg to about 775 µg, about 250 µg to about 800 µg, about 250 µg to about 825 µg, about 250 µg to about 850 µg, about 250 µg to about 875 µg, about 250 µg to about 900 µg, about 250 µg to about 925 µg, about 250 µg to about 950 µg, about 250 µg to about 975 µg, about 250 µg to about 1,000 µg, about 300 µg to about 325 µg, about 300 µg to about 350 µg, about 300 µg to about 375 µg, about 300 µg to about 400 µg, about 300 µg to about 425 µg, about 300 µg to about 450 µg, about 300 µg to about 475 µg, about 300 µg to about 500 µg, about 300 µg to about 525 µg, about 300 µg to about 550 µg, about 300 µg to about 575 µg, about 300 µg to about 600 µg, about 300 µg to about 625 µg, about 300 µg to about 650 µg, about 300 µg to about 675 µg, about 300 µg to about 700 µg, about 300 µg to about 725 µg, about 300 µg to about 750 µg, about 300 µg to about 775 µg, about 300 µg to about 800 µg, about 300 µg to about 825 µg, about 300 µg to about 850 µg, about 300 µg to about 875 µg, about 300 µg to about 900 µg, about 300 µg to about 925 µg, about 300 µg to about 950 µg, about 300 µg to about 975 µg, about 300 µg to about 1,000 µg, about 400 µg to about 425 µg, about 400 µg to about 450 µg, about 400 µg to about 475 µg, about 400 µg to about 500 µg, about 400 µg to about 525 µg, about 400 µg to about 550 µg, about 400 µg to about 575 µg, about 400 µg to about 600 µg, about 400 µg to about 625 µg, about 400 µg to about 650 µg, about 400 µg to about 675 µg, about 400 µg to about 700 µg, about 400 µg to about 725 µg, about 400 µg to about 750 µg, about 400 µg to about 775 µg, about 400 µg to about 800 µg, about 400 µg to about 825 µg, about 400 µg to about 850 µg, about 400 µg to about 875 µg, about 400 µg to about 900 µg, about 400 µg to about 925 µg, about 400 µg to about 950 µg, about 400 µg to about 975 µg, or about 400 µg to about 1,000 µg.

[0111] In still other aspects of this embodiment, an amount of a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, included in a pharmaceutical composition may be in the range of, *e.g.*, about 500 µg to about 525 µg, about 500 µg to about 550 µg, about 500 µg to about 575 µg, about 500 µg to about 600 µg, about 500 µg to about 625 µg, about 500 µg to about 650 µg, about 500 µg to about 675 µg, about 500 µg to about 700 µg, about 500 µg to about 725 µg, about 500 µg to about 750 µg, about 500 µg to about 775 µg, about 500 µg to about 800 µg, about 500 µg to about 825 µg, about 500 µg to about 850 µg, about 500 µg to about 875 µg, about 500 µg to about 900 µg, about 500 µg to about 925 µg, about 500 µg to about 950 µg, about 500 µg to about 975 µg, about 500 µg to about 1,000 µg, about 600 µg to about 625 µg, about 600 µg to about 650 µg, about 600 µg to about 675 µg, about 600 µg to about 700 µg, about 600 µg to about 725 µg, about 600 µg to about 750 µg, about 600 µg to about 775 µg, about 600 µg to about 800 µg, about 600 µg to about 825 µg, about 600 µg to about 850 µg, about 600 µg to about 875 µg, about 600 µg to about 900 µg, about 600 µg to about 925 µg, about 600 µg to about 950 µg, about 600 µg to about 975 µg, about 600 µg to about 1,000 µg, about 700 µg to about 725 µg, about 700 µg to about 750 µg, about 700 µg to about 775 µg, about 700 µg to about 800 µg, about 700 µg to about 825 µg, about 700 µg to about 850 µg, about 700 µg to about 875 µg, about 700 µg to about 900 µg, about 700 µg to about 925 µg, about 700 µg to about 950 µg, about 700 µg to about 975 µg, about 700 µg to about 1,000 µg, about 800 µg to about 825 µg, about 800 µg to about 850 µg, about 800 µg to about 875 µg, about 800 µg to about 900 µg, about 800 µg to about 925 µg, about 800 µg to about 950 µg, about 800 µg to about 975 µg, or about 800 µg to about 1,000 µg.

[0112] A pharmaceutical composition disclosed herein can optionally include one or more pharmaceutically acceptable carriers that facilitate processing of an active ingredient into therapeutic compositions. As used herein "pharmaceutically acceptable" refers to any molecular entity or composition that does not produce an adverse, allergic or other untoward or unwanted reaction when administered to an individual. As used herein, the term "pharmacologically acceptable carriers" is synonymous with "pharmacological carriers" and means any compound that has substantially no long term or permanent detrimental effect when administered and encompasses terms such as "pharmacologically acceptable vehicle, stabilizer, diluent, additive, auxiliary or excipient." Such a carrier generally is mixed with an active compound, or permitted to dilute or enclose the active compound and can be a solid, semi-solid, or liquid agent. It is understood that the active ingredients can be soluble or can be delivered as a suspension in the desired carriers. Any of a variety of pharmaceutically acceptable carrier can be used including, without limitation, aqueous media such as, *e.g.*, water, saline, glycine, hyaluronic acid and the like; solid carriers such as, *e.g.*, mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like; solvents; dispersion media; coatings; antibacterial and antifungal agents; isotonic and absorption delaying agents; or any other inactive ingredient. Selection of a pharmacologically acceptable carrier can depend on the mode of administration. Except insofar as any pharmacologically acceptable carrier is incompatible with the active ingredient, its use in pharmaceutically acceptable compositions is contemplated. Non-limiting examples of specific uses of such pharmaceutical carriers can be found in PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS (Howard C. Ansel et al., eds., Lippincott Williams & Wilkins Publishers, 7th ed. 1999); REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (Alfonso R. Gennaro ed., Lippincott, Williams & Wilkins, 20th ed. 2000); GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS (Joel G. Hardman et al., eds., McGraw-Hill Professional, 10th ed. 2001); and HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (Raymond C. Rowe et al., APhA Publications, 4th edition 2003). These protocols are routine procedures and any modifications are well within the scope of one skilled in the art and from the teaching herein.

[0113] A pharmaceutical composition disclosed herein may optionally include, without limitation, other pharmaceutically acceptable components (or pharmaceutical components), including, without limitation, buffers, preservatives, tonicity adjusters, salts, antioxidants, osmolality adjusting agents, physiological substances, pharmacological substances, bulking agents, emulsifying agents, wetting agents, sweetening or flavoring agents, and the like. Various buffers and means for adjusting pH can be used to prepare a therapeutic composition disclosed herein, provided that the resulting preparation is pharmaceutically acceptable. Such buffers include, without limitation, acetate buffers, citrate buffers, phosphate buffers, neutral buffered saline, phosphate buffered saline and borate buffers. It is understood that acids or bases can be used to adjust the pH of a composition as needed. Pharmaceutically acceptable antioxidants include, without limitation, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene. Useful preservatives include, without limitation, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, phenylmercuric nitrate, a stabilized oxy chloro composition and chelants, such as, *e.g.*, DTPA or DTPA-bisamide, calcium DTPA, and CaNaDTPA-bisamide. Tonicity adjusters useful in a pharmaceutical composition include, without

limitation, salts such as, e.g., sodium chloride, potassium chloride, mannitol or glycerin and other pharmaceutically acceptable tonicity adjustor. An active ingredient, such as, e.g., an α -HIV antibody disclosed herein, may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. It is understood that these and other substances known in the art of pharmacology can be included in a therapeutic composition.

[0114] A pharmaceutical composition comprising one or more EphA4 antagonist, like an APY cyclic peptide disclosed herein, is useful for medical and veterinary applications. A pharmaceutical composition may be administered to an individual alone, or in combination with other supplementary active ingredients, agents, drugs or hormones. The pharmaceutical compositions may be manufactured using any of a variety of processes, including, without limitation, conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, and lyophilizing. The pharmaceutical composition can take any of a variety of forms including, without limitation, a sterile solution, suspension, emulsion, lyophilizate, tablet, pill, pellet, capsule, powder, syrup, elixir or any other dosage form suitable for administration.

[0115] Aspects of the present specification disclose, in part, a method of treating an EphA4-based disease, disorder or pathology. An EphA4-based disease, disorder or pathology refers to any condition, disease or disorder or pathology where a pathophysiology effect is due to dysregulation of EphA4 signaling in a manner that causes EphA4 signaling hyperactivity in cells or spatially or temporally aberrant EphA4 signaling.

[0116] Such methods include therapeutic (following onset of an EphA4-based disease) and prophylactic (prior to onset of an EphA4-based disease). For example, therapeutic and prophylactic methods of treating an individual for an EphA4-based disease, disorder or pathology include treating an individual at risk of having an EphA4-based disease, disorder or pathology, treating an individual having an EphA4-based disease, disorder or pathology, and methods of protecting an individual from an EphA4-based disease, disorder or pathology, to decrease or reduce the probability of an EphA4-based disease, disorder or pathology in an individual, to decrease or reduce susceptibility of an individual to an EphA4-based disease, disorder or pathology, or to inhibit or prevent an EphA4-based disease, disorder or pathology in an individual, and to decrease, reduce, inhibit or suppress transmission of an EphA4-based disease, disorder or pathology from an afflicted individual to an unafflicted individual. Such methods include administering a pharmaceutical composition disclosed herein to therapeutically or prophylactically treat an individual having or at risk of having an EphA4-based disease, disorder or pathology. Accordingly, methods can treat an EphA4-based disease or pathology, or provide the individual with protection from an EphA4-based disease, disorder or pathology (e.g., prophylactic protection).

[0117] In an embodiment, a method of treating an EphA4-based disease, disorder or pathology, comprises administering one or more EphA4 antagonists, like one or more APY cyclic peptides disclosed

herein, or a pharmaceutical composition disclosed herein to an individual in need thereof in an amount sufficient to reduce one or more physiological conditions or symptom associated with an EphA4-based disease, disorder or pathology, thereby treating the EphA4-based disease, disorder or pathology. In aspects of this embodiment, an EphA4-based disease, disorder or pathology includes, without limitation, a neurodegenerative disease, a hearing loss, promotion of nerve regeneration, promotion of neuroprotection, and a cancer.

[0118] Neurodegenerative diseases are conditions that affect brain or peripheral nerve function. They result from the deterioration of neurons and they are characterized by progressive central or peripheral nervous dysfunction. They are divided into two groups: conditions causing problems with movement or sensation and conditions affecting memory or related to dementia. EphA4 signaling activity has important functions in both categories. For example, increased expression of EphA4 and its activation by ephrin ligands contribute to the pathogenesis of ALS, Alzheimer's disease, multiple sclerosis, stroke and traumatic brain injury and other neurodegenerative disease because EphA4 signaling leads to abnormal inhibition of axon growth, aberrant synaptic function and poor neuronal survival. Thus, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein can be useful in treating any neurodegenerative disease expressing high EphA4 levels because these APY cyclic peptides inhibit EphA4 signaling. A neurodegenerative disease includes, without limitation, an Alexander disease, an Alper's disease, Alzheimer's disease, an amyotrophic lateral sclerosis, an ataxia telangiectasia, a Canavan disease, a Cockayne syndrome, a corticobasal degeneration, a Creutzfeldt-Jakob disease, a Guillain-Barre Syndrome a HIV-induced neurodegeneration, a Huntington disease, a Kennedy's disease, a Krabbe disease, a Lewy body dementia, a Machado-Joseph disease, a multiple sclerosis, a Parkinson's disease, a Pelizaeus-Merzbacher disease, a Pick's disease, a primary lateral sclerosis, a Refsum's disease, a Sandhoff disease, a Schilder's disease, a spinal cord injury, a Steele-Richardson-Olszewski disease, a stroke, a tabes dorsalis and/or a traumatic brain injury. Symptoms associated with a neurodegenerative disease include, without limitation, abnormal movement, abnormal sensation, limb grasping, muscle weakness, atrophy, paralysis, abnormal inhibition of axon growth, abnormal axonal transport, aberrant synaptic function, synaptic transmission loss, impaired synaptic plasticity, synaptic loss, neuronal degeneration, motor neuron degeneration, motor neuron loss, poor neuronal survival, memory loss, impaired learning, dementia, β -amyloid plaque deposits, aberrant neurofilament accumulation, reactive astroglia and/or reactive microglia.

[0119] In another embodiment, a method of treating an EphA4-based disease, disorder or pathology includes a method of treating a neurodegenerative disease. In an aspect of this embodiment, a method of treating a neurodegenerative disease comprises administering one or more EphA4 antagonists, like one or more APY cyclic peptides disclosed herein, or a pharmaceutical composition disclosed herein to an individual in need thereof in an amount sufficient to reduce one or more physiological conditions or symptom associated with a neurodegenerative disease, thereby treating the neurodegenerative disease.

[0120] Cochlear hair cells are the primary sensory receptors of both the auditory system and the vestibular system in all vertebrates. Through mechanotransduction, hair cells detect movement in their environment (*i.e.*, sound) and are responsible for the sense of hearing. Hair cell damage results in

decreased hearing sensitivity, i.e. sensorineural hearing loss. Such damage can occur due to hereditary and/or environmental causes. For example, hair cell degenerate and/or death can be caused by lack of essential growth factors, exogenous toxins (such as ototoxic drugs), overstimulation by noise or sound, viral or bacterial infections, autoimmune conditions or hereditary disease. Since human cochlear hair cells are incapable of regeneration, damaged cells cannot be replaced, and as such, their loss leads to permanent hearing loss. Symptoms associated with a neurodegenerative disease include, without limitation, decreased hearing sensitivity and/or sensorineural hearing loss. It is now known that EpHA4 signaling prevents the generation of new cochlear hair cells suggesting that inhibition of EpHA4 activity could be an effective therapy in the treatment of hearing loss.

[0121] In another embodiment, a method of treating an EphA4-based disease, disorder or pathology includes a method of treating a hearing loss. In an aspect of this embodiment, a method of treating a hearing loss comprises administering one or more EphA4 antagonists, like one or more APY cyclic peptides disclosed herein, or a pharmaceutical composition disclosed herein to an individual in need thereof in an amount sufficient to reduce one or more physiological conditions or symptom associated with a hearing loss, thereby treating the hearing loss. In an aspect of this embodiment, administration of one or more EphA4 antagonists, like one or more APY cyclic peptides disclosed herein, or a pharmaceutical composition disclosed herein promotes the generation of cochlear sensory hair cells. In an aspect of this embodiment, administration is by injection to the ear region.

[0122] Nerve regeneration or neuroregeneration, refers to the regrowth or repair of nervous tissues, cells or cell products. Such mechanisms may include generation of new neurons, glia, axons, myelin, or synapses. Although neuroregeneration differs between the peripheral nervous system (PNS) and the central nervous system (CNS) by the functional mechanisms that control axon regrowth, both are influenced by EphA4 signaling which contribute to the inhibition of axon regeneration following injury. Thus, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein can be useful in promoting neuroregeneration by inhibiting the activity of EphA4 signaling. Symptoms associated with a lack of nerve regeneration include, without limitation, abnormal movement, abnormal sensation, limb grasping, muscle weakness, atrophy, paralysis, loss of neuronal function, loss of motor neuron function, loss of sensory neuron function, inhibited neuronal growth, inhibited axon growth, inhibited synaptic plasticity, synaptic loss, astrocytic gliosis and/or glial scarring.

[0123] In another embodiment, a method of treating an EphA4-based disease, disorder or pathology includes a method of promoting nerve regeneration. In an aspect of this embodiment, a method of promoting nerve regeneration comprises administering one or more EphA4 antagonists, like one or more APY cyclic peptides disclosed herein, or a pharmaceutical composition disclosed herein to an individual in need thereof in an amount sufficient to stimulate or facilitate neuronal differentiation and/or growth, thereby promoting nerve regeneration.

[0124] Following the primary cerebral insult, a cascade of events amplifies the initial damage regardless of the etiology of the precipitating event. Secondary biochemical changes contribute to subsequent tissue

damage with associated neuronal cell death. One such secondary chemical response is a growth inhibitory response that prevents axonal regeneration, neurogenesis, synaptogenesis and angiogenesis. EphA4 signaling is known to inhibit neuronal growth following neuronal injury. Thus, a modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein can be useful in providing neuroprotection that minimizes this subsequent damage, where the secondary tissue damage is dependent EphA4 signaling activity because these APY cyclic peptides inhibit EphA4 signaling.

[0125] In another embodiment, a method of treating an EphA4-based disease, disorder or pathology includes a method of promoting neuroprotection. In an aspect of this embodiment, a method of promoting neuroprotection comprises administering one or more EphA4 antagonists, like one or more APY cyclic peptides disclosed herein, or a pharmaceutical composition disclosed herein to an individual in need thereof in an amount sufficient to protect neurons or nerve tissue from damage, thereby promoting neuroprotection.

[0126] Originally identified as axon guidance molecules, ephrins and Eph receptors are now known to be involved in a vast array of cell communication events. Many A- and B-class receptors were shown to be overexpressed in a wide variety of tumors, including malignant melanoma, glioma, prostate cancer, breast cancer, small cell lung cancer, endometrial cancer, esophageal cancer, gastric cancer, and colorectal cancer. Subsequent work has shown the Eph receptors regulate critical steps of blood vessel formation (vasculogenesis) and remodeling (angiogenesis) and hence tumor growth. Increasing evidence has implicated EphA4 in various types of cancer, including glioblastoma, gastric cancer, pancreatic cancer, prostate cancer and breast cancer. For example, EphA4 downregulation studies have suggested a role for EphA4 in leukemia, prostate cancer, pancreatic cancer and gastric cancer cell growth and in liver cancer metastasis. High EphA4 expression has also been correlated with shorter survival in breast and gastric cancer patients, although the opposite correlation was found in lung cancer patients. EphA4 is also highly upregulated in Sezary syndrome, a leukemic variant of cutaneous T-cell lymphomas. Finally, EphA4 can enhance the oncogenic effects of fibroblast growth factor receptor 1 in glioblastoma cells. Hence, inhibiting EphA4-ephrin interaction could be useful for promoting axon regeneration and neural repair, providing neuroprotection and regulating synaptic plasticity in the nervous system as well as inhibiting the progression of cancer.

[0127] In another embodiment, a method of treating an EphA4-based disease, disorder or pathology includes a method of treating a cancer. In an aspect of this embodiment, a method of treating a cancer comprising administering one or more EphA4 antagonists, like one or more APY cyclic peptides disclosed herein, or a pharmaceutical composition disclosed herein to an individual in need thereof in an amount sufficient to reduce one or more physiological conditions or symptom associated with a cancer, thereby treating the cancer. A modified EphA4 antagonist, like an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein can be useful in treating any cancer expressing high EphA4 levels. IN an aspect of this embodiment, a cancer, includes, without limitation, glioblastoma, a gastric cancer, a pancreatic cancer, a prostate cancer, a breast cancer, a liver cancer, a leukemia and Sezary syndrome, a leukemic variant of cutaneous T-cell lymphomas.

[0128] Aspects of the present invention provide, in part, an individual. An individual comprises any mammal including a human, and a human can be a patient.

[0129] Aspects of the present invention provide, in part, administering an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein. As used herein, the term “administering” refers to any delivery mechanism that provides an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein to an individual that potentially results in a clinically, therapeutically, or experimentally beneficial result. The actual delivery mechanism used to administer an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein to an individual can be determined by a person of ordinary skill in the art by taking into account factors, including, without limitation, the type of Eph4A-based disease, the location of the Eph4A-based disease, the cause of the Eph4A-based disease, the severity of the Eph4A-based disease, the degree of relief desired for Eph4A-based disease, the duration of relief desired for Eph4A-based disease, the particular APY cyclic peptide or a pharmaceutical composition used, the rate of excretion of the particular APY cyclic peptide or a pharmaceutical composition used, the pharmacodynamics of the particular APY cyclic peptide or a pharmaceutical composition used, the nature of the other compounds to be included in the pharmaceutical composition, the particular route of administration, the particular characteristics, history and risk factors of the individual, such as, *e.g.*, age, weight, general health and the like, or any combination thereof.

[0130] A composition disclosed herein can be administered to an individual using a cellular uptake approach. Administration of a composition disclosed herein using a cellular uptake approach comprise a variety of enteral or parenteral approaches including, without limitation, oral administration in any acceptable form, such as, *e.g.*, tablet, liquid, capsule, powder, or the like; topical administration in any acceptable form, such as, *e.g.*, drops, spray, creams, gels or ointments; intravascular administration in any acceptable form, such as, *e.g.*, intravenous injection, intravenous infusion, intra-arterial injection, intra-arterial infusion and catheter instillation into the vasculature; peri- and intra-tissue administration in any acceptable form, such as, *e.g.*, intraperitoneal injection, intramuscular injection, subcutaneous injection, subcutaneous infusion, intraocular injection, retinal injection, sub-retinal injection, intrathecal injection, intracerebroventricular injection or epidural injection; intravesicular administration in any acceptable form, such as, *e.g.*, catheter instillation; and by placement device, such as, *e.g.*, an implant, a patch, a pellet, a catheter, an osmotic pump, a suppository, a bioerodible delivery system, a non-bioerodible delivery system or another implanted extended or slow release system. An exemplary list of biodegradable polymers and methods of use are described in, *e.g.*, *Handbook of Biodegradable Polymers* (Abraham J. Domb et al., eds., Overseas Publishers Association, 1997).

[0131] An APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein is administered in an amount sufficient to treat an EphA4-based disease, disorder or pathology. In aspects of this embodiment, the amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein administered is an amount sufficient to reduce one or more physiological conditions or symptom associated with an EphA4-based disease, disorder or pathology or an amount sufficient to protect the individual against an EphA4-based disease, disorder or pathology. As used

herein, the term “amount sufficient” includes “effective amount”, “effective dose”, “therapeutically effective amount” or “therapeutically effective dose” and refers to the minimum amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein necessary to achieve the desired therapeutic effect and includes an amount sufficient to reduce or inhibit one or more physiological conditions or symptom associated with an EphA4-based disease, disorder or pathology.

[0132] In aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein reduces or inhibits one or more physiological conditions or symptom associated with an EphA4-based disease, disorder or pathology by, *e.g.*, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% or at least 100%. In other aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein reduces or inhibits one or more physiological conditions or symptom associated with an EphA4-based disease, disorder or pathology by, *e.g.*, at most 10%, at most 20%, at most 30%, at most 40%, at most 50%, at most 60%, at most 70%, at most 80%, at most 90% or at most 100%. In yet other aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein reduces or inhibits one or more physiological conditions or symptom associated with an EphA4-based disease, disorder or pathology by, *e.g.*, about 10% to about 100%, about 10% to about 90%, about 10% to about 80%, about 10% to about 70%, about 10% to about 60%, about 10% to about 50%, about 10% to about 40%, about 20% to about 100%, about 20% to about 90%, about 20% to about 80%, about 20% to about 70%, about 20% to about 60%, about 20% to about 50%, about 20% to about 40%, about 30% to about 100%, about 30% to about 90%, about 30% to about 80%, about 30% to about 70%, about 30% to about 60%, or about 30% to about 50%. In still other aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein reduces or inhibits one or more physiological conditions or symptom associated with an EphA4-based disease, disorder or pathology for, *e.g.*, at least one week, at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven months, or at least twelve months.

[0133] The actual effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein to be administered to an individual can be determined by a person of ordinary skill in the art by taking into account factors, including, without limitation, the type of EphA4-based disease, disorder or pathology, the location of the EphA4-based disease, disorder or pathology, the cause of the EphA4-based disease, disorder or pathology, the severity of the EphA4-based disease, disorder or pathology, the degree of relief desired for EphA4-based disease, disorder or pathology, the duration of relief desired for EphA4-based disease, disorder or pathology, the particular APY cyclic peptide or a pharmaceutical composition used, the rate of excretion of the particular APY cyclic peptide or a pharmaceutical composition used, the pharmacodynamics of the particular APY cyclic peptide or a pharmaceutical composition used, the nature of the other compounds to be included in the pharmaceutical composition, the particular route of administration used, the particular characteristics, history and risk factors of the individual, such as, *e.g.*, age, weight, general health and the like, or any

combination thereof. Additionally, where repeated administration of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein is used, the actual therapeutically effective amount will further depend upon factors, including, without limitation, the frequency of administration, the half-life of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein, or any combination thereof. It is known by a person of ordinary skill in the art that an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein can be extrapolated from *in vitro* assays and *in vivo* administration studies using animal models prior to administration to humans. Wide variations in the necessary effective amount are to be expected in view of the differing efficiencies of the various routes of administration. For instance, oral administration generally would be expected to require higher dosage levels than administration by intravenous or intravitreal injection. Variations in these dosage levels can be adjusted using standard empirical routines of optimization, which are well-known to a person of ordinary skill in the art. The precise therapeutically effective dosage levels and patterns are preferably determined by the attending physician in consideration of the above-identified factors.

[0134] In other aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein generally is in the range of about 0.001 µg/kg/day to about 100 µg/kg/day. In aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein may be, *e.g.*, at least 0.001 µg/kg/day, at least 0.01 µg/kg/day, at least 0.1 µg/kg/day, at least 1.0 µg/kg/day, at least 5.0 µg/kg/day, at least 10 µg/kg/day, at least 15 µg/kg/day, at least 20 µg/kg/day, at least 25 µg/kg/day, at least 30 µg/kg/day, at least 35 µg/kg/day, at least 40 µg/kg/day, at least 45 µg/kg/day, or at least 50 µg/kg/day.

[0135] In other aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein may be in the range of, *e.g.*, about 0.001 µg/kg/day to about 10 µg/kg/day, about 0.001 µg/kg/day to about 15 µg/kg/day, about 0.001 µg/kg/day to about 20 µg/kg/day, about 0.001 µg/kg/day to about 25 µg/kg/day, about 0.001 µg/kg/day to about 30 µg/kg/day, about 0.001 µg/kg/day to about 35 µg/kg/day, about 0.001 µg/kg/day to about 40 µg/kg/day, about 0.001 µg/kg/day to about 45 µg/kg/day, about 0.001 µg/kg/day to about 50 µg/kg/day, about 0.001 µg/kg/day to about 75 µg/kg/day, or about 0.001 µg/kg/day to about 100 µg/kg/day. In yet other aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein may be in the range of, *e.g.*, about 0.01 µg/kg/day to about 10 µg/kg/day, about 0.01 µg/kg/day to about 15 µg/kg/day, about 0.01 µg/kg/day to about 20 µg/kg/day, about 0.01 µg/kg/day to about 25 µg/kg/day, about 0.01 µg/kg/day to about 30 µg/kg/day, about 0.01 µg/kg/day to about 35 µg/kg/day, about 0.01 µg/kg/day to about 40 µg/kg/day, about 0.01 µg/kg/day to about 45 µg/kg/day, about 0.01 µg/kg/day to about 50 µg/kg/day, about 0.01 µg/kg/day to about 75 µg/kg/day, or about 0.01 µg/kg/day to about 100 µg/kg/day. In still other aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein may be in the range of, *e.g.*, about 0.1 µg/kg/day to about 10 µg/kg/day, about 0.1 µg/kg/day to about 15 µg/kg/day, about 0.1 µg/kg/day to about 20 µg/kg/day, about 0.1 µg/kg/day to about 25 µg/kg/day, about 0.1 µg/kg/day to about 30 µg/kg/day, about 0.1 µg/kg/day to about 35 µg/kg/day, about 0.1 µg/kg/day to

about 40 µg/kg/day, about 0.1 µg/kg/day to about 45 µg/kg/day, about 0.1 µg/kg/day to about 50 µg/kg/day, about 0.1 µg/kg/day to about 75 µg/kg/day, or about 0.1 µg/kg/day to about 100 µg/kg/day.

[0136] In other aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein may be in the range of, *e.g.*, about 1 µg/kg/day to about 10 µg/kg/day, about 1 µg/kg/day to about 15 µg/kg/day, about 1 µg/kg/day to about 20 µg/kg/day, about 1 µg/kg/day to about 25 µg/kg/day, about 1 µg/kg/day to about 30 µg/kg/day, about 1 µg/kg/day to about 35 µg/kg/day, about 1 µg/kg/day to about 40 µg/kg/day, about 1 µg/kg/day to about 45 µg/kg/day, about 1 µg/kg/day to about 50 µg/kg/day, about 1 µg/kg/day to about 75 µg/kg/day, or about 1 µg/kg/day to about 100 µg/kg/day. In yet other aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein may be in the range of, *e.g.*, about 5 µg/kg/day to about 10 µg/kg/day, about 5 µg/kg/day to about 15 µg/kg/day, about 5 µg/kg/day to about 20 µg/kg/day, about 5 µg/kg/day to about 25 µg/kg/day, about 5 µg/kg/day to about 30 µg/kg/day, about 5 µg/kg/day to about 35 µg/kg/day, about 5 µg/kg/day to about 40 µg/kg/day, about 5 µg/kg/day to about 45 µg/kg/day, about 5 µg/kg/day to about 50 µg/kg/day, about 5 µg/kg/day to about 75 µg/kg/day, or about 5 µg/kg/day to about 100 µg/kg/day.

[0137] In other aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein generally is in the range of about 0.001 µg/day to about 100 µg/day. In aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein may be, *e.g.*, at least 0.001 µg/day, at least 0.01 µg/day, at least 0.1 µg/day, at least 1.0 µg/day, at least 5.0 µg/day, at least 10 µg/day, at least 15 µg/day, at least 20 µg/day, at least 25 µg/day, at least 30 µg/day, at least 35 µg/day, at least 40 µg/day, at least 45 µg/day, or at least 50 µg/day.

[0138] In other aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein may be in the range of, *e.g.*, about 0.001 µg/day to about 10 µg/day, about 0.001 µg/day to about 15 µg/day, about 0.001 µg/day to about 20 µg/day, about 0.001 µg/day to about 25 µg/day, about 0.001 µg/day to about 30 µg/day, about 0.001 µg/day to about 35 µg/day, about 0.001 µg/day to about 40 µg/day, about 0.001 µg/day to about 45 µg/day, about 0.001 µg/day to about 50 µg/day, about 0.001 µg/day to about 75 µg/day, or about 0.001 µg/day to about 100 µg/day. In yet other aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein may be in the range of, *e.g.*, about 0.01 µg/day to about 10 µg/day, about 0.01 µg/day to about 15 µg/day, about 0.01 µg/day to about 20 µg/day, about 0.01 µg/day to about 25 µg/day, about 0.01 µg/day to about 30 µg/day, about 0.01 µg/day to about 35 µg/day, about 0.01 µg/day to about 40 µg/day, about 0.01 µg/day to about 45 µg/day, about 0.01 µg/day to about 50 µg/day, about 0.01 µg/day to about 75 µg/day, or about 0.01 µg/day to about 100 µg/day. In still other aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein may be in the range of, *e.g.*, about 0.1 µg/day to about 10 µg/day, about 0.1 µg/day to about 15 µg/day, about 0.1 µg/day to about 20 µg/day, about 0.1 µg/day to about 25 µg/day, about 0.1 µg/day to about 30 µg/day, about 0.1

µg/day to about 35 µg/day, about 0.1 µg/day to about 40 µg/day, about 0.1 µg/day to about 45 µg/day, about 0.1 µg/day to about 50 µg/day, about 0.1 µg/day to about 75 µg/day, or about 0.1 µg/day to about 100 µg/day.

[0139] In other aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein may be in the range of, e.g., about 1 µg/day to about 10 µg/day, about 1 µg/day to about 15 µg/day, about 1 µg/day to about 20 µg/day, about 1 µg/day to about 25 µg/day, about 1 µg/day to about 30 µg/day, about 1 µg/day to about 35 µg/day, about 1 µg/day to about 40 µg/day, about 1 µg/day to about 45 µg/day, about 1 µg/day to about 50 µg/day, about 1 µg/day to about 75 µg/day, or about 1 µg/day to about 100 µg/day. In yet other aspects of this embodiment, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein may be in the range of, e.g., about 5 µg/day to about 10 µg/day, about 5 µg/day to about 15 µg/day, about 5 µg/day to about 20 µg/day, about 5 µg/day to about 25 µg/day, about 5 µg/day to about 30 µg/day, about 5 µg/day to about 35 µg/day, about 5 µg/day to about 40 µg/day, about 5 µg/day to about 45 µg/day, about 5 µg/day to about 50 µg/day, about 5 µg/day to about 75 µg/day, or about 5 µg/day to about 100 µg/day.

[0140] Dosing can be single dosage or cumulative (serial dosing), and can be readily determined by one skilled in the art. For instance, treatment of an EphA4-based disease, disorder or pathology may comprise a one-time administration of an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein. As a non-limiting example, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein can be administered once to an individual, e.g., as a single injection or deposition. Alternatively, treatment of a HIV-based disease may comprise multiple administrations of an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein carried out over a range of time periods, such as, e.g., daily, once every few days, weekly, monthly or yearly. As a non-limiting example, an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein can be administered one, two, three, four, five or six times yearly to an individual. The timing of administration can vary from individual to individual, depending upon such factors as the severity of an individual's symptoms. For example, an effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein can be administered to an individual once every three months for an indefinite period of time, or until the individual no longer requires therapy. A person of ordinary skill in the art will recognize that the condition of the individual can be monitored throughout the course of treatment and that the effective amount of an APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein that is administered can be adjusted accordingly.

[0141] An APY cyclic peptide disclosed herein, or a pharmaceutical composition disclosed herein can also be administered to an individual in combination with other therapeutic compounds to increase the overall therapeutic effect of the treatment. The use of multiple compounds to treat an indication can increase the beneficial effects while reducing the presence of side effects.

[0142] Aspects of the present specification can also be described as follows:

1. A modified EphA4 receptor antagonist comprising a cyclic peptide comprising or consisting essentially or consisting of the sequence $X_1-X_2-X_3-C_4-X_5-X_6-X_7-\beta A_8-X_9-W-X_{11}-C_{12}$ (SEQ ID NO: 3), $X_2-X_3-C_4-X_5-X_6-X_7-\beta A_8-X_9-W-X_{11}-C_{12}$ (SEQ ID NO: 4), or $X_3-C_4-X_5-X_6-X_7-\beta A_8-X_9-W-X_{11}-C_{12}$ (SEQ ID NO: 5), wherein X_1 is independently Ahx, Ava, γ Abu, β A, Sar, D-A, A, E, G, Q, D, L, S, F, or Y; X_2 is independently P, A, G, Ahx, Ava, γ Abu, β A or Sar; X_3 is independently Y, F, W, V, L, H or I; X_5 is independently V or L; X_6 is independently Y, F, W or H; X_7 is independently any amino acid; X_9 is independently any amino acid; and X_{11} is independently any amino acid; wherein C_4 and C_{12} form a disulfide bridge; wherein C_{12} is optionally amidated; wherein the amino-terminal residue is optionally acetylated; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.
2. The modified EphA4 receptor antagonist according to embodiment 1, wherein X_1 is independently β A, D-A, A, E, G or Q.
3. The modified EphA4 receptor antagonist according to embodiment 1 or embodiment 2, wherein X_1 is independently β A, D-A, A or E.
4. The modified EphA4 receptor antagonist according to any one of embodiments 1-3, wherein X_2 is P.
5. The modified EphA4 receptor antagonist according to any one of embodiments 1-4, wherein X_3 is independently Y, F, W, V, L or H.
6. The modified EphA4 receptor antagonist according to any one of embodiments 1-5, wherein X_3 is independently Y, F or W.
7. The modified EphA4 receptor antagonist according to any one of embodiments 1-6, wherein X_5 is V.
8. The modified EphA4 receptor antagonist according to any one of embodiments 1-7, wherein X_6 is independently Y, F or W.
9. The modified EphA4 receptor antagonist according to any one of embodiments 1-8, wherein X_7 is independently any amino acid except P; X_9 is independently any amino acid except P; and X_{11} is independently any amino acid except P.
10. The modified EphA4 receptor antagonist according to any one of embodiments 1-9, wherein X_7 is independently R, T, N, D, S, Q, Y, K, A, G or E; X_9 is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X_{11} is independently S, E, L, N, V, I, H, K, M, D, W, T or G.
11. The modified EphA4 receptor antagonist according to any one of embodiments 1-10, wherein X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, W, R, L, D, Y; and X_{11} is independently S, E, L, N, T, K, V, I or H.
12. The modified EphA4 receptor antagonist according to any one of embodiments 1-11, wherein X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, D, Y; and X_{11} is independently S, E, L, N, K, V, I or H.
13. The modified EphA4 receptor antagonist according to any one of embodiments 1-12, wherein X_7 is independently R, T, or N; X_9 is independently S, E, T or V; and X_{11} is independently S, E, L or N.
14. The modified EphA4 receptor antagonist according to any one of embodiments 1, 2, 4, 5 or 10-13, wherein the sequence comprises or consists essentially of or consists of $X_1-P_2-X_3-C_4-X_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 6), $P_2-X_3-C_4-X_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 7) or $X_3-C_4-X_5-$

X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 8), wherein X₁ is independently βA, D-A, A, E, G or Q; X₃ is independently Y, F, W, V, L or H; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently any amino acid except P; X₉ is independently any amino acid except P; and X₁₁ is independently any amino acid except P; wherein C₄ and C₁₂ form a disulfide bridge; wherein C₁₂ is optionally amidated; wherein the amino-terminal residue is optionally acetylated; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.

15. The modified EphA4 receptor antagonist according to embodiment 14, wherein X₁ is independently βA, D-A, A or E.
16. The modified EphA4 receptor antagonist according to embodiment 14 or embodiment 15, wherein X₃ is independently Y, F or W.
17. The modified EphA4 receptor antagonist according to any one of embodiments 14-16, wherein X₅ is V.
18. The modified EphA4 receptor antagonist according to any one of embodiments 14-17, wherein X₆ is independently Y, F or W.
19. The modified EphA4 receptor antagonist according to any one of embodiments 14-18, wherein X₇ is independently R, T, N, D, S, Q, Y, K, A, G or E; X₉ is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X₁₁ is independently S, E, L, N, V, I, H, K, M, D, W, T or G.
20. The modified EphA4 receptor antagonist according to any one of embodiments 14-10, wherein X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, W, R, L, D, Y; and X₁₁ is independently S, E, L, N, T, K, V, I or H.
21. The modified EphA4 receptor antagonist according to any one of embodiments 14-20, wherein X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, D, Y; and X₁₁ is independently S, E, L, N, K, V, I or H.
22. The modified EphA4 receptor antagonist according to any one of embodiments 11-21, wherein X₇ is independently R, T, or N; X₉ is independently S, E, T or V; and X₁₁ is independently S, E, L or N.
23. The modified EphA4 receptor antagonist according to any one of embodiments 1, 2, 5, 7 or 10-13, wherein the sequence comprises or consists essentially of or consists of X₁-X₂-X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 9), X₂-X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 10) or X₃-C₄-V₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 11), wherein X₁ is independently Ahx, Ava, γAbu, βA, Sar, D-A, A, E, G or Q; X₂ is independently P, A, G, Ahx, Ava, γAbu, βA or Sar; X₃ is independently Y, F, W, V, L or H; X₆ is independently Y, F, W or H; X₇ is independently any amino acid except P; X₉ is independently any amino acid except P; and X₁₁ is independently any amino acid except P; wherein C₄ and C₁₂ form a disulfide bridge; wherein C₁₂ is optionally amidated; wherein the amino-terminal residue is optionally acetylated; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.
24. The modified EphA4 receptor antagonist according to embodiment 23, wherein X₁ is independently βA, D-A, A or E.
25. The modified EphA4 receptor antagonist according to embodiment 23 or embodiment 24, wherein X₂ is P.

26. The modified EphA4 receptor antagonist according to any one of embodiments 23-25, wherein X_3 is independently Y, F or W.
27. The modified EphA4 receptor antagonist according to any one of embodiments 23-26, wherein X_6 is independently Y, F or W.
28. The modified EphA4 receptor antagonist according to any one of embodiments 23-27, wherein X_7 is independently R, T, N, D, S, Q, Y, K, A, G or E; X_9 is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X_{11} is independently S, E, L, N, V, I, H, K, M, D, W, T or G.
29. The modified EphA4 receptor antagonist according to any one of embodiments 23-28, wherein X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, W, R, L, D, Y; and X_{11} is independently S, E, L, N, T, K, V, I or H.
30. The modified EphA4 receptor antagonist according to any one of embodiments 23-29, wherein X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, D, Y; and X_{11} is independently S, E, L, N, K, V, I or H.
31. The modified EphA4 receptor antagonist according to any one of embodiments 23-30, wherein X_7 is independently R, T, or N; X_9 is independently S, E, T or V; and X_{11} is independently S, E, L or N.
32. The modified EphA4 receptor antagonist according to any one of embodiments 1, 2, 5 or 10-13, wherein the sequence comprises or consists essentially of or consists of X_1 - P_2 - X_3 - C_4 - V_5 - X_6 - X_7 - βA_8 - X_9 - W_{10} - X_{11} - C_{12} (SEQ ID NO: 12), P_2 - X_3 - C_4 - V_5 - X_6 - X_7 - βA_8 - X_9 - W_{10} - X_{11} - C_{12} (SEQ ID NO: 13) or X_3 - C_4 - V_5 - X_6 - X_7 - βA_8 - X_9 - W_{10} - X_{11} - C_{12} (SEQ ID NO: 14), wherein X_1 is independently βA , D-A, A, E, G or Q; X_3 is independently Y, F, W, V, L or H; X_6 is independently Y, F, W or H; X_7 is independently any amino acid except P; X_9 is independently any amino acid except P; and X_{11} is independently any amino acid except P; wherein C_4 and C_{12} form a disulfide bridge; wherein C_{12} is optionally amidated; wherein the amino-terminal residue is optionally acetylated; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.
33. The modified EphA4 receptor antagonist according to embodiment 32, wherein X_1 is independently βA , D-A, A or E.
34. The modified EphA4 receptor antagonist according to embodiment 32 or embodiment 33, wherein X_3 is independently Y, F or W.
35. The modified EphA4 receptor antagonist according to any one of embodiments 32-34, wherein X_6 is independently Y, F or W.
36. The modified EphA4 receptor antagonist according to any one of embodiments 32-35, wherein X_7 is independently R, T, N, D, S, Q, Y, K, A, G or E; X_9 is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X_{11} is independently S, E, L, N, V, I, H, K, M, D, W, T or G.
37. The modified EphA4 receptor antagonist according to any one of embodiments 32-36, wherein X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, W, R, L, D, Y; and X_{11} is independently S, E, L, N, T, K, V, I or H.
38. The modified EphA4 receptor antagonist according to any one of embodiments 32-37, wherein X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, D, Y; and X_{11} is independently S, E, L, N, K, V, I or H.

39. The modified EphA4 receptor antagonist according to any one of embodiments 32-38, wherein X_7 is independently R, T, or N; X_9 is independently S, E, T or V; and X_{11} is independently S, E, L or N.
40. The modified EphA4 receptor antagonist according to any one of embodiments 1, 2 or 10-13, wherein the sequence comprises or consists essentially of or consists of X_1 - P_2 - Y_3 - C_4 - V_5 - X_6 - X_7 - βA_8 - X_9 - W_{10} - X_{11} - C_{12} (SEQ ID NO: 15), P_2 - Y_3 - C_4 - V_5 - X_6 - X_7 - βA_8 - X_9 - W_{10} - X_{11} - C_{12} (SEQ ID NO: 16) or Y_3 - C_4 - V_5 - X_6 - X_7 - βA_8 - X_9 - W_{10} - X_{11} - C_{12} (SEQ ID NO: 17), wherein X_1 is independently βA , D-A, A, E, G or Q; X_6 is independently Y, F, W or H; X_7 is independently any amino acid except P; X_9 is independently any amino acid except P; and X_{11} is independently any amino acid except P; wherein C_4 and C_{12} form a disulfide bridge; wherein C_{12} is optionally amidated; wherein the amino-terminal residue is optionally acetylated; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.
41. The modified EphA4 receptor antagonist according to embodiment 40, wherein X_1 is independently βA , D-A, A or E.
42. The modified EphA4 receptor antagonist according to embodiment 40 or embodiment 41, wherein X_6 is independently Y, F or W.
43. The modified EphA4 receptor antagonist according to any one of embodiments 40-42, wherein X_7 is independently R, T, N, D, S, Q, Y, K, A, G or E; X_9 is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X_{11} is independently S, E, L, N, V, I, H, K, M, D, W, T or G.
44. The modified EphA4 receptor antagonist according to any one of embodiments 40-43, wherein X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, W, R, L, D, Y; and X_{11} is independently S, E, L, N, T, K, V, I or H.
45. The modified EphA4 receptor antagonist according to any one of embodiments 40-44, wherein X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, D, Y; and X_{11} is independently S, E, L, N, K, V, I or H.
46. The modified EphA4 receptor antagonist according to any one of embodiments 40-45, wherein X_7 is independently R, T, or N; X_9 is independently S, E, T or V; and X_{11} is independently S, E, L or N.
47. The modified EphA4 receptor antagonist according to any one of embodiments 1, 2, 5 or 10-13, wherein the sequence comprises or consists essentially of or consists of X_1 - P_2 - X_3 - C_4 - V_5 - Y_6 - X_7 - βA_8 - X_9 - W_{10} - X_{11} - C_{12} (SEQ ID NO: 18), P_2 - X_3 - C_4 - V_5 - Y_6 - X_7 - βA_8 - X_9 - W_{10} - X_{11} - C_{12} (SEQ ID NO: 19) or X_3 - C_4 - V_5 - Y_6 - X_7 - βA_8 - X_9 - W_{10} - X_{11} - C_{12} (SEQ ID NO: 20), wherein X_1 is independently βA , D-A, A, E, G or Q; X_3 is independently Y, F, W, V, L or H; X_7 is independently any amino acid except P; X_9 is independently any amino acid except P; and X_{11} is independently any amino acid except P; wherein C_4 and C_{12} form a disulfide bridge; wherein C_{12} is optionally amidated; wherein the amino-terminal residue is optionally acetylated; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.
48. The modified EphA4 receptor antagonist according to embodiment 47, wherein X_1 is independently βA , D-A, A or E.
49. The modified EphA4 receptor antagonist according to embodiment 47 or embodiment 48, wherein X_3 is independently Y, F or W.

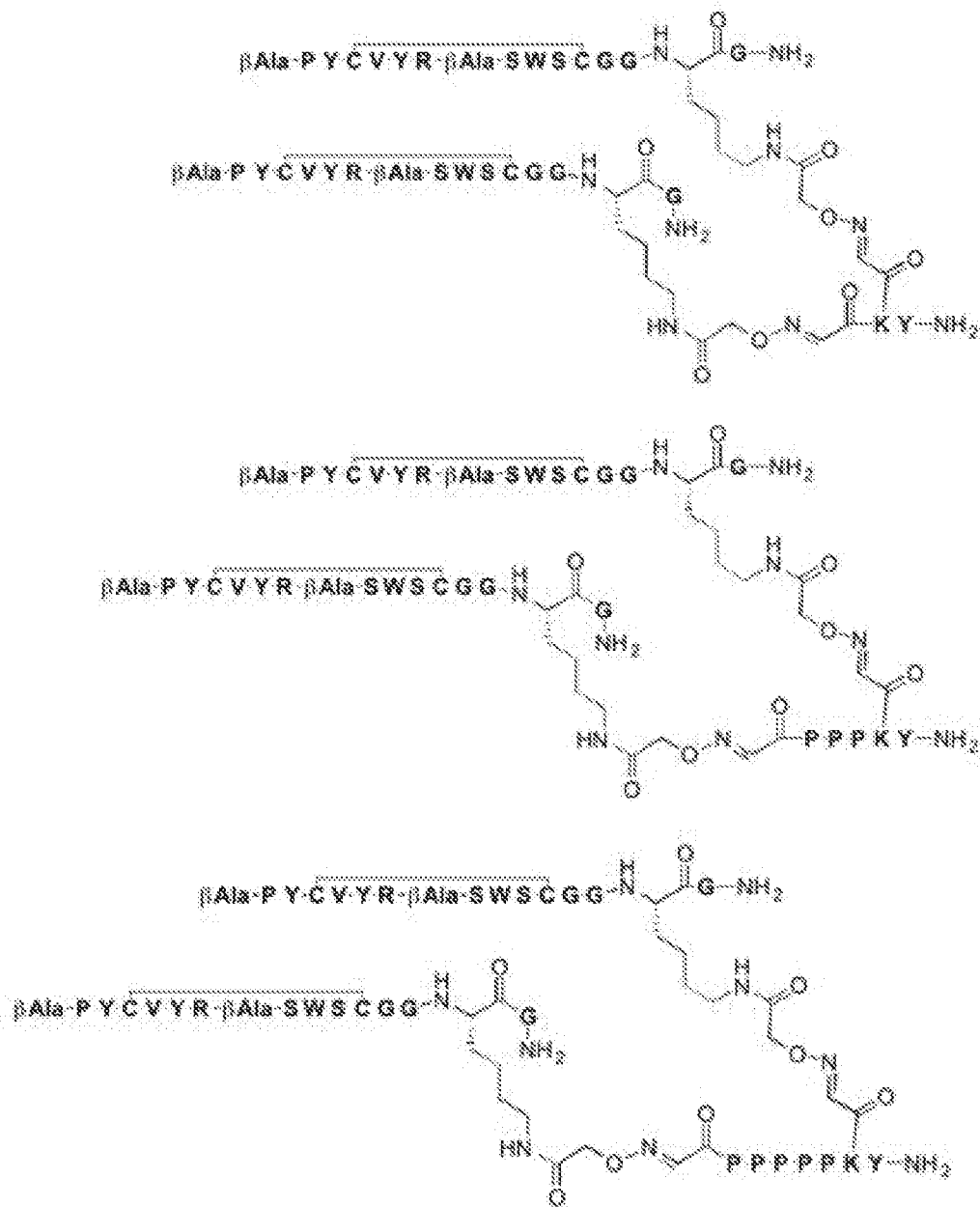
50. The modified EphA4 receptor antagonist according to any one of embodiments 47-49, wherein X_7 is independently R, T, N, D, S, Q, Y, K, A, G or E; X_9 is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X_{11} is independently S, E, L, N, V, I, H, K, M, D, W, T or G.
51. The modified EphA4 receptor antagonist according to any one of embodiments 47-50, wherein X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, W, R, L, D, Y; and X_{11} is independently S, E, L, N, T, K, V, I or H.
52. The modified EphA4 receptor antagonist according to any one of embodiments 47-51, wherein X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, D, Y; and X_{11} is independently S, E, L, N, K, V, I or H.
53. The modified EphA4 receptor antagonist according to any one of embodiments 47-52, wherein X_7 is independently R, T, or N; X_9 is independently S, E, T or V; and X_{11} is independently S, E, L or N.
54. The modified EphA4 receptor antagonist according to any one of embodiments 1, 2 or 10-13, wherein the sequence comprises or consists essentially of or consists of X_1 -P₂-Y₃-C₄-V₅-Y₆-X₇- β A₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 21), P₂-Y₃-C₄-V₅-Y₆-X₇- β A₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 22) or Y₃-C₄-V₅-Y₆-X₇- β A₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 23), wherein X_1 is independently β A, D-A, A, E, G or Q; X_7 is independently any amino acid except P; X_9 is independently any amino acid except P; and X_{11} is independently any amino acid except P; wherein C₄ and C₁₂ form a disulfide bridge; wherein C₁₂ is optionally amidated; wherein the amino-terminal residue is optionally acetylated; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.
55. The modified EphA4 receptor antagonist according to embodiment 54, wherein X_1 is independently β A, D-A, A or E.
56. The modified EphA4 receptor antagonist according to embodiment 54 or embodiment 55, wherein X_7 is independently R, T, N, D, S, Q, Y, K, A, G or E; X_9 is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X_{11} is independently S, E, L, N, V, I, H, K, M, D, W, T or G.
57. The modified EphA4 receptor antagonist according to any one of embodiments 54-56, wherein X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, W, R, L, D, Y; and X_{11} is independently S, E, L, N, T, K, V, I or H.
58. The modified EphA4 receptor antagonist according to any one of embodiments 54-57, wherein X_7 is independently R, T, N, D, S, or Q; X_9 is independently S, E, T, V, D, Y; and X_{11} is independently S, E, L, N, K, V, I or H.
59. The modified EphA4 receptor antagonist according to any one of embodiments 54-57, wherein X_7 is independently R, T, or N; X_9 is independently S, E, T or V; and X_{11} is independently S, E, L or N.
60. The modified EphA4 receptor antagonist according to any one of embodiments 1, 2 or 10-13, wherein the sequence comprises or consists essentially of or consists of X_1 -P₂-Y₃-C₄-V₅-Y₆-R₇- β A₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 24), P₂-Y₃-C₄-V₅-Y₆-R₇- β A₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 25) or Y₃-C₄-V₅-Y₆-R₇- β A₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 26), wherein X_1 is independently β A, D-A, A, E, G or Q; X_9 is independently any amino acid except P; and X_{11} is independently any amino acid except P; wherein C₄ and C₁₂ form a disulfide bridge; wherein C₁₂ is optionally amidated; wherein the amino-terminal residue is optionally acetylated; and wherein the cyclic peptide has a modification that increase

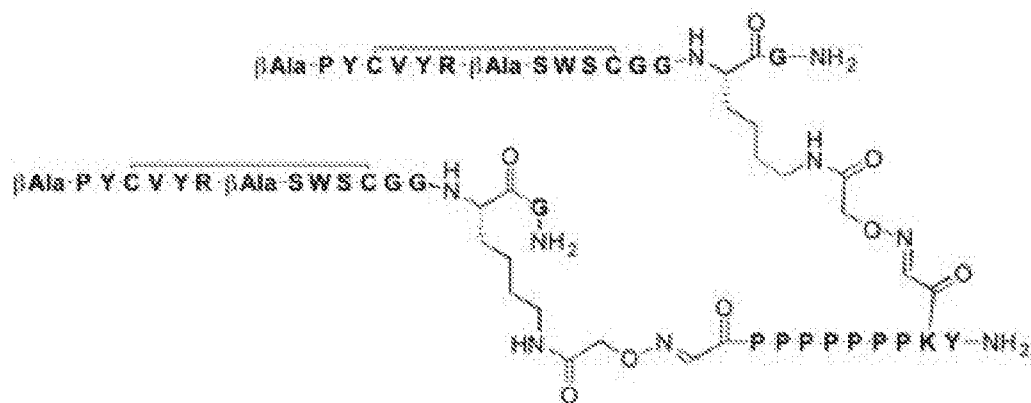
binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.

61. The modified EphA4 receptor antagonist according to embodiment 60, wherein X_1 is independently β A, D-A, A or E.
62. The modified EphA4 receptor antagonist according to embodiment 60 or embodiment 61, wherein X_9 is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X_{11} is independently S, E, L, N, V, I, H, K, M, D, W, T or G.
63. The modified EphA4 receptor antagonist according to any one of embodiments 60-62, wherein X_9 is independently S, E, T, V, W, R, L, D, Y; and X_{11} is independently S, E, L, N, T, K, V, I or H.
64. The modified EphA4 receptor antagonist according to any one of embodiments 60-63, wherein X_9 is independently S, E, T, V, D, Y; and X_{11} is independently S, E, L, N, K, V, I or H.
65. The modified EphA4 receptor antagonist according to any one of embodiments 60-64 wherein X_9 is independently S, E, T or V; and X_{11} is independently S, E, L or N.
66. The modified EphA4 receptor antagonist according to any one of embodiments 1-65, wherein C_{12} is amidated.
67. The modified EphA4 receptor antagonist according to any one of embodiments 1-66, having a length of about 10 amino acids to about 20 amino acids.
68. The modified EphA4 receptor antagonist according to any one of embodiments 1-67, having a length 12 amino acids.
69. The modified EphA4 receptor antagonist according to any one of embodiments 1-67, having a length 16 amino acids.
70. The modified EphA4 receptor antagonist according to any one of embodiments 1-69, wherein the sequence is APYCVYR β ASWSC (SEQ ID NO: 35), APYCVYR β ASWSC-am (SEQ ID NO: 36), APYCVYK β ASWSC-am (SEQ ID NO: 45), β APYCVYR β ASWSC (SEQ ID NO: 46), β APYCVYR β ASWSC-am (SEQ ID NO: 47), β APYCVYK β ASWSC-am (SEQ ID NO: 48), β APYCVYR β AEWEC (SEQ ID NO: 49), β APYCVYR β AEWEC-am (SEQ ID NO: 50), D-APYCVYR β ASWSC (SEQ ID NO: 51), D-APYCVYR β ASWSC-am (SEQ ID NO: 52), APYCVWR β ASWSC (SEQ ID NO: 53), APYCVYT β AEWLC (SEQ ID NO: 54), APYCVYN β ATWNC (SEQ ID NO: 55), APYCVYR β AVWEC (SEQ ID NO: 56), APYCVWR β ASWSC (SEQ ID NO: 57), APLCVWR β ASWSC (SEQ ID NO: 58), APLCVYR β ASWSC (SEQ ID NO: 59), APWCVFR β ASWSC (SEQ ID NO: 60), APHCVFR β ASWSC (SEQ ID NO: 61), APFCLYT β ADWVC (SEQ ID NO: 62), APYCVYD β ATWIC (SEQ ID NO: 63), APYCVYS β ATWHC (SEQ ID NO: 64), APYCVYD β ASWNC (SEQ ID NO: 65), APYCVYQ β AYWKC (SEQ ID NO: 66), APYCVYR β ASWSC (SEQ ID NO: 67), EPYCVYR β ASWSC (SEQ ID NO: 68), APLCVYR β ASWSC (SEQ ID NO: 69), Ahx-YCVYR β ASWSC-am (SEQ ID NO: 91), Ava-YCVYR β ASWSC-am (SEQ ID NO: 92), γ Abu-YCVYR β ASWSC-am (SEQ ID NO: 93), β A-YCVYR β ASWSC-am (SEQ ID NO: 94), GYCVYR β ASWSC-am (SEQ ID NO: 95) or Sar1-Y- β Ala8.am (SEQ ID NO: 96).
71. The modified EphA4 receptor antagonist according to embodiment 70, wherein the sequence is APYCVYR β ASWSC-am (SEQ ID NO: 36), APYCVYK β ASWSC-am (SEQ ID NO: 45), β APYCVYR β ASWSC (SEQ ID NO: 46), β APYCVYR β ASWSC-am (SEQ ID NO: 47), β APYCVYR β AEWEC-am (SEQ ID NO: 50), D-APYCVYR β ASWSC-am (SEQ ID NO: 52),

- APYCVWR β ASWSC (SEQ ID NO: 53), APYCVYT β AEWLC (SEQ ID NO: 54), APYCVYN β ATWNC (SEQ ID NO: 55) or APYCVYR β AVWEC (SEQ ID NO: 56).
72. The modified EphA4 receptor antagonist according to embodiment 71, wherein the sequence is APYCVYR β ASWSC-am (SEQ ID NO: 36), β APYCVYR β ASWSC-am (SEQ ID NO: 47) or β APYCVYR β AEWEC-am (SEQ ID NO: 50).
73. The modified EphA4 receptor antagonist according to any one of embodiments 1-72, wherein the amino-terminal residue is acetylated or wherein the amino-terminal residue is modified with carboxybenzyl or wherein the amino-terminal residue is not acetylated or is not modified with carboxybenzyl.
74. The modified EphA4 receptor antagonist according to any one of embodiments 1-73, wherein the modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide is by lipidation, PEGylation, polysialylation, a Blood-Brain Barrier (BBB) shuttle, hyperglycosylation, N-(2-hydroxypropyl) methacrylamide (HPMA) copolymers, and polyglutamic acid, poly(lactic acid) (PLA) polymers, poly(glycolic acid) (PGA) polymers and poly(D,L-lactic-coglycolic-acid) (PLGA) polymers.
75. The modified EphA4 receptor antagonist according to any one of embodiments 1-69, wherein the sequence is β APYCVYK(octanoyl) β ASWSC-am (SEQ ID NO: 71), β APYCVYK(octanoyl-G) β ASWSC-am (SEQ ID NO: 72), β APYCVYK(lauroyl) β ASWSC-am (SEQ ID NO: 73), β APYCVYK(lauroyl-G) β ASWSC-am (SEQ ID NO: 74), β APYCVYK(lauroyl- β D) β ASWSC-am (SEQ ID NO: 75), β APYCVYK(lauroyl- γ E) β ASWSC-am (SEQ ID NO: 76), β APYCVYK(palmitoyl- γ E) β ASWSC-am (SEQ ID NO: 77), β APYCVYR β ASWSCGGK(octanoyl)G-am (SEQ ID NO: 79), β APYCVYR β ASWSCGGK(lauroyl)G-am (SEQ ID NO: 80), β APYCVYR β ASWSCGGK(lauroyl- β D)G-am (SEQ ID NO: 81), β APYCVYR β ASWSCGGK(lauroyl- γ E)G-am (SEQ ID NO: 82), β APYCVYR β ASWSCGGK(palmitoyl- γ E)G-am (SEQ ID NO: 83), β APYCVYK β ASWSCGGK(octanoyl)G-am (SEQ ID NO: 87), D-APYCVYR β ASWSCGGK(octanoyl)G-am (SEQ ID NO: 89), β Ala1-PY- β Ala8-GGK(lauroyl- γ Glu- γ Glu)-G.am (SEQ ID NO: 97), β Ala1-PY- β Ala8-GGK(myristoyl- γ Glu- γ Glu)-G.am (SEQ ID NO: 98), β Ala1-PY- β Ala8-GGK(palmitoyl- γ Glu- γ Glu)-G.am (SEQ ID NO: 99) or β Ala1-PY- β Ala8-GGGSK(palmitoyl- γ Glu- γ Glu)-G.am (SEQ ID NO: 100).
76. The modified EphA4 receptor antagonist according to any one of embodiments 1-75, wherein the cyclic peptide form a homomultimer or a heteromultimer.
77. The modified EphA4 receptor antagonist according to embodiment 76, wherein the homomultimer is a homodimer comprising two cyclic peptides having the same sequence.
78. The modified EphA4 receptor antagonist according to embodiment 77, wherein the homomultimer is a homodimer of APYCVYR β ASWSC-am (SEQ ID NO: 36), a homodimer of β APYCVYR β ASWSC-am (SEQ ID NO: 47), a homodimer of β APYCVYR β AEWEC-am (SEQ ID NO: 50), a homodimer of D-APYCVYR β ASWSC-am (SEQ ID NO: 52), a homodimer of APYCVWR β ASWSC (SEQ ID NO: 53), a homodimer of APYCVYT β AEWLC (SEQ ID NO: 54), a homodimer of APYCVYN β ATWNC (SEQ ID NO: 55) or a homodimer of APYCVYR β AVWEC (SEQ ID NO: 56).
79. The modified EphA4 receptor antagonist according to embodiment 77 or embodiment 78, wherein each of the two cyclic peptides is covalently linked by a peptide linker.

80. The modified EphA4 receptor antagonist according to embodiment 79, wherein the peptide linker is a tetrapeptide.
81. The modified EphA4 receptor antagonist according to embodiment 80, wherein the tetrapeptide is SEQ ID NO: 70.
82. The modified EphA4 receptor antagonist according to embodiment 81, wherein the homodimer is





83. The modified EphA4 receptor antagonist according to embodiment 76, wherein the heteromultimer is a heterodimer comprising two cyclic peptides each having a different sequence.
84. The modified EphA4 receptor antagonist according to embodiment 83, wherein the heteromultimer is a heterodimer of any of the following APY cyclic peptides: APYCVYRβASWSC-am (SEQ ID NO: 36), βAPYCVYRβASWSC-am (SEQ ID NO: 47), βAPYCVYRβAEWEC-am (SEQ ID NO: 50), D-APYCVYRβASWSC-am (SEQ ID NO: 52), APYCVWRβASWSC (SEQ ID NO: 53), APYCVYTβAEWLC (SEQ ID NO: 54), APYCVYNβATWNC (SEQ ID NO: 55) or APYCVYRβAVWEC (SEQ ID NO: 56).
85. The modified EphA4 receptor antagonist according to embodiment 83 or embodiment 84, wherein each of the two cyclic peptides is covalently linked by a peptide linker.
86. The modified EphA4 receptor antagonist according to embodiment 85, wherein the peptide linker is a tetrapeptide.
87. The modified EphA4 receptor antagonist according to embodiment 86, wherein the tetrapeptide is SEQ ID NO: 70.
88. The modified EphA4 receptor antagonist according to any one of embodiments 1-87, wherein the modified EphA4 receptor antagonist has an association rate constant for an EphA4 receptor of less than $1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, $5 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, less than $5 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, less than $5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ or less than $1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$.
89. The modified EphA4 receptor antagonist according to any one of embodiments 1-88, wherein the modified EphA4 receptor antagonist has an association rate constant for an EphA4 receptor of between $1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ to $1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ to $1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, $1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ to $1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ or $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ to $1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$.
90. The modified EphA4 receptor antagonist according to any one of embodiments 1-89, wherein the modified EphA4 receptor antagonist has a disassociation rate constant for an EphA4 receptor of less than $1 \times 10^{-3} \text{ s}^{-1}$, $5 \times 10^{-3} \text{ s}^{-1}$, less than $1 \times 10^{-4} \text{ s}^{-1}$, less than $5 \times 10^{-4} \text{ s}^{-1}$ or less than $1 \times 10^{-5} \text{ s}^{-1}$.
91. The modified EphA4 receptor antagonist according to any one of embodiments 1-90, wherein the modified EphA4 receptor antagonist has a disassociation rate constant for an EphA4 receptor of between $1 \times 10^{-3} \text{ s}^{-1}$ to $1 \times 10^{-5} \text{ s}^{-1}$, $1 \times 10^{-3} \text{ s}^{-1}$ to $1 \times 10^{-4} \text{ s}^{-1}$ or $1 \times 10^{-4} \text{ s}^{-1}$ to $1 \times 10^{-5} \text{ s}^{-1}$.
92. The modified EphA4 receptor antagonist according to any one of embodiments 1-91, wherein the modified EphA4 receptor antagonist has a disassociation rate constant for an ephrin receptor other than an EphA4 receptor of less than $1 \times 10^0 \text{ M}^{-1} \text{ s}^{-1}$, $5 \times 10^0 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$, less than

- $5 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, less than $5 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$, less than $5 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ or less than $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.
93. The modified EphA4 receptor antagonist according to any one of embodiments 1-92, wherein the modified EphA4 receptor antagonist has a disassociation rate constant for an ephrin receptor other than an EphA4 receptor of at most $1 \times 10^0 \text{ M}^{-1} \text{ s}^{-1}$, at most $5 \times 10^0 \text{ M}^{-1} \text{ s}^{-1}$, at most $1 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$, at most $5 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$, at most $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, at most $5 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, at most $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$, at most $5 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ or at most $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.
94. The modified EphA4 receptor antagonist according to any one of embodiments 1-93, wherein the modified EphA4 receptor antagonist has an equilibrium disassociation rate constant for an EphA4 receptor less than 500 nM, less than 450 nM, less than 400 nM, less than 350 nM, less than 300 nM, less than 250 nM, less than 200 nM, less than 150 nM, less than 100 nM, less than 75 nM, less than 50 nM, less than 25 nM, less than 20 nM, less than 15 nM, less than 10 nM, less than 5 nM, less than 1 nM, less than 0.5 nM, or less than 0.1 nM.
95. The modified EphA4 receptor antagonist according to any one of embodiments 1-94, wherein the modified EphA4 receptor antagonist has an equilibrium disassociation rate constant for an EphA4 receptor of between about 0.1 nM to about 10 nM, about 0.1 nM to about 25 nM, about 0.1 nM to about 75 nM, about 0.1 nM to about 100 nM, about 0.1 nM to about 125 nM, about 0.1 nM to about 150 nM, about 0.5 nM to about 10 nM, about 0.5 nM to about 25 nM, about 0.5 nM to about 75 nM, about 0.5 nM to about 100 nM, about 0.5 nM to about 125 nM, about 0.5 nM to about 150 nM, about 1 nM to about 10 nM, about 1 nM to about 25 nM, about 1 nM to about 75 nM, about 1 nM to about 100 nM, about 1 nM to about 125 nM, about 1 nM to about 150 nM, about 5 nM to about 10 nM, about 5 nM to about 25 nM, about 5 nM to about 75 nM, about 5 nM to about 100 nM, about 5 nM to about 125 nM, about 5 nM to about 150 nM, about 10 nM to about 25 nM, about 10 nM to about 50 nM, about 10 nM to about 75 nM, about 10 nM to about 100 nM, about 10 nM to about 125 nM, about 10 nM to about 150 nM, about 10 nM to about 175 nM or about 10 nM to about 200 nM.
96. The modified EphA4 receptor antagonist according to any one of embodiments 1-95, wherein the modified EphA4 receptor antagonist has an association rate constant for an ephrin-binding pocket of an ephrin receptor other than an EphA4 receptor of less than $1 \times 10^0 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ or less than $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.
97. The modified EphA4 receptor antagonist according to any one of embodiments 1-96, wherein the modified EphA4 receptor antagonist has an association rate constant for an ephrin-binding pocket of an ephrin receptor other than an EphA4 receptor of at most $1 \times 10^0 \text{ M}^{-1} \text{ s}^{-1}$, at most $1 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$, at most $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, at most $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ or at most $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.
98. The modified EphA4 receptor antagonist according to any one of embodiments 1-97, wherein the modified EphA4 receptor antagonist has an association rate constant for an ephrin-binding pocket of an ephrin receptor other than an EphA4 receptor of at least 2-fold more, at least 3-fold more, at least 4-fold more, at least 5-fold more, at least 6-fold more, at least 7-fold more, at least 8-fold more, or at least 9-fold more, at least 10-fold more, at least 20-fold more, at least 30-fold more, at least 40-fold more, at least 50-fold more, at least 60-fold more, at least 70-fold more, at least 80-fold more, at least 90-fold more, at least 100-fold more, at least 200-fold more, at least 300-fold more, at least 400-fold more, at least 500-fold more, at least 600-fold more, at least 700-fold more, at least 800-fold more, at

- least 900-fold more, at least 1,000-fold more, at least 2,500-fold more, at least 5,000-fold more, at least 7,500-fold more or at least 10,000-fold more.
99. The modified EphA4 receptor antagonist according to any one of embodiments 1-98, wherein the modified EphA4 receptor antagonist has an association rate constant for an ephrin-binding pocket of an ephrin receptor other than an EphA4 receptor of at most 1-fold more, at most 2-fold more, at most 3-fold more, at most 4-fold more, at most 5-fold more, at most 6-fold more, at most 7-fold more, at most 8-fold more, or at most 9-fold more, at most 10-fold more, at most 20-fold more, at most 30-fold more, at most 40-fold more, at most 50-fold more, at most 60-fold more, at most 70-fold more, at most 80-fold more, at most 90-fold more, at most 100-fold more, at most 200-fold more, at most 300-fold more, at most 400-fold more, at most 500-fold more, at most 600-fold more, at most 700-fold more, at most 800-fold more, at most 900-fold more, at most 1,000-fold more, at most 2,500-fold more, at most 5,000-fold more, at most 7,500-fold more or at most 10,000-fold more.
100. The modified EphA4 receptor antagonist according to any one of embodiments 1-99, wherein the modified EphA4 receptor antagonist has a binding specificity ratio for the ephrin-binding pocket in the EphA4 ligand binding domain relative to an ephrin-binding pocket of an ephrin receptor other than an EphA4 receptor of at least 2:1, at least 3:1, at least 4:1, at least 5:1, at least 6:1, at least 7:1, at least 8:1, at least 9:1, at least 10:1, at least 15:1, at least 20:1, at least 25:1, at least 30:1, at least 35:1, or at least 40:1.
101. The modified EphA4 receptor antagonist according to any one of embodiments 1-100, wherein the modified EphA4 receptor antagonist reduces EphA4 receptor activity by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100%.
102. The modified EphA4 receptor antagonist according to any one of embodiments 1-101, wherein the modified EphA4 receptor antagonist has a biological half-life of at least 12 hours, at least 18 hours, at least 24 hours, at least 30 hours, at least 36 hours, at least 42 hours, at least 48 hours, at least 54 hours, at least 60 hours, at least 66 hours, at least 72 hours, at least 78 hours, at least 84 hours, at least 90 hours or at least 96 hours.
103. The modified EphA4 receptor antagonist according to any one of embodiments 1-102, wherein the modified EphA4 receptor antagonist has a biological half-life of about 12 hours to about 24 hours, about 12 hours to about 36 hours, about 12 hours to about 48 hours, about 12 hours to about 60 hours, about 12 hours to about 72 hours, about 12 hours to about 84 hours, about 12 hours to about 96 hours, about 24 hours to about 36 hours, about 24 hours to about 48 hours, about 24 hours to about 60 hours, about 24 hours to about 72 hours, about 24 hours to about 84 hours, about 24 hours to about 96 hours, about 36 hours to about 48 hours, about 36 hours to about 60 hours, about 36 hours to about 72 hours, about 36 hours to about 84 hours, about 36 hours to about 96 hours, about 48 hours to about 60 hours, about 48 hours to about 72 hours, about 48 hours to about 84 hours, about 48 hours to about 96 hours, about 60 hours to about 72 hours, about 60 hours to about 84 hours, about 60 hours to about 96 hours, about 72 hours to about 84 hours, about 72 hours to about 96 hours or about 84 hours to about 96 hours.
104. The modified EphA4 receptor antagonist according to any one of embodiments 1-103, wherein the modified EphA4 receptor antagonist has a plasma half-life of at least 12 hours, at least 18 hours, at

least 24 hours, at least 30 hours, at least 36 hours, at least 42 hours, at least 48 hours, at least 54 hours, at least 60 hours, at least 66 hours, at least 72 hours, at least 78 hours, at least 84 hours, at least 90 hours or at least 96 hours.

105. The modified EphA4 receptor antagonist according to any one of embodiments 1-104, wherein the modified EphA4 receptor antagonist has a plasma half-life of about 12 hours to about 24 hours, about 12 hours to about 36 hours, about 12 hours to about 48 hours, about 12 hours to about 60 hours, about 12 hours to about 72 hours, about 12 hours to about 84 hours, about 12 hours to about 96 hours, about 24 hours to about 36 hours, about 24 hours to about 48 hours, about 24 hours to about 60 hours, about 24 hours to about 72 hours, about 24 hours to about 84 hours, about 24 hours to about 96 hours, about 36 hours to about 48 hours, about 36 hours to about 60 hours, about 36 hours to about 72 hours, about 36 hours to about 84 hours, about 36 hours to about 96 hours, about 48 hours to about 60 hours, about 48 hours to about 72 hours, about 48 hours to about 84 hours, about 48 hours to about 96 hours, about 60 hours to about 72 hours, about 60 hours to about 84 hours, about 60 hours to about 96 hours, about 72 hours to about 84 hours, about 72 hours to about 96 hours or about 84 hours to about 96 hours.
106. A pharmaceutical composition comprising one or more modified EphA4 receptor antagonist according to any one of embodiments 1-105.
107. The pharmaceutical composition according to embodiment 106, wherein the one or more EphA4 receptor antagonist are each present in an amount of between about 100 ng to about 1,000 µg.
108. The pharmaceutical composition according to embodiment 106 or embodiment 107, wherein the pharmaceutical composition further comprises one or more pharmaceutical acceptable carriers.
109. A method of treating an EphA4-based disease, disorder or pathology, the method comprising administering a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 or a pharmaceutical composition as defined in any one of embodiments 106-108 to an individual in need thereof, wherein administration reduces one or more symptoms associated with the EphA4-based disease, disorder or pathology.
110. The method according to embodiment 109, wherein the EphA4-based disease, disorder or pathology comprises a condition, a disease, a disorder and/or pathology where a pathophysiology effect is due to dysregulation of EphA4 signaling in a manner that causes EphA4 signaling hyperactivity in cells or spatially or temporally aberrant EphA4 signaling.
111. The method according to embodiment 109 or embodiment 110, wherein the EphA4-based disease, disorder or pathology is a neurodegenerative disease, a hearing loss, a promotion of nerve regeneration, a promotion of neuroprotection, or a cancer.
112. A method of treating a neurodegenerative disease, the method comprising administering a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 or a pharmaceutical composition as defined in any one of embodiments 106-108 to an individual in need thereof, wherein administration reduces one or more symptoms associated with the neurodegenerative disease.
113. The method according to embodiment 112, wherein the neurodegenerative disease is an Alexander disease, an Alper's disease, Alzheimer's disease, an amyotrophic lateral sclerosis, an ataxia telangiectasia, a Canavan disease, a Cockayne syndrome, a corticobasal degeneration, a Creutzfeldt-Jakob disease, a Guillain-Barre Syndrome a HIV-induced neurodegeneration, a

Huntington disease, a Kennedy's disease, a Krabbe disease, a Lewy body dementia, a Machado-Joseph disease, a multiple sclerosis, a Parkinson's disease, a Pelizaeus-Merzbacher disease, a Pick's disease, a primary lateral sclerosis, a Refsum's disease, a Sandhoff disease, a Schilder's disease, a spinal cord injury, a Steele-Richardson-Olszewski disease, a stroke, a tabes dorsalis and/or a traumatic brain injury.

114. The method according to embodiment 112 or embodiment 113, wherein the one or more symptoms include abnormal movement, abnormal sensation, limb grasping, muscle weakness, atrophy, paralysis, abnormal inhibition of axon growth, abnormal axonal transport, aberrant synaptic function, synaptic transmission loss, impaired synaptic plasticity, synaptic loss, neuronal degeneration, motor neuron degeneration, motor neuron loss, poor neuronal survival, memory loss, impaired learning, dementia, β -amyloid plaque deposits, aberrant neurofilament accumulation, reactive astroglia and/or reactive microglia.
115. A method of treating a hearing loss, the method comprising administering a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 or a pharmaceutical composition as defined in any one of embodiments 106-108 to an individual in need thereof, wherein administration reduces one or more symptoms associated with the hearing loss.
116. The method according to embodiment 115, wherein administration of the pharmaceutical composition promotes generation of new cochlear sensory hair cells.
117. The method according to embodiment 115 or embodiment 116, wherein the one or more symptoms include decreased hearing sensitivity and sensorineural hearing loss.
118. A method of promoting nerve regeneration, the method comprising administering a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 or a pharmaceutical composition as defined in any one of embodiments 106-108 to an individual in need thereof in an amount sufficient to stimulate or facilitate neuronal differentiation and/or growth, thereby promoting nerve regeneration.
119. A method of promoting neuroprotection, the method comprising administering a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 or a pharmaceutical composition as defined in any one of embodiments 106-108 to an individual in need thereof in an amount sufficient to protect neurons or nerve tissue from damage, thereby promoting neuroprotection.
120. A method of treating a cancer, the method comprising administering a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 or a pharmaceutical composition as defined in any one of embodiments 106-108 to an individual in need thereof, wherein administration reduces one or more symptoms associated with the cancer.
121. The method according to embodiment 120, wherein the cancer comprises a condition, where a pathophysiology effect is due to dysregulation of EphA4 signaling in a manner that causes EphA4 signaling hyperactivity in cells or spatially or temporally aberrant EphA4 signaling.
122. The method according to embodiment 120 or embodiment 121, wherein the cancer is a glioblastoma, a gastric cancer, a pancreatic cancer, a prostate cancer, a breast cancer, a liver cancer, a leukemia or a Sezary syndrome.
123. Use of a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 in the manufacture of a medicament for treating an EphA4-based disease, disorder or pathology.

124. Use of a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 or a pharmaceutical composition as defined in any one of embodiments 106-108 in the treatment of an EphA4-based disease, disorder or pathology.
125. The use according to embodiment 123 or embodiment 124, wherein the EphA4-based disease, disorder or pathology comprises a condition, a disease, a disorder and/or pathology where a pathophysiology effect is due to dysregulation of EphA4 signaling in a manner that causes EphA4 signaling hyperactivity in cells or spatially or temporally aberrant EphA4 signaling.
126. The use according to any one of embodiments 123-125, wherein the EphA4-based disease, disorder or pathology is a neurodegenerative disease, a hearing loss, a promotion of nerve regeneration, a promotion of neuroprotection, or a cancer.
127. Use of a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 in the manufacture of a medicament for treating a neurodegenerative disease.
128. Use of a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 or a pharmaceutical composition as defined in any one of embodiments 106-108 in the treatment of a neurodegenerative disease.
129. The use according to embodiment 127 or embodiment 128, wherein the neurodegenerative disease is an Alexander disease, an Alper's disease, Alzheimer's disease, an amyotrophic lateral sclerosis, an ataxia telangiectasia, a Canavan disease, a Cockayne syndrome, a corticobasal degeneration, a Creutzfeldt-Jakob disease, a Guillain-Barre Syndrome, a HIV-induced neurodegeneration, a Huntington disease, a Kennedy's disease, a Krabbe disease, a Lewy body dementia, a Machado-Joseph disease, a multiple sclerosis, a Parkinson's disease, a Pelizaeus-Merzbacher disease, a Pick's disease, a primary lateral sclerosis, a Refsum's disease, a Sandhoff disease, a Schilder's disease, a spinal cord injury, a Steele-Richardson-Olszewski disease, a stroke, a tabes dorsalis and/or a traumatic brain injury.
130. Use of a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 in the manufacture of a medicament for treating a hearing loss.
131. Use of a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 or a pharmaceutical composition as defined in any one of embodiments 106-108 in the treatment of a hearing loss.
132. The use according to embodiment 130 or embodiment 131, wherein the medicament, the modified EphA4 receptor antagonist, or the pharmaceutical composition promotes generation of new cochlear sensory hair cells.
133. Use of a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 in the manufacture of a medicament for promoting nerve regeneration.
134. Use of a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 or a pharmaceutical composition as defined in any one of embodiments 106-108 in the promotion of nerve regeneration.
135. Use of a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 in the manufacture of a medicament for promoting neuroprotection.

136. Use of a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 or a pharmaceutical composition as defined in any one of embodiments 106-108 in the promotion of neuroprotection.
137. Use of a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 in the manufacture of a medicament for treating cancer.
138. Use of a modified EphA4 receptor antagonist as defined in any one of embodiments 1-105 or a pharmaceutical composition as defined in any one of embodiments 106-108 in the treatment of cancer.
139. The method according to embodiment 137 or embodiment 138, wherein the cancer comprises a condition where a pathophysiology effect is due to dysregulation of EphA4 signaling in a manner that causes EphA4 signaling hyperactivity in cells or spatially or temporally aberrant EphA4 signaling.
140. The method according to any one of embodiments 137-139, wherein the cancer is a glioblastoma, a gastric cancer, a pancreatic cancer, a prostate cancer, a breast cancer, a liver cancer, a leukemia or a Sezary syndrome.

EXAMPLES

[0143] The following non-limiting examples are provided for illustrative purposes only in order to facilitate a more complete understanding of representative embodiments now contemplated. These examples should not be construed to limit any of the embodiments described in the present specification, including those pertaining to the compounds, pharmaceutical compositions, or methods or uses of treating a disorder disclosed herein.

Example 1

Synthesis of APY Cyclic Peptides

[0144] APY cyclic peptides with a free amine at the N terminus and either an amidated C terminus or a free carboxylic acid at the C terminus were obtained from a commercial vendor (GenScript). Peptide amides were synthesized using manual synthetic cycles for 9-fluorenylmethoxycarbonyl (Fmoc) solid phase peptide synthesis. Typically syntheses were performed on a 0.2 mmol scale using Rink amide resin (0.69 mmol/g, Novabiochem). Couplings were performed for 20 minutes using Fmoc protected amino acids (1.1 mmol) dissolved in 2.5 mL 0.4 M HCTU (1.0 mmol) and DIEA (261 μ L, 1.5 mmol). Fmoc deprotection was facilitated by treating with an excess of 20% 4-Me piperidine for a total of 7 min. Peptides were deprotected and cleaved from resin using TFA:TIS:EDT:H₂O (92.5:2.5:2.5:2.5) while agitating for 2 hours at room temperature. The TFA was 80% evaporated under N₂, precipitated using ice-cold diethyl ether, filtered and further washed with cold ether. The crude peptides were dissolved in 45% acetonitrile/water, 0.05% TFA and lyophilized. Samples were solubilized with 20% acetic acid prior to analysis by reversed-phase high-performance liquid chromatography (HPLC) and electrospray ionization mass spectrometry. If the sample was sufficiently homogeneous, it was oxidatively folded in 0.1 M NH₄HCO₃ (pH 8) at a peptide concentration of 0.1 mg/mL followed by HPLC purification. If significant synthetic byproducts were present, the peptide was purified by HPLC prior to oxidation. The identity and

purity of the peptides (>95%) were verified by reversed-phase HPLC and electrospray ionization mass spectrometry. For further analysis, peptides were dissolved in DMSO or water at a concentration of about 10 mM and the concentration was verified by measuring the optical density at 280 nm.

Example 2

Preparation of Lipidated APY Cyclic Peptides

[0145] This example describes one way to conjugate a lipid to an APY cyclic peptide disclosed herein. As a general procedure, an APY cyclic peptide disclosed herein was synthesized by replacing Arg7 with a Lys or by adding a GGKG tetrapeptide (SEQ ID NO: 70) to the carboxyl terminus. In addition, the N-terminus was protected to block lipidation at this site. An acylation reaction was then performed where the free amino functional group present in the Lys 7 or the lysine of the GGKG tetrapeptide of the APY-Lys7 and APY-GGKG cyclic peptides was then reacted with a functional group present in the fatty acid. The resulting product is an APY cyclic peptide conjugated with a fatty acid.

[0146] For example, β Ala1-PY-Lys7- β Ala8.am (SEQ ID NO: 48) was synthesized using Fmoc solid-phase synthesis. β Ala1-PY-Lys7- β Ala8.am peptides were then reacted with the fatty acid octanoic acid (C8), lauric acid (C12) or palmitic acid (C16) to produce the following lipidated APY cyclic peptides: β Ala1-PY-Lys7(octanoyl)- β Ala8.am (SEQ ID NO: 71), β Ala1-PY-Lys7(octanoyl-Gly)- β Ala8.am (SEQ ID NO: 72), β Ala1-PY-Lys7(lauroyl)- β Ala8.am (SEQ ID NO: 73), β Ala1-PY-Lys7(lauroyl-Gly)- β Ala8.am (SEQ ID NO: 74), β Ala1-PY-Lys7(lauroyl- β Asp)- β Ala8.am (SEQ ID NO: 75), β Ala1-PY-Lys7(lauroyl- γ Glu)- β Ala8.am (SEQ ID NO: 76) and β Ala1-PY-Lys7(palmitoyl- γ Glu)- β Ala8.am (SEQ ID NO: 77).

[0147] As another example, β Ala1-PY- β Ala8-GGKG.am (SEQ ID NO: 78) was synthesized using Fmoc solid-phase synthesis. β Ala1-PY-Lys7- β Ala8.am peptides were then reacted with the fatty acid octanoic acid (C8), lauric acid (C12) or palmitic acid (C16) to produce the following lipidated APY cyclic peptides: β Ala1-PY- β Ala8-GGK(octanoyl)-G.am (SEQ ID NO: 79), β Ala1-PY- β Ala8-GGK(lauroyl)-G.am (SEQ ID NO: 80), β Ala1-PY- β Ala8-GGK(lauroyl- β Asp)-G.am (SEQ ID NO: 81), β Ala1-PY- β Ala8-GGK(lauroyl- γ Glu)-G.am (SEQ ID NO: 82) and β Ala1-PY- β Ala8-GGK(palmitoyl- γ Glu)-G.am (SEQ ID NO: 83).

[0148] As another example, DAla1-PY- β Ala8-GGKG.am (SEQ ID NO: 88) was synthesized using Fmoc solid-phase synthesis. DAla1-PY- β Ala8-GGKG.am peptides were then reacted with the fatty acid octanoic acid (C8) to produce the lipidated APY cyclic peptides: DAla1-PY- β Ala8-GGK(octanoyl)-G.am (SEQ ID NO: 88).

Example 3

Preparation of PEGylated APY Cyclic Peptides

[0149] This example describes one way to conjugate a poly(ethylene glycol) (PEG) to an APY cyclic peptide disclosed herein.

[0150] PEG-NHS and PEG-maleimide will be purchased from a commercial supplier (Thermo Scientific). In addition, the N-terminus of an APY cyclic peptide was protected to block PEGylation at this site.

[0151] A PEG-APY cyclic peptide conjugate will be prepared by adding a molar ratio of 5:1 to 20:1 of PEG-NHS (24):APY cyclic peptide containing a lysine or other appropriate reactive amino acid in 150 mM PBS (pH 7.2) and incubating the mixture at 20°C for 30 minutes (or on ice for 2 hours). After the reaction, PEG-APY cyclic peptide conjugates will be characterized by SDS-PAGE and the conjugation yield will be determined by HPLC-size exclusion chromatography. Controls included subjecting the APY cyclic peptide to the conjugation procedure in the absence of any PEG-NHS. PEG-NH₂ was also subjected to the conjugation procedure in the absence of the APY cyclic peptide. Using a similar strategy, this conjugation reaction can be performed using PEG-NHS of different molecular weights.

[0152] A PEG-APY cyclic peptide conjugate will be prepared by adding a molar ratio of 5:1 to 20:1 of PEG-maleimide (24):APY cyclic peptide containing a cysteine or other appropriate reactive amino acid in 150 mM PBS (pH 7.2) and incubating the mixture at 20°C for 2 hours minutes (or on ice for about 12 hours). After the reaction, PEG-APY cyclic peptide conjugates will be characterized by SDS-PAGE and the conjugation yield will be determined by HPLC-size exclusion chromatography. Controls included subjecting the APY cyclic peptide to the conjugation procedure in the absence of any PEG-NHS. PEG-NH₂ was also subjected to the conjugation procedure in the absence of the APY cyclic peptide. Using a similar strategy, this conjugation reaction can be performed using PEG-NHS of different molecular weights.

Example 4

Preparation of Polysialylated APY Cyclic Peptides

[0153] This example describes ways to conjugate PSA polymers to an APY cyclic peptide disclosed herein.

[0154] APY cyclic peptides disclosed herein were prepared as described in Example 1. The N-terminus of an APY cyclic peptide was protected to block PEGylation at this site.

[0155] To prepare activated PSA, freshly prepared 0.02 M sodium metaperiodate (NaIO₄; 6 fold molar excess over PSA) solution will be mixed with PSA (35 kDa) at 20°C and the reaction mixture will be stirred for 15 min in the dark. The oxidized PSA will be precipitated with 70% (final concentration) ethanol and by centrifuging the mixture at 3000g for 20 minutes. The supernatant will be removed and the pellet will be dissolved in a minimum quantity of deionized water. The PSA will again precipitated with 70% ethanol and will then centrifuged at 12,000 g. The pellet containing the activated PSA will be dissolved in a minimum quantity of water, lyophilized and stored at -20°C until further use. Using a similar strategy, activated PSA of different molecular weights can be produced.

[0156] To prepare PSA-NH₂, 10-100 mg/mL activated PSA (35 kDa) will be dissolved in deionized water with a 300-fold molar excess of NH₄Cl and then NaCNBH₄ (5 M stock in 1 N NaOH(aq)) will be added at a final concentration of 5 mg/mL. The mixture will be incubated at room temperature for 5 days. A control reaction will be also set up with PSA instead of activated PSA. The resulting PSA amine derivative product will be precipitated by the addition of 5 mL ice-cold ethanol. The precipitate will be recovered by centrifugation at 4000 rpm, 30 minutes, room temperature. The pellet will be retained and resuspended in 2 mL of deionised water, then will be precipitated again with 5 mL of ice-cold ethanol in a 10 mL ultracentrifuge tube. The precipitate will be collected by centrifugation at 30,000 rpm for 30 minutes at room temperature. The pellet will again resuspended in 2 mL of deionized water and freeze-dried. Using a similar strategy, PSA-NH₂ of different molecular weights can be produced.

[0157] To prepare PSA-SH, 10-100 mg/mL activated PSA (35 kDa) will be dissolved in deionized water with a 100-fold molar excess of cystamine and then NaCNBH₄ (5 M stock in 1 N NaOH(aq)) will be added at a final concentration of 5 mg/mL. The mixture will be incubated at room temperature for 5 days, and then will be treated with 50 mM DTT at 37°C for 1 hour. Alternatively, 10-100 mg/mL activated PSA will be dissolved in 10 mM PBS with 1 mM EDTA (pH 8.0) with a 50-fold molar excess of 2-iminothiolane and the reaction allowed to proceed for 1 h at 25°C. Unreacted 2-iminothiolate is removed by gel filtration on a sephadex G25 column equilibrated with the reaction buffer. A control reaction will be also set up with PSA instead of activated PSA. The resulting PSA sulfhydryl derivative product will be precipitated by the addition of 5 mL ice-cold ethanol. The precipitate will be recovered by centrifugation at 4000 rpm, 30 minutes, room temperature. The pellet will be retained and resuspended in 2 mL of deionized water, then will be precipitated again with 5 mL of ice-cold ethanol in a 10 mL ultracentrifuge tube. The precipitate will be collected by centrifugation at 30,000 rpm for 30 minutes at room temperature. The pellet will again resuspended in 2 mL of deionized water, will be subjected to size exclusion chromatography on sepharose G25, and the elute will be collected and freeze-dried. Using a similar strategy, PSA-SH of different molecular weights can be produced.

[0158] To prepare PSA-NHS, 15-20 mg of PSA-NH₂ (35 kDa) will be dissolved in 150 mM PBS (pH 7.2) and then 50 to 75 molar equivalents of BS³ in 150 mM PBS (pH 7.2) will be added to the PSA-NH solution. The mixture will be vortexed for 5 seconds and then will be reacted for 30 minutes at 20°C. The PSA-NHS product will be purified by PD-10 column using PBS (pH 7.2) as eluent and used immediately for site-specific conjugation to the NH₂ groups in an APY cyclic peptide disclosed herein. Determination of the PSA concentration from the PD 10 fractions will be achieved by analyzing the sialic acid content using the resorcinol assay. The NHS content on the PSA polymer will be measured by UV spectroscopy by analyzing the PSA and NHS reaction solution at 260 nm and also by thin layer chromatography with visualization at 254 nm. Using a similar strategy, PSA-NHS of different molecular weights can be produced.

[0159] Alternatively to prepare PSA-NHS, 15-20 mg of PSA-NH₂ (35 kDa) will be either dissolved in >95% DMSO and then 75 molar equivalents of DSG in DMSO will be added to the PSA-NH solution. The mixture will be vortexed for 5 seconds and then will be reacted for 30 minutes at 20°C. The PSA-NHS product will be purified either with dioxane precipitation (x2) or by PD-10 column using PBS (pH 7.2) as

eluent and will be used immediately for site-specific conjugation to the NH₂ groups an APY cyclic peptide disclosed herein. As before determination of the PSA concentration from the PD-10 fractions was measured using the resorcinol assay. The NHS content on the PSA polymer will be measured by UV spectroscopy (260 nm) and by thin layer chromatography (254 nm). Using a similar strategy, PSA-NHS of different molecular weights can be produced.

[0160] To prepare PSA-I, 40 mg of PSA-NH₂ (35 kDa) will be dissolved in 150 mM PBS (pH 7.2) and then 5 mg of N-succinimidyl iodoacetate (SIA) will be added to the PSA-NH solution. The mixture will be vortexed for 5 seconds and then will be reacted for 60 minutes at 25°C in the dark. The PSA-SIA product will be purified using a HIGHTRAP™ Desalting column (AP Bioscience) using PBS (pH 7.2) as eluent and used immediately for site-specific conjugation to the thiol groups in an APY cyclic peptide disclosed herein. Determination of the PSA concentration from the HIGHTRAP™ fractions will be achieved by analyzing the sialic acid content using the resorcinol assay. Using a similar strategy, PSA-I of different molecular weights can be produced.

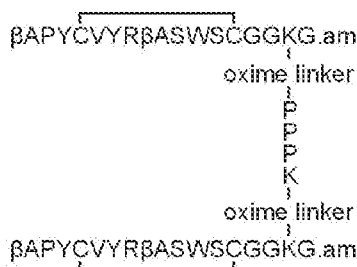
[0161] A PSA-APY cyclic peptide conjugate will be prepared by adding a molar ratio of 25:1 to 50:1 of PSA-NHS (35 kDa):APY cyclic peptide in 150 mM PBS (pH 7,2) and incubating the mixture in an excess of BS³ for 30 minutes at 20°C After the reaction, PSA-APY cyclic peptide conjugates will be characterized by SDS-PAGE and the conjugation yield will be determined by HPLC-size exclusion chromatography. Controls included subjecting the APY cyclic peptide to the conjugation procedure using BS³ in the absence of any PSA-NHS. PSA-NH₂ was also subjected to the conjugation procedure using BS³ in the absence of the APY cyclic peptide. Using a similar strategy, this conjugation reaction can be performed using PSA-NHS of different molecular weights.

[0162] A PSA-APY cyclic peptide conjugate will be prepared by adding a molar ratio of 25:1 to 50:1 of PSA-NHS (35 kDa):APY cyclic peptide in 150 mM PBS (pH 7,2) and incubating the mixture in an excess of DSG for 30 minutes at 20°C. After the reaction, PSA-APY cyclic peptide conjugates will be characterized by SDS-PAGE and the conjugation yield will be determined by HPLC-size exclusion chromatography. Controls included subjecting the APY cyclic peptide to the conjugation procedure using BS³ in the absence of any PSA-NHS. PSA-NH₂ was also subjected to the conjugation procedure using BS³ in the absence of the APY cyclic peptide. Using a similar strategy, this conjugation reaction can be performed using PSA-NHS of different molecular weights.

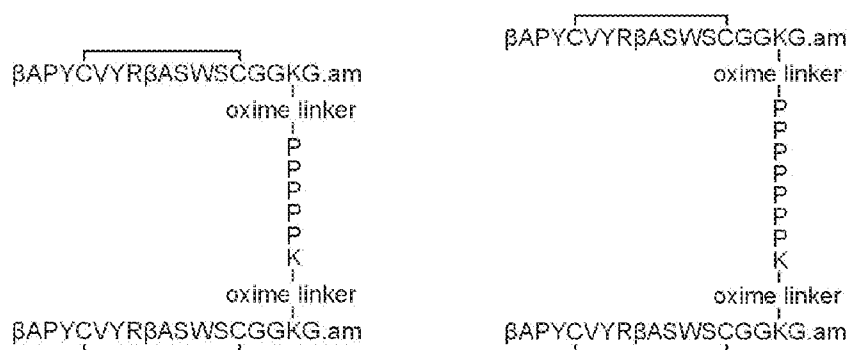
[0163] A PSA-APY cyclic peptide conjugate will be prepared by adding a molar ratio of 15:1 of PSA-I (35 kDa):APY cyclic peptide in 150 mM PBS (pH 7,2) and incubating the reaction at room temperature for 60 minutes with gentle mixing in the dark. After the reaction, PSA-APY cyclic peptide conjugates will be characterized by SDS-PAGE and the conjugation yield will be determined by HPLC-size exclusion chromatography. Controls included subjecting the APY cyclic peptide to the conjugation procedure in the absence of any PSA-I. Using a similar strategy, this conjugation reaction can be performed using PSA-I of different molecular weights.

Example 5
Construction of APY Cyclic Dimers

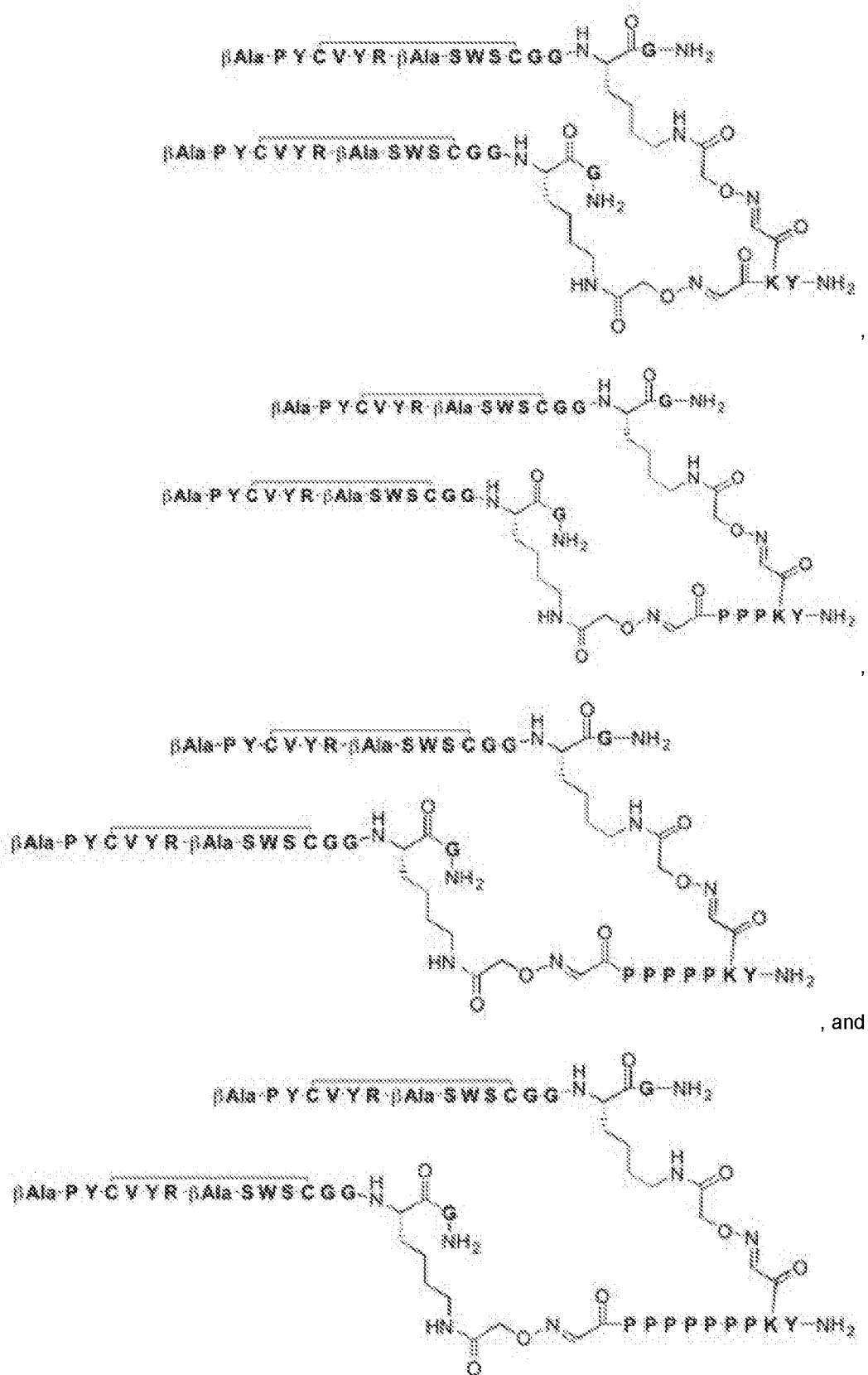
[0164] This example describes one way to make a dimer using an APY cyclic peptide disclosed herein. As a general procedure, an APY cyclic peptide disclosed herein is synthesized with a GGKG tetrapeptide (SEQ ID NO: 70) added to the carboxyl terminus. These APY-GGKG cyclic peptides are then reacted with an amideP_nK(amide)G.am peptide, where n is 3-7 in the presence of oxime. Oxime reacts with the free amino functional group present in the lysine of the GGKG tetrapeptide and the free amino functional groups present in the amideP_nK(amide)G.am peptide. The resulting product is a dimer where each APY cyclic peptide is joined to another via an oxime-P_nK-oxime linker. For example, βAPYCVYRβASWSCGGKG.am (SEQ ID NO: 79) was synthesized using Fmoc solid-phase synthesis. βAPYCVYRβASWSCGGKG.am peptides are then reacted with amidePPPK(amide)G.am peptides (SEQ ID NO: 84) in the presence of oxime to produce the following homodimer:



Similarly, βAPYCVYRβASWSCGGKG.am (SEQ ID NO: 79) can be reacted with amidePPPPPK(amide)G.am peptides (SEQ ID NO: 85) or amidePPPPPPPK(amide)G.am peptides (SEQ ID NO: 86) in the presence of oxime to produce the following homodimers:



Similarly, βAPYCVYRβASWSCGGKG.am (SEQ ID NO: 79) can be reacted with amideK(amide)Y.am, amidePPPK(amide)Y.am (SEQ ID NO: 102), amidePPPPPK(amide)Y.am peptides (SEQ ID NO: 103) or amidePPPPPPPK(amide)Y.am peptides (SEQ ID NO: 104) in the presence of oxime to produce the following homodimers:



Example 6

Construction of anti-TfR-APY Cyclic Peptide Conjugates

[0165] An anti-TfR-APY cyclic peptide construct will be engineered by fusing a sc Fab fragment of an antibody against the mTfR to the C terminus of an APY cyclic peptide disclosed herein using standard molecular genetic techniques.

Example 7

Structure-Guided Optimization of APY Cyclic Peptide Antagonists

[0166] To assess the effects the various modifications had on the activity of an APY cyclic peptide, the ability of modified APY cyclic peptides to inhibit ephrin-A5 binding to EphA4 was measured using ELISAs. To determine peptide IC₅₀ values for inhibition of EphA4-ephrin-A5 binding, protein A coated 96-well plates (Pierce/Thermo Scientific) were incubated with 1 µg/mL EphA4 Fc in 80 µl/well TBST (50 mM Tris HCl, 150 mM NaCl, pH 7.5 containing 0.01 % Tween-20) for 1 hour at room temperature. The wells were washed 3 times with TBST and incubated for 1.5 hours at room temperature with 0.05 nM ephrin-A5 alkaline phosphatase (AP) and different concentrations of peptides in 40 µl/well TBST. The wells were then washed and bound ephrin-A5 AP was quantified by adding 1 mg/mL p-nitrophenylphosphate substrate (Pierce/ThermoScientific) diluted in SEAP buffer (105 mM diethanolamine, 0.5 mM MgCl₂, pH 9.8). OD₄₀₅ was measured and the absorbance from wells coated with Fc was subtracted as background.

[0167] Several lipidated APY cyclic peptides exhibited significant inhibition of ephrin-A5 binding to EphA4. For example, βAla1-PY-Lys7(octanoyl-Gly)-βAla8.am (SEQ ID NO: 72), βAla1-PY-βAla8-GGK(octanoyl)-G.am (SEQ ID NO: 79), βAla1-PY-βAla8-GGK(lauroyl-βAsp)-G.am (SEQ ID NO: 81) and βAla1-PY-βAla8-GGK(lauroyl-γGlu)-G.am (SEQ ID NO: 82) each specifically inhibit EphA4-ephrin binding with IC₅₀ values of 52 nM or lower (Table 1). More dramatically, βAla1-PY-Lys7(octanoyl)-βAla8.am (SEQ ID NO: 71) specifically inhibits EphA4-ephrin binding with an IC₅₀ value of about 38 nM whereas βAla1-PY-Lys7(octanoyl)-βAla8-GGRG.am (SEQ ID NO: 87) specifically inhibits EphA4-ephrin binding with an IC₅₀ value of about 31 nM (Table 1).

[0168] Furthermore, these results indicate that formation of APY cyclic peptide dimers dramatically improve EphA4 inhibitory activity (Table 1). For example, APY-d3.am-dimer (3Pro) specifically inhibits EphA4-ephrin binding with an IC₅₀ value of about 0.39 nM in ELISA, APY-d3.am-dimer (5Pro) specifically inhibits EphA4-ephrin binding with an IC₅₀ value of about 0.64 nM in ELISA, while APY-d3.am-dimer (7Pro) specifically inhibits EphA4-ephrin binding with an IC₅₀ value of about 0.37 nM in ELISA. Thus, sub nanomolar concentrations of APY cyclic APY dimers can inhibit EphA5 binding to EphA4.

Peptide	SEQ ID NO:	IC ₅₀ ± SE (n) ^a (nM)	K _D (nM)	Selectivity (µM)
APY	2	2,900 ± 300 (9)	1,400	> 15-fold
βAla1-PY-Lys7-βAla8.am	32	70 ± 17 (5)	nd	nd
βAla1-PY-Lys7(octanoyl)-βAla8.am	71	38 ± 11 (6)	nd	> 60-fold
βAla1-PY-Lys7(octanoyl)-βAla8-GGRG.am	87	31 ± 6 (5)	27	~ 300-fold

β Ala1-PY-Lys7(octanoyl-Gly)- β Ala8.am	72	52 $\pm$ 15 (5)	23	~ 100-fold
β Ala1-PY-Lys7(lauroyl)- β Ala8.am	73	392 $\pm$ 93 (5)	nd	nd
β Ala1-PY-Lys7(lauroyl-Gly)- β Ala8.am	74	620 $\pm$ 112 (5)	nd	nd
β Ala1-PY-Lys7(lauroyl- β Asp)- β Ala8.am	75	127 $\pm$ 17 (8)	nd	nd
β Ala1-PY-Lys7(lauroyl- γ Glu)- β Ala8.am	76	118 $\pm$ 24 (5)	nd	nd
β Ala1-PY-Lys7(palmitoyl- γ Glu)- β Ala8.am	77	2,160 $\pm$ 616 (5)	nd	nd
DAla1-PY- β Ala8.am	36	50 $\pm$ 4 (5)	45	> 150-fold
DAla1-PY- β Ala8-GGKG.am	88	nd	nd	nd
DAla1-PY- β Ala8-GGK(octanoyl)-G.am	89	64 $\pm$ 6 (6)	nd	> 150-fold
APY- β Ala8.am (APY-d2)	20	27 $\pm$ 2 (25)	30	> 120-fold
APY- β Ala8-GGKG.am	90	52 $\pm$ 13 (3)	nd	nd
β Ala1-PY- β Ala8.am (APY-d3)	30	19 $\pm$ 2 (23)	27 $\pm$ 5 (3)	> 300-fold
APY-DAla8.am (APY-d4)	34	12 $\pm$ 2 (5)	19 $\pm$ 1 (2)	> 300-fold
β Ala1-PY- β Ala8-GGKG.am	78	nd	nd	nd
β Ala1-PY- β Ala8-GGK(octanoyl)-G.am	79	51 $\pm$ 8 (5)	60	> 200-fold
β Ala1-PY- β Ala8-GGK(lauroyl)-G.am	80	312 $\pm$ 37 (9)	nd	nd
β Ala1-PY- β Ala8-GGK(lauroyl- β Asp)-G.am	81	50 $\pm$ 10 (4)	nd	nd
β Ala1-PY- β Ala8-GGK(lauroyl- γ Glu)-G.am	82	51 $\pm$ 12 (4)	nd	nd
β Ala1-PY- β Ala8-GGK(lauroyl- γ Glu- γ Glu)-G.am	97	32 $\pm$ 3 (3)	nd	nd
β Ala1-PY- β Ala8-GGK(myristoyl- γ Glu- γ Glu)-G.am	98	92 $\pm$ 12 (3)	nd	nd
β Ala1-PY- β Ala8-GGK(palmitoyl- γ Glu)-G.am	83	389 $\pm$ 76 (5)	nd	nd
β Ala1-PY- β Ala8-GGK(palmitoyl- γ Glu- γ Glu)-G.am	99	123 $\pm$ 25 (3)	nd	nd
β Ala1-PY- β Ala8-GGGSK(palmitoyl- γ Glu- γ Glu)-G.am	100	194 $\pm$ 29 (3)	nd	nd
APY-dimer (3Pro)	—	0.39 $\pm$ 0.05 (5)	nd	> 1,200-fold
APY-dimer (5Pro)	—	0.64 $\pm$ 0.10 (8)	nd	> 600-fold
APY-dimer (7Pro)	—	0.37 $\pm$ 0.06 (8)	nd	> 1,200-fold
^a n = number of experiments				
^b nd = not determined				

[0169] Complementary determination of dissociation constant (K_D) values for peptide binding to the EphA4 ligand binding domain was confirmed using isothermal titration calorimetry (ITC). The EphA4 ligand binding domain and APY cyclic peptides were diluted to obtain a final buffer containing 5% DMSO in 10 mM Hepes, pH 7.6 and 100 mM NaCl. Isothermal Titration Calorimetry (ITC) experiments were carried out using an ITC200 calorimeter (Microcal). Two μ L aliquots of a 1 mM peptide solution were injected into the cell containing 205 μ L EphA4 ligand-binding domain solution at a concentration of 65-95 μ M. Experimental data were analyzed using the Origin software package (Microcal). The ITC analysis confirmed that the binding affinity (K_D) of the best peptides is in the 20-30 nanomolar range (Table 1).

[0170] To assess the Eph receptor selectivity of APY cyclic peptides disclosed herein, Eph receptor Fc fusion proteins were immobilized at 1 μ g/mL on protein A-coated wells and incubated with 0.05 nM ephrin-A5 AP (for EphA receptors) or ephrin-B2 AP (for Eph B receptors) in the presence or in the absence of the peptide. Ephrin-A5 AP and ephrin-B2 AP for the ELISAs were produced in transiently transfected HEK293T cells according to the method disclosed in Lamberto, *et al.*, *Distinctive Binding of Three Antagonistic Peptides to the Ephrin-Binding Pocket of the EphA4 Receptor*, Biochem J. 445: 47-56

(2012), which is hereby incorporated by reference in its entirety. Bound ephrin-A5 values are normalized to that for bound ephrin-A5 in the absence of peptide and IC₅₀ values are indicated under each curve.

[0171] Importantly, despite the increased binding affinity, modified APY cyclic peptides remain highly selective for EphA4. ELISA measuring inhibition of ephrin-A5 AP binding to immobilized EphA Fc receptors and ephrin-B2 AP binding to EphB Fc receptors shows that several lipidated APY cyclic peptides selectively inhibits ephrin binding to EphA4, including β Ala1-PY-Lys7(octanoyl)- β Ala8.am, β Ala1-PY-Lys7(octanoyl)- β Ala8-GGRG.am, β Ala1-PY-Lys7(octanoyl-Gly)- β Ala8.am, DAla1-PY- β Ala8-GGK(octanoyl)-G.am, β Ala1-PY- β Ala8-GGK(octanoyl)-G.am. Furthermore, these results indicate that APY cyclic peptide dimers remain highly selective for EphA4 (Table 1). For example, APY-d3.am-dimer (3Pro), APY-d3.am-dimer (5Pro) and APY-d3.am-dimer (7Pro) each selectively inhibits ephrin binding to EphA4 at levels from 600-fold to 1,200-fold (Table 1). In addition, the APY cyclic peptides disclosed herein do not inhibit other Eph receptors when used at a concentration of about 100-fold higher than the IC₅₀ value for EphA4. For example, no appreciable APY cyclic peptide binding was detected for the ephrin receptors EphA2, EphA3, EphA5, EphA6, EphA7, EphA8, EphB1, EphB2, EphB3, EphB4 or EphB6.

Example 8

Submicromolar Amounts of APY Cyclic Peptides Inhibit EphA4 Activation in Cells

[0172] To assess the antagonistic potency of modified APY cyclic peptides disclosed herein in live cells, EphA4 receptor-mediate phosphorylation was determined using a cell culture assay. EphA4 was immunoprecipitated from stably transfected human embryonal kidney (HEK293) cells treated with ephrin-A5 Fc (+) or Fc control (-) in the presence of various concentrations of modified APY cyclic peptides disclosed herein. The immunoprecipitates were probed for phosphotyrosine (PTyr) and reprobed for EphA4. These experiments revealed that the concentrations of the best APY cyclic peptides necessary to inhibit EphA4 biological activities in cells will be about 0.5 μ M to about 1 μ M. Thus, these results indicate that the modified APY cyclic peptides disclosed herein are also a potent inhibitor of ephrin-induced EphA4 activation in cells.

[0173] Impaired axon sprouting and lack of reinnervation are regarded as part of the pathology underlying neurodegenerative diseases such as ALS, ultimately causing neuronal cell death. Because growth cone collapse is linked to the failure of injured axons to sprout and regenerate, the ability of modified APY cyclic peptides to inhibit the collapse of neuronal growth cones (enlarged structures at the leading tip of axons) will be assessed using used nasal retinal explants, where ephrin-A5-induced collapse depends on EphA4 activation and can be blocked by 5 μ M KYL peptide. Explants from embryonic day 6 (E6) chicken nasal retinas will be cultured on 35 mm glass-bottom MatTek plates pre-coated overnight with 200 μ g/mL poly-D-Lysine in PBS: and then for 3 hours with 20 μ g/mL laminin in PBS at 37°C. Explants will be cultured overnight in DMEM-F12 containing 0.4% methylcellulose (Sigma-Aldrich), 0.45% glucose, N-2 supplement (Life Technologies), 2 mM L-Glutamine (Life Technologies), 1 mM sodium pyruvate, 0.1% BSA and antibiotics. The culture medium will then be replaced with medium without methylcellulose and 3 hours later the retinal explants will be incubated with about 0.1 μ M to about

0.3 μ M of a modified APY cyclic peptide disclosed herein for 30 min before stimulation with 1 μ g/mL preclustered ephrin-A5 Fc or Fc as a control for 30 min in the continued presence of the modified APY cyclic peptide. Ephrin-A5 Fc will be preclustered by incubating it for 30 min on ice with 1/10 polyclonal α -Fc antibody (Jackson Laboratories). The explants will then be fixed for 30 min in 3.7% formaldehyde, 4% sucrose in PBS at room temperature, permeabilized for 3 minutes with 0.1% Triton X-100 in PBS, and filamentous actin will be stained with rhodamine-conjugated phalloidin (Life Technologies). Growth cones will be photographed under a fluorescence microscope and will be scored in a blinded manner. A growth cone will be scored as collapsed when no lamellipodia or filopodia are present at the tip of the neurite. Histograms will be generated showing mean percentages of collapsed growth cones (about 70 to 500 per condition in each experiment). Error bars will represent standard errors from 3 experiments. *, $P < 0.05$ compared to Fc without peptide by one-way ANOVA.

[0174] The results will indicate that modified APY cyclic peptides effectively blocked growth cone collapse. Histograms will illustrate that control neurites treated only with Fc will show low levels of growth cone collapse while cells treated with Fc and ephrin-A5 will statistically significance increase in growth cone collapse. On the other hand, neurites treated with Fc and a modified APY cyclic peptide will show low levels of growth cone collapse while cells treated with Fc, ephrin-A5, and a modified APY cyclic peptide will similarly exhibit growth cone collapse at a level comparable to the unstimulated neurites. The modified APY cyclic peptides will not detectably affect the morphology of growth cones in the absence of ephrin, consistent with the lack of nonspecific effects or toxicity. These data will show that modified APY cyclic peptides disclosed herein will effectively blocked growth cone collapse in the presence of EphA4 receptor signaling.

[0175] To evaluate modified APY cyclic peptide cytotoxicity, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) colorimetric assays will be conducted. HT22 mouse hippocampal neurons will be grown in DMEM supplemented with 10% FBS, 1 mM sodium pyruvate and antibiotics. Cells will be seeded in 96 well plates and incubated for 24 hours with about 1 μ M to about 30 μ M of a modified APY cyclic peptide disclosed herein or with no peptide as a control. The cells will then be incubated for 2 hours in 5 mg/mL MTT (Sigma-Aldrich) in PBS at 37°C in a CO₂ incubator. The resulting formazan crystals will be solubilized by adding of 100% DMSO and OD₅₇₀ will be measured. This cell viability assay will not reveal significant cytotoxicity in the hippocampal neuron-derived HT22 cell line treated for 24 hours with a modified APY cyclic peptide disclosed herein. These data will show that modified APY cyclic peptides disclosed herein are not cytotoxic.

Example 9

In vitro and in vivo Stability of APY cyclic peptides

[0176] To evaluate the stability of APY cyclic peptides disclosed herein, the ability of these peptides to inhibit EphA4-ephrin-A5 interaction was assessed using an in vitro stability assay. APY cyclic peptide antagonistic activity remaining after incubation in plasma or cerebral spinal fluid (CSF) for different time periods was determined in ELISAs by measuring inhibition of ephrin-A5-EphA4 binding. In these assays,

APY cyclic peptides were incubated at 37°C in 40 μ L heparinized mouse plasma or Sprague Dawley rat CSF for up to 3 days at concentrations based on their potency and ranging from 1.2 μ M to 6.6 μ M. Aliquots of 6 μ L were collected at different time points and used in ELISA measuring inhibition of ephrin-A5 AP binding to immobilized EphA4 Fc. For ELISA, ephrin-A5 Fc was immobilized at 1 μ g/mL for 1 hour at room temperature in protein A-coated 96-well plates as described above. Plasma or CSF containing the peptides were incubated in the wells at a 1:20 dilution (corresponding to final concentrations yielding about 80% inhibition of ephrin-A5 AP binding to EphA4 Fc in the absence of proteolytic degradation) with 0.05 nM ephrin-A5 AP for 30 minutes at 4°C. These peptide concentrations yield about 80% inhibition of EphA4 AP binding to ephrin-A5 Fc. The amount of bound ephrin-A5 AP was quantified by measuring the absorbance at 405 nm. The absorbance obtained from wells coated with Fc and incubated with ephrin-A5 AP and plasma or CSF was subtracted as the background. The absorbance in wells incubated with plasma or CSF not containing any peptide was used to determine the 0% inhibition level (remaining antagonistic activity = 0) and the absorbance in the presence of peptide not incubated in plasma or CSF was used for normalization (remaining antagonistic activity = 1).

[0177] To evaluate the half-life of APY cyclic peptides disclosed herein, APY cyclic peptide antagonistic activity remaining after circulation in mouse blood for different time periods was determined in ELISAs by measuring inhibition of ephrin-A5-EphA4 binding. In these assays, APY cyclic peptides were intraperitoneally injected into mice and blood collected at 1, 2 and 4 hours post-injection. In order to determine APY cyclic peptide antagonistic activity, plasma was prepared, diluted, and used to determine the apparent IC₅₀ value for inhibition of ephrin-A5 AP binding to immobilized EphA4 Fc. The concentration of active APY cyclic peptide remaining in the blood was determined by comparing the apparent IC₅₀ value for the peptide recovered from plasma in vivo with the IC₅₀ value of the same peptide diluted in plasma in vitro (corresponding to the theoretical 0 time point). The fold increase in the apparent IC₅₀ value reflects the decrease in peptide concentration in the blood. For example, a 10-fold increase in the apparent IC₅₀ value at a given time point after peptide administration would indicate a 10-fold decrease in peptide concentration in the blood, and therefore that 10% of the injected peptide remains in the blood. The % peptide remaining in the blood at different times is then used to calculate the half-life (Table 2).

Table 2. Half-life of APY Cyclic Peptides	
Peptide	Half-life (t_{1/2})
KYL	11 minutes (in vitro)
APY	16 minutes (in vitro)
β Ala1-PY- β Ala8-GGK(lauroyl-Glu)-G.am	~1 hour (in vivo) ^a
β Ala1-PY- β Ala8-GGK(lauroyl- γ -Glu-Glu)-G.am	~1 hour (in vivo) ^a
β Ala1-PY- β Ala8-GGK(myristoyl- γ -Glu-Glu)-G.am	~2 hour (in vivo) ^a
β Ala1-PY- β Ala8-GGK(myristoyl γ -Glu-Glu)-G.am	~2 hour (in vivo) ^b
β Ala1-PY- β Ala8-GGK(palmitoyl- γ -Glu)-G.am	~2 hour (in vivo) ^a
β Ala1-PY- β Ala8-GGK(palmitoyl- γ -Glu-Glu)-G.am	~2 hour (in vivo) ^a
^a The peptide was injected intraperitoneally mixed with 40 mg/ml BSA to improve solubility.	
^b The peptide was injected intraperitoneally mixed with 6.4 mM methyl- β -cyclodextrin to improve solubility.	

[0178] The results indicate that KYL and APY peptides loss their antagonistic activity rapidly, having half-lives of 11 minutes and 16 minutes respectively when incubated in mouse plasma in vitro. In vivo these peptides would likely be lost in less than 2 minutes from the circulation due to both degradation by plasma proteases and filtration through the kidneys. On the other hand, β Ala1-PY- β Ala8-GGK(lauroyl- γ Glu)-G.am and β Ala1-PY- β Ala8-GGK(lauroyl- γ Glu γ Glu)-G.am each showed an in vivo half-life of about 1 hour after intraperitoneal injection, likely because the N-terminal unnatural amino acid blocks degradation by plasma proteases while lipidation mediates binding to serum albumin reducing kidney excretion. In addition, β Ala1-PY- β Ala8-GGK(myristoyl- γ Glu γ Glu)-G.am, β Ala1-PY- β Ala8-GGK(myristoyl- γ Glu γ Glu)-G.am, β Ala1-PY- β Ala8-GGK(palmitoyl- γ Glu)-G.am and β Ala1-PY- β Ala8-GGK(palmitoyl- γ Glu γ Glu)-G.am each showed an in vivo half-life of about 2 hours, indicating that longer-chained fatty acids appear to increase the in vivo half-life of the APY cyclic peptide more relative to shorter-chained fatty acids. These results indicate that the APY cyclic peptide disclosed herein can be modified to significantly increase half-life of the active peptide antagonist.

Example 10

Structure Function Analysis of Positive Charges

[0179] Structure function analysis of APY cyclic peptides disclosed herein revealed that positive charges located at the N-terminus appeared to increase the binding affinity of an APY cyclic peptides disclosed herein for the EphA4 receptor. To test this, the first and/or second amino acids of APY-2 were substituted a series of N-terminal primary amines spaced 2-6 carbons (corresponding to ~4-8 Å) from Tyr3 as wells as an N-terminal secondary amine (SEQ ID NO: 96). Dissociation constant (K_D) values for APY cyclic peptide binding to the EphA4 ligand binding domain was confirmed using ITC, as disclosed in Example 7. APY cyclic peptide half-life was assessed using in vitro stability assays, as disclosed in Example 9.

[0180] All of these derivatives have inhibitory potencies (IC_{50} values) within 0.5-2.5 fold that of PY- β Ala8.am (Table 3), indicating that the precise location and size of the positively charged group is not as important as its presence.

Table 3. Potency and Stability of APY Cyclic Peptides with Positive Charge Modifications			
Peptide	SEQ ID NO:	$IC_{50} \pm SE$ (n) ^a (nM)	Half-life ($t_{1/2}$) Plasma
APY-d2	20	27 ± 2 (25)	< 3 hours
PY- β Ala8.am	101	38 ± 2 (6)	about 15 hours
Ahx1-Y- β Ala8.am	91	83 ± 16 (6)	> 72 hours
Ava1-Y- β Ala8.am	92	54 ± 4 (4)	> 72 hours
γ Abu1-Y- β Ala8.am	93	34 ± 7 (4)	> 72 hours
β Ala1-Y- β Ala8.am	94	25 ± 4 (5)	about 30 hours
Gly1Y- β Ala8.am	95	41 ± 5 (4)	about 6 hours
Sar1-Y- β Ala8.am	96	40 ± 9 (4)	> 72 hours
β Ala = β -Alanine, DAla = D-Alanine; Ahx = Aminohexanoic acid; Ava = aminopentanoic acid (Valeric acid); γ Abu = γ -aminobutyric acid; Sar = Sarcosine (N-methylglycine).			

Example 11***Therapeutic Usefulness of Modified APY Cyclic Peptides in ALS***

[0181] To evaluate the therapeutic effects of modified APY cyclic peptides disclosed herein on ALS, EphA4 signaling inhibition by APY cyclic peptides will be examined using a mouse SOD1*G93A model of ALS. SOD1*G93A transgenic mice express human Cu/Zn superoxide dismutase 1 (SOD1) harboring a single amino acid substitution of glycine to alanine at codon 93. This pathogenic mutation is associated with early-onset familial ALS with hemizygotic SOD1*G93A animals exhibit neuronal degeneration due to progressive accumulation of detergent-resistant SOD-ubiquitin aggregates and aberrant neurofilament accumulations in degenerating motor neurons as well as reactive astroglia and microglia. The neuronal degeneration leads to limb grasping, widespread muscle weakness, atrophy and paralysis in one or more limbs due to loss of motor neurons from the spinal cord due to abnormal axonal transport. Transgenic mice also have an abbreviated life span.

[0182] Both SOD1*G93A mice, as well as non-transgenic mice used as age-matched controls, will be administered an APY cyclic peptide, such as APY- β A8.am, APY-d3 or APY-d4, or APY-d3 dimers disclosed herein, into the cerebral ventricles of the brain using a minipump. Behavioral analyses will reveal muscle function of SOD1*G93A mice compared to controls. Muscle and neuromuscular junction pathology of SOD1*G93A mice and controls then will be assayed using standard histological staining and immunohistochemistry using an amyloid beta ($A\beta$) antibody. These results will show that modified APY cyclic peptides disclosed herein will delay disease onset and pathogenesis, will decrease motor neuron loss, and/or will extend survival of the mice, thereby demonstrating the therapeutic effects of modified APY cyclic peptides disclosed herein in inhibiting EphA4 signaling and their usefulness in treating ALS. In addition, these data will confirm the findings obtained with the KYL peptide (a less potent EphA4 peptide antagonist) that inhibition of EphA4 signaling provides therapeutic benefits in Alzheimer's disease.

Example 12***Therapeutic Usefulness of Modified APY Cyclic Peptides in Alzheimer's disease***

[0183] To evaluate the therapeutic effects of modified APY cyclic peptides disclosed herein on Alzheimer's disease, EphA4 signaling inhibition by APY cyclic peptides will be examined using an APP/PS1 or other mouse model for Alzheimer's disease, including the TgCRND8 model encoding a double mutant form of amyloid precursor protein 695 (KM670/671NL+V717F) under the control of the PrP gene promoter. See, e.g., Chrishti, et al., *Early-Onset Amyloid Deposition and Cognitive Deficits in Transgenic Mice Expressing a Double Mutant Form of Amyloid Precursor Protein 695*, J. Biol. Chem 276(24): 21562-21570 (2001), which is hereby incorporated by reference in its entirety. APP/PS1 double transgenic mice express a chimeric mouse/human amyloid precursor protein (Mo/HuAPP695swe) and a mutant human presenilin 1 (PS1-dE9) both directed to CNS neurons. Both pathogenic mutations are associated with early-onset Alzheimer's disease with transgenic mice showing visible β -amyloid plaque deposits in the brains by 6 to 7 months of age resulting in synaptic loss. APP/PS1 mice also exhibit

certain behavioral abnormalities such as, impaired reversal learning of a food-rewarded four-arm spatial maze task, cognitive deficits in spatial learning and memory in the Morris water maze, and inhibition of hippocampal CA1 long-term potentiation (LTP). Thus, APP/PS1 mice demonstrate synaptic loss, reduced glutamatergic synaptic transmission and impaired synaptic plasticity in the hippocampus.

[0184] Both APP/PS1 mice, as well as non-transgenic mice used as age-matched controls, will be administered an APY cyclic peptide, such as APY- β A8.am, APY-d3 or APY-d4, or APY-d3 dimers disclosed herein, into the brain by intracerebral infusion for about 3 weeks. β -amyloid deposition and neuron loss in the cerebral cortex and hippocampus of APP/PS1 mice and controls then will be assayed using standard histological staining and immunohistochemistry using an amyloid beta ($A\beta$) antibody. These results will show that modified APY cyclic peptides disclosed herein will inhibit $A\beta$ toxicity and/or will restore normal synaptic function and/or will restore LTP formation in APP/PS1 mice, thereby demonstrating the therapeutic effects of modified APY cyclic peptides disclosed herein in inhibiting EphA4 signaling and their usefulness in treating Alzheimer's disease. In addition, these data will confirm the findings obtained with the KYL peptide (a less potent EphA4 peptide antagonist) that inhibition of EphA4 signaling provides therapeutic benefits in Alzheimer's disease.

Example 13

Therapeutic Usefulness of Modified APY Cyclic Peptides in Stroke

[0185] To evaluate the therapeutic effects of modified APY cyclic peptides disclosed herein on stroke recovery, EphA4 signaling inhibition by APY cyclic peptides will be examined using a mouse photothrombosis model for stroke. See, e.g., Lemmens, et al., *Modifying Expression of EphA4 and its Downstream Targets Improves Functional Recovery after Stroke*, Hum. Mol. Genet. 22(11): 2214-2220 (2013), which is hereby incorporated by reference in its entirety. Focal cortical ischemia will be induced by photothrombosis in a wild-type strain of mice aged 3-4 months. Before the induction of photothrombosis, animals will receive training daily for 1 week on an accelerating rotarod treadmill (Ugo Basile), rotating from 4 to 40 r.p.m. over the course of 300 seconds in order to record three motor performance evaluations. The baseline performance will be recorded over six attempts the week after training. Induction of stroke will be evaluated 1 day after the procedure and animals will be excluded if the average and/or maximum performance over three attempts was 75% compared with baseline. Infarct volume will also be calculated using serial coronal sections immune-stained with antibodies against glial fibrillary acidic protein (GFAP) and compared to the contralateral side. Nerve regeneration will be evaluated by immunohistochemistry using antibodies against EphA4 and glial fibrillary acidic protein (GFAP).

[0186] Three days after induction of experimental stroke, mice will be divided into a treated group and an untreated group that will be used as age-matched controls. Treated mice will be administered an APY cyclic peptide, such as APY- β A8.am, APY-d3 or APY-d4, or APY-d3 dimers disclosed herein once daily for four weeks. Motor performance evaluations of treated and untreated animals will be conducted on post-stroke days 1, 7, 13, 19, 26, and 34. Infarct volume will also be measured.

[0187] These results will show that treatment with a modified APY cyclic peptide disclosed herein will substantially improve motor function after experimental stroke. Mice treated with an APY cyclic peptide disclosed herein will exhibit on improved rotarod performance relative to control animals (untreated) as well as increased axonal sprouting. These results will demonstrate the therapeutic effects of modified APY cyclic peptides disclosed herein in inhibiting EphA4 signaling and their usefulness in treating stroke.

Example 14

Therapeutic Usefulness of Modified APY Cyclic Peptides in Nerve Regeneration

[0188] To evaluate the therapeutic effects of modified APY cyclic peptides disclosed herein on nerve regeneration, EphA4 signaling inhibition by APY cyclic peptides will be examined using a mouse corticospinal tract injury model for nerve regeneration. Spinal cord injury often leads to permanent incapacity because long axons cannot regenerate in the CNS. Eph receptors inhibit axon extension through an effect on the actin cytoskeleton. Severing of corticospinal axons causes EphA4 to accumulate at high levels in stumps of corticospinal axons, while a cognate ligand, ephrinB2, is upregulated at the lesion site so as to confine the injured axons.

[0189] Wild-type mice will be anesthetized and a spinal hemisection surgery will be performed in order to sever corticospinal axons in the T12-L1 region. Animals will be allowed to recover from the surgery and mice showing only complete paralysis will be used. Both hemisectioned mice, as well as un-operated mice used as age-matched controls, will be administered an APY cyclic peptide, such as APY- β A8.am, APY-d3 or APY-d4, or APY-d3 dimers disclosed herein, into the cervical spinal cord region by intracerebral infusion. Five weeks after spinal cord lesion, mice will be evaluated for nerve regeneration by using an anterograde tracing technique and immunohistochemistry using antibodies against EphA4 and glial fibrillary acidic protein (GFAP) as well as by using behavioral assessments before and after spinal hemisection like measuring stride length, ability to walk or climb on a grid and/or hindpaw grip strength.

[0190] These results will show that treatment with a modified APY cyclic peptide disclosed herein will substantially improve recovery in hemisectioned animals relative to controls by promoting axon sprouting and/or improving limb function and recovery. Mice treated with a modified APY cyclic peptide disclosed herein will exhibit axon sprouting, will show a reduction astrocytic gliosis and glial scarring, will demonstrate recovered stride length, the ability to walk on and/or climb a grid, and/or the ability to grasp with the affected hindpaw within 1-3 months of injury. These results will demonstrate the therapeutic effects of modified APY cyclic peptides disclosed herein in inhibiting EphA4 signaling and their usefulness in promoting nerve regeneration. In addition, these data will confirm the findings obtained with the KYL peptide (a less potent EphA4 peptide antagonist) that inhibition of EphA4 signaling provides therapeutic benefits in neuroregeneration.

Example 15***Therapeutic Treatments using an APY Cyclic Peptide***

[0191] A 46 year old male complains of muscle weakness and numbness in his hands and arms. After routine history and physical examination, a physician diagnosis the woman with ALS. The man is treated by oral administration a pharmaceutical composition comprising a modified APY cyclic peptide disclosed herein taken twice daily. Alternatively, the man is treated by administering the pharmaceutical composition once every three days. The man's condition is monitored and after about one month of treatment the man indicates there is improvement in his health, the numbness is not as severe and some strength has returned to his hands and arms. At a three month check-up, the man indicates that his numbness is gone, he does not suffer from any muscle weakness. This reduction in symptoms in ALS indicates successful treatment with the pharmaceutical composition disclosed herein. In a similar manner, a pharmaceutical composition disclosed herein may be used to treat other neurodegenerative diseases, such as, e.g., an Alexander disease, an Alper's disease, Alzheimer's disease, an ataxia telangiectasia, a Canavan disease, a Cockayne syndrome, a corticobasal degeneration, a Creutzfeldt-Jakob disease, a Guillain-Barre Syndrome a HIV-induced neurodegeneration, a Huntington disease, a Kennedy's disease, a Krabbe disease, a Lewy body dementia, a Machado-Joseph disease, a multiple sclerosis, a Parkinson's disease, a Pelizaeus-Merzbacher disease, a Pick's disease, a primary lateral sclerosis, a Refsum's disease, a Sandhoff disease, a Schilder's disease, a spinal cord injury, a Steele-Richardson-Olszewski disease, a stroke, a tabes dorsalis and/or a traumatic brain injury.

[0192] A 69 year old male complains of forgetfulness and not being able to remember certain events or activities. After routine history and physical examination, a physician diagnosis the woman with Alzheimer's disease. The man is treated by oral administration a pharmaceutical composition comprising a modified APY cyclic peptide disclosed herein taken twice daily. Alternatively, the man is treated by administering the pharmaceutical composition once every three days. The man's condition is monitored and after about one month of treatment the man indicates there is improvement in his health, his forgetfulness is not as severe and he can remember events or activities better. At a three month check-up, the man indicates that his forgetfulness and memory continue to improve. This reduction in symptoms in Alzheimer's disease indicates successful treatment with the pharmaceutical composition disclosed herein. In a similar manner, a pharmaceutical composition disclosed herein may be used to treat other neurodegenerative diseases, such as, e.g., an Alexander disease, an Alper's disease, an amyotrophic lateral sclerosis, an ataxia telangiectasia, a Canavan disease, a Cockayne syndrome, a corticobasal degeneration, a Creutzfeldt-Jakob disease, a Guillain-Barre Syndrome a HIV-induced neurodegeneration, a Huntington disease, a Kennedy's disease, a Krabbe disease, a Lewy body dementia, a Machado-Joseph disease, a multiple sclerosis, a Parkinson's disease, a Pelizaeus-Merzbacher disease, a Pick's disease, a primary lateral sclerosis, a Refsum's disease, a Sandhoff disease, a Schilder's disease, a spinal cord injury, a Steele-Richardson-Olszewski disease, a stroke, a tabes dorsalis and/or a traumatic brain injury.

[0193] A 51 year old female complains of hand tremors, eye pain and blurred vision, and fatigue. After routine history and physical examination, a physician diagnosis the woman with multiple sclerosis. The woman is treated by oral administration a pharmaceutical composition comprising a modified APY cyclic peptide disclosed herein taken once daily. The woman's condition is monitored and after about one week of treatment the woman indicates there is improvement in her health, her eye pain and blurred vision has subsided, her hand tremors are less and some energy has returned. At one and three month check-ups, the woman indicates that her eye pain and blurred vision is gone, she does not suffer from hand tremors, and she is not tired. This reduction in symptoms in multiple sclerosis indicates successful treatment with the pharmaceutical composition disclosed herein. In a similar manner, a pharmaceutical composition disclosed herein may be used to treat other neurodegenerative diseases, such as, e.g., an Alexander disease, an Alper's disease, Alzheimer's disease, an amyotrophic lateral sclerosis, an ataxia telangiectasia, a Canavan disease, a Cockayne syndrome, a corticobasal degeneration, a Creutzfeldt-Jakob disease, a Guillain-Barre Syndrome a HIV-induced neurodegeneration, a Huntington disease, a Kennedy's disease, a Krabbe disease, a Lewy body dementia, a Machado-Joseph disease, a Parkinson's disease, a Pelizaeus-Merzbacher disease, a Pick's disease, a primary lateral sclerosis, a Refsum's disease, a Sandhoff disease, a Schilder's disease, a spinal cord injury, a Steele-Richardson-Olszewski disease, a stroke, a tabes dorsalis and/or a traumatic brain injury.

[0194] A 66 year old male complains of severe pain after losing consciousness. A physician determines that the pain is due to central neuropathic pain caused by a stroke. The man is treated by administering a pharmaceutical composition comprising a modified APY cyclic peptide disclosed herein taken once every other day. Alternatively, the man is treated by administering the pharmaceutical composition once every three days. The man's condition is monitored and after about 7 days of treatment the man indicates that there is a reduction in pain. At one and three month check-ups, the man indicates that he continues to have reduced pain. Tests performed on the man indicate that neuronal regeneration is occurring. This reduction in central neuropathic pain symptoms and/or regenerative growth of neurons indicates successful treatment with the pharmaceutical composition disclosed herein. In a similar manner, a pharmaceutical composition disclosed herein may be used to promote neuroregeneration and/or neuroprotection caused by another condition, disease or disorder, such as hearing loss.

[0195] A 49 year old woman was diagnosed by her physician with advanced metastatic breast cancer. The metastatic breast cancer consisted of tumors, including several found in both lungs. The woman is treated by administering a pharmaceutical composition comprising a modified APY cyclic peptide disclosed herein taken once every third day. Alternatively, the woman is treated by administering the pharmaceutical composition once daily. One month after following this treatment, the patient was administered a CAT scan, which revealed that tumor growth had stopped and the breast cancer did not progress in the patient during this period of treatment. This reduction in tumor growth indicates successful treatment with the pharmaceutical composition disclosed herein. In a similar manner, a pharmaceutical composition disclosed herein may be used to treat a different type of cancer, such as, a glioblastoma, a gastric cancer, a pancreatic cancer, a prostate cancer, a breast cancer, a liver cancer, a leukemia or a Sezary syndrome.

[0196] In closing, it is to be understood that although aspects of the present specification are highlighted by referring to specific embodiments, one skilled in the art will readily appreciate that these disclosed embodiments are only illustrative of the principles of the subject matter disclosed herein. Therefore, it should be understood that the disclosed subject matter is in no way limited to a particular compound, composition, article, apparatus, methodology, protocol, and/or reagent, etc., described herein, unless expressly stated as such. In addition, those of ordinary skill in the art will recognize that certain changes, modifications, permutations, alterations, additions, subtractions and sub-combinations thereof can be made in accordance with the teachings herein without departing from the spirit of the present specification. It is therefore intended that the following appended claims and claims hereafter introduced are interpreted to include all such changes, modifications, permutations, alterations, additions, subtractions and sub-combinations as are within their true spirit and scope.

[0197] Certain embodiments of the present invention are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the present invention to be practiced otherwise than specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described embodiments in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

[0198] Groupings of alternative embodiments, elements, or steps of the present invention are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other group members disclosed herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

[0199] Unless otherwise indicated, all numbers expressing a characteristic, item, quantity, parameter, property, term, and so forth used in the present specification and claims are to be understood as being modified in all instances by the term "about." As used herein, the term "about" means that the characteristic, item, quantity, parameter, property, or term so qualified encompasses a range of plus or minus ten percent above and below the value of the stated characteristic, item, quantity, parameter, property, or term. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary. For instance, as mass spectrometry instruments can vary slightly in determining the mass of a given analyte, the term "about" in the context of the mass of an ion or the mass/charge ratio of an ion refers to ± 0.50 atomic mass unit. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims,

each numerical indication should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0200] Use of the terms “may” or “can” in reference to an embodiment or aspect of an embodiment also carries with it the alternative meaning of “may not” or “cannot.” As such, if the present specification discloses that an embodiment or an aspect of an embodiment may be or can be included as part of the inventive subject matter, then the negative limitation or exclusionary proviso is also explicitly meant, meaning that an embodiment or an aspect of an embodiment may not be or cannot be included as part of the inventive subject matter. In a similar manner, use of the term “optionally” in reference to an embodiment or aspect of an embodiment means that such embodiment or aspect of the embodiment may be included as part of the inventive subject matter or may not be included as part of the inventive subject matter. Whether such a negative limitation or exclusionary proviso applies will be based on whether the negative limitation or exclusionary proviso is recited in the claimed subject matter.

[0201] Notwithstanding that the numerical ranges and values setting forth the broad scope of the invention are approximations, the numerical ranges and values set forth in the specific examples are reported as precisely as possible. Any numerical range or value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements. Recitation of numerical ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate numerical value falling within the range. Unless otherwise indicated herein, each individual value of a numerical range is incorporated into the present specification as if it were individually recited herein.

[0202] The terms “a,” “an,” “the” and similar references used in the context of describing the present invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Further, ordinal indicators – such as “first,” “second,” “third,” etc. – for identified elements are used to distinguish between the elements, and do not indicate or imply a required or limited number of such elements, and do not indicate a particular position or order of such elements unless otherwise specifically stated. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein is intended merely to better illuminate the present invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the present specification should be construed as indicating any non-claimed element essential to the practice of the invention.

[0203] When used in the claims, whether as filed or added per amendment, the open-ended transitional term “comprising” (and equivalent open-ended transitional phrases thereof like including, containing and having) encompasses all the expressly recited elements, limitations, steps and/or features alone or in combination with unrecited subject matter; the named elements, limitations and/or features are essential, but other unnamed elements, limitations and/or features may be added and still form a construct within the scope of the claim. Specific embodiments disclosed herein may be further limited in the claims using

the closed-ended transitional phrases “consisting of” or “consisting essentially of” in lieu of or as an amended for “comprising.” When used in the claims, whether as filed or added per amendment, the closed-ended transitional phrase “consisting of” excludes any element, limitation, step, or feature not expressly recited in the claims. The closed-ended transitional phrase “consisting essentially of” limits the scope of a claim to the expressly recited elements, limitations, steps and/or features and any other elements, limitations, steps and/or features that do not materially affect the basic and novel characteristic(s) of the claimed subject matter. Thus, the meaning of the open-ended transitional phrase “comprising” is being defined as encompassing all the specifically recited elements, limitations, steps and/or features as well as any optional, additional unspecified ones. The meaning of the closed-ended transitional phrase “consisting of” is being defined as only including those elements, limitations, steps and/or features specifically recited in the claim whereas the meaning of the closed-ended transitional phrase “consisting essentially of” is being defined as only including those elements, limitations, steps and/or features specifically recited in the claim and those elements, limitations, steps and/or features that do not materially affect the basic and novel characteristic(s) of the claimed subject matter. Therefore, the open-ended transitional phrase “comprising” (and equivalent open-ended transitional phrases thereof) includes within its meaning, as a limiting case, claimed subject matter specified by the closed-ended transitional phrases “consisting of” or “consisting essentially of.” As such embodiments described herein or so claimed with the phrase “comprising” are expressly or inherently unambiguously described, enabled and supported herein for the phrases “consisting essentially of” and “consisting of.”

[0204] All patents, patent publications, and other publications referenced and identified in the present specification are individually and expressly incorporated herein by reference in their entirety for the purpose of describing and disclosing, for example, the compositions and methodologies described in such publications that might be used in connection with the present invention. These publications are provided solely for their disclosure prior to the filing date of the present application. Nothing in this regard should be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention or for any other reason. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents.

[0205] Lastly, the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention, which is defined solely by the claims. Accordingly, the present invention is not limited to that precisely as shown and described.

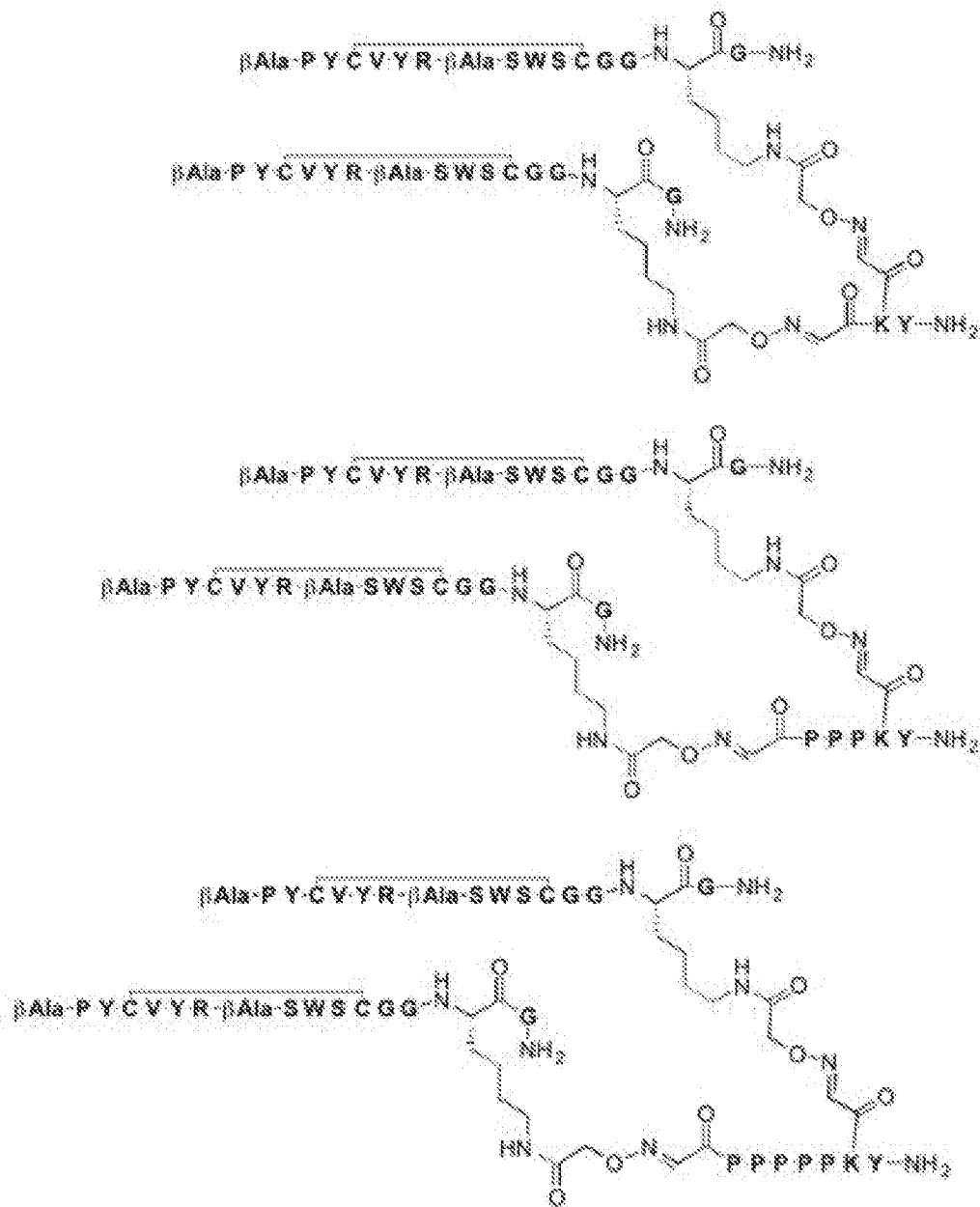
CLAIMS

1. A modified EphA4 receptor antagonist comprising a cyclic peptide having a length of 11 to 20 amino acids and including the sequence X₁-X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 3) or X₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W-X₁₁-C₁₂ (SEQ ID NO: 4), wherein X₁ is independently Ahx, Ava, γAbu, βA, Sar, D-A, A, E, G, Q, D, L, S, F, or Y; X₂ is independently P, A, G, Ahx, Ava, γAbu, βA or Sar; X₃ is independently Y, F, W, V, L, H or I; X₅ is independently V or L; X₆ is independently Y, F, W or H; X₇ is independently any amino acid; X₉ is independently any amino acid; and X₁₁ is independently any amino acid; wherein C₄ and C₁₂ form a disulfide bridge; wherein C₁₂ is optionally amidated; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.
2. The modified EphA4 receptor antagonist according to Claim 1, wherein X₁ is independently βA, D-A, A, E, G or Q.
3. The modified EphA4 receptor antagonist according to Claim 1 or Claim 2, wherein X₁ is independently βA, D-A, A or E.
4. The modified EphA4 receptor antagonist according to any one of Claims 1-3, wherein X₂ is P.
5. The modified EphA4 receptor antagonist according to any one of Claims 1-4, wherein X₃ is independently Y, F, W, V, L or H.
6. The modified EphA4 receptor antagonist according to any one of Claims 1-5, wherein X₃ is independently Y, F or W.
7. The modified EphA4 receptor antagonist according to any one of Claims 1-6, wherein X₅ is V.
8. The modified EphA4 receptor antagonist according to any one of Claims 1-7, wherein X₆ is independently Y, F or W.
9. The modified EphA4 receptor antagonist according to any one of Claims 1-8, wherein X₇ is independently any amino acid except P; X₉ is independently any amino acid except P; and X₁₁ is independently any amino acid except P.
10. The modified EphA4 receptor antagonist according to any one of Claims 1-9, wherein X₇ is independently R, T, N, D, S, Q, Y, K, A, G or E; X₉ is independently S, E, T, V, D, Y, Q, V, W, R, N, L, K or H; and X₁₁ is independently S, E, L, N, V, I, H, K, M, D, W, T or G.
11. The modified EphA4 receptor antagonist according to any one of Claims 1-10, wherein X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, W, R, L, D, Y; and X₁₁ is independently S, E, L, N, T, K, V, I or H.
12. The modified EphA4 receptor antagonist according to any one of Claims 1-11, wherein X₇ is independently R, T, N, D, S, or Q; X₉ is independently S, E, T, V, D, Y; and X₁₁ is independently S, E, L, N, K, V, I or H.
13. The modified EphA4 receptor antagonist according to any one of Claims 1-12, wherein X₇ is independently R, T, or N; X₉ is independently S, E, T or V; and X₁₁ is independently S, E, L or N.
14. The modified EphA4 receptor antagonist according to any one of Claims 1, 2, 4, 5 or 10-13, wherein the sequence comprises X₁-P₂-X₃-C₄-X₅-X₆-X₇-βA₈-X₉-W₁₀-X₁₁-C₁₂ (SEQ ID NO: 6), wherein C₄ and C₁₂ form a disulfide bridge; wherein C₁₂ is optionally amidated; and wherein the cyclic peptide has a

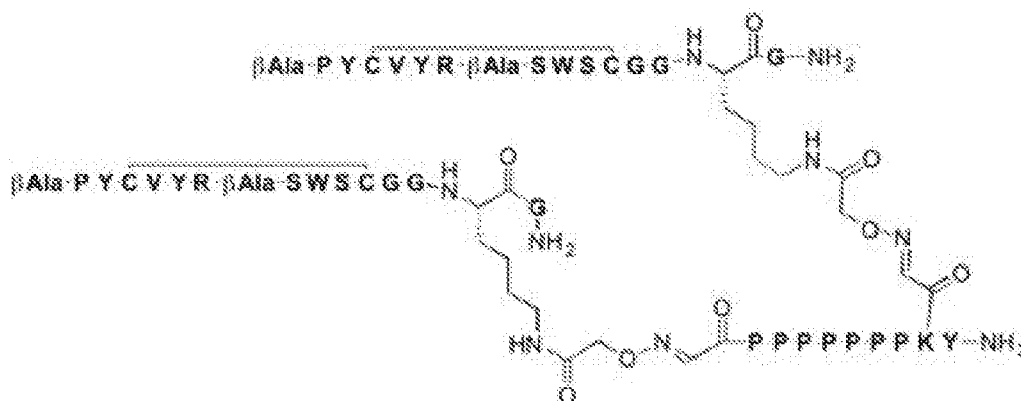
- modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.
15. The modified EphA4 receptor antagonist according to any one of Claims 1, 2, 5, 7 or 10-13, wherein the sequence comprises $X_1-X_2-X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 9), wherein C_4 and C_{12} form a disulfide bridge; wherein C_{12} is optionally amidated; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.
 16. The modified EphA4 receptor antagonist according to any one of Claims 1, 2, 5 or 10-13, wherein the sequence comprises $X_1-P_2-X_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 12), wherein C_4 and C_{12} form a disulfide bridge; wherein C_{12} is optionally amidated; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.
 17. The modified EphA4 receptor antagonist according to any one of Claims 1, 2 or 10-13, wherein the sequence comprises $X_1-P_2-Y_3-C_4-V_5-X_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 15), wherein C_4 and C_{12} form a disulfide bridge; wherein C_{12} is optionally amidated; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.
 18. The modified EphA4 receptor antagonist according to any one of Claims 1, 2, 5 or 10-13, wherein the sequence comprises $X_1-P_2-X_3-C_4-V_5-Y_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 18), wherein X_1 is independently βA , D-A, A, E, G or Q; X_3 is independently Y, F, W, V, L or H; X_7 is independently any amino acid except P; X_9 is independently any amino acid except P; and X_{11} is independently any amino acid except P; wherein C_4 and C_{12} form a disulfide bridge; wherein C_{12} is optionally amidated; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.
 19. The modified EphA4 receptor antagonist according to any one of Claims 1, 2 or 10-13, wherein the sequence comprises $X_1-P_2-Y_3-C_4-V_5-Y_6-X_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 21), wherein X_1 is independently βA , D-A, A, E, G or Q; X_7 is independently any amino acid except P; X_9 is independently any amino acid except P; and X_{11} is independently any amino acid except P; wherein C_4 and C_{12} form a disulfide bridge; wherein C_{12} is optionally amidated; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.
 20. The modified EphA4 receptor antagonist according to any one of Claims 1, 2 or 10-13, wherein the sequence comprises $X_1-P_2-Y_3-C_4-V_5-Y_6-R_7-\beta A_8-X_9-W_{10}-X_{11}-C_{12}$ (SEQ ID NO: 24), wherein X_1 is independently βA , D-A, A, E, G or Q; X_9 is independently any amino acid except P; and X_{11} is independently any amino acid except P; wherein C_4 and C_{12} form a disulfide bridge; wherein C_{12} is optionally amidated; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.
 21. The modified EphA4 receptor antagonist according to any one of Claims 1-20, wherein C_{12} is amidated.

22. The modified EphA4 receptor antagonist according to any one of Claims 1-21, wherein the sequence is APYCVYR β ASWSC (SEQ ID NO: 35), APYCVYR β ASWSC-am (SEQ ID NO: 36), APYCVYK β ASWSC-am (SEQ ID NO: 45), β APYCVYR β ASWSC (SEQ ID NO: 46), β APYCVYR β ASWSC-am (SEQ ID NO: 47), β APYCVYK β ASWSC-am (SEQ ID NO: 48), β APYCVYR β AEWEC (SEQ ID NO: 49), β APYCVYR β AEWEC-am (SEQ ID NO: 50), D-APYCVYR β ASWSC (SEQ ID NO: 51), D-APYCVYR β ASWSC-am (SEQ ID NO: 52), APYCVWR β ASWSC (SEQ ID NO: 53), APYCVYT β AEWLC (SEQ ID NO: 54), APYCVYN β ATWNC (SEQ ID NO: 55), APYCVYR β AVWEC (SEQ ID NO: 56), APVCVWR β ASWSC (SEQ ID NO: 57), APLCVWR β ASWSC (SEQ ID NO: 58), APLCVYR β ASWSC (SEQ ID NO: 59), APWCVFR β ASWSC (SEQ ID NO: 60), APHCVFR β ASWSC (SEQ ID NO: 61), APFCLYT β ADWVC (SEQ ID NO: 62), APYCVYD β ATWIC (SEQ ID NO: 63), APYCVYS β ATWHC (SEQ ID NO: 64), APYCVYD β ASWNC (SEQ ID NO: 65), APYCVYQ β AYWKC (SEQ ID NO: 66), APYCVYR β ASWSC (SEQ ID NO: 67), EPYCVYR β ASWSC (SEQ ID NO: 68), APLCVYR β ASWSC (SEQ ID NO: 69), Ahx-YCVYR β ASWSC-am (SEQ ID NO: 91), Ava-YCVYR β ASWSC-am (SEQ ID NO: 92), γ Abu-YCVYR β ASWSC-am (SEQ ID NO: 93), β A-YCVYR β ASWSC-am (SEQ ID NO: 94), GYCVYR β ASWSC-am (SEQ ID NO: 95) or Sar1-Y- β Ala8.am (SEQ ID NO: 96).
23. The modified EphA4 receptor antagonist according to any one of Claims 1-22, wherein the modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide is by lipidation, PEGylation, polysialylation, a Blood-Brain Barrier (BBB) shuttle, hyperglycosylation, N-(2-hydroxypropyl) methacrylamide (HPMA) copolymers, and polyglutamic acid, poly(lactic acid) (PLA) polymers, poly(glycolic acid) (PGA) polymers and poly(D,L-lactic-coglycolic-acid) (PLGA) polymers.
24. The modified EphA4 receptor antagonist according to any one of Claims 1-23, wherein the sequence is β APYCVYK(octanoyl) β ASWSC-am (SEQ ID NO: 71), β APYCVYK(octanoyl-G) β ASWSC-am (SEQ ID NO: 72), β APYCVYK(lauroyl) β ASWSC-am (SEQ ID NO: 73), β APYCVYK(lauroyl-G) β ASWSC-am (SEQ ID NO: 74), β APYCVYK(lauroyl- β D) β ASWSC-am (SEQ ID NO: 75), β APYCVYK(lauroyl- γ E) β ASWSC-am (SEQ ID NO: 76), β APYCVYK(palmitoyl- γ E) β ASWSC-am (SEQ ID NO: 77), β APYCVYR β ASWSCGGK(octanoyl)G-am (SEQ ID NO: 79), β APYCVYR β ASWSCGGK(lauroyl)G-am (SEQ ID NO: 80), β APYCVYR β ASWSCGGK(lauroyl- β D)G-am (SEQ ID NO: 81), β APYCVYR β ASWSCGGK(lauroyl- γ E)G-am (SEQ ID NO: 82), β APYCVYR β ASWSCGGK(γ E-palmitoyl)G-am (SEQ ID NO: 83), β APYCVYK β ASWSCGGK(octanoyl)G-am (SEQ ID NO: 87), D-APYCVYR β ASWSCGGK(octanoyl)G-am (SEQ ID NO: 89), β Ala1-PY- β Ala8-GGK(lauroyl- γ Glu- γ Glu)-G.am (SEQ ID NO: 97), β Ala1-PY- β Ala8-GGK(myristoyl- γ Glu- γ Glu)-G.am (SEQ ID NO: 98), β Ala1-PY- β Ala8-GGK(palmitoyl- γ Glu- γ Glu)-G.am (SEQ ID NO: 99) or β Ala1-PY- β Ala8-GGGSK(palmitoyl- γ Glu- γ Glu)-G.am (SEQ ID NO: 100).
25. The modified EphA4 receptor antagonist according to any one of Claims 1-24, wherein the cyclic peptide form a homomultimer or a heteromultimer.
26. The modified EphA4 receptor antagonist according to Claim 25, wherein the homomultimer is a homodimer comprising two cyclic peptides having the same sequence.
27. The modified EphA4 receptor antagonist according to Claim 25 or Claim 26, wherein each of the two cyclic peptides is covalently linked by a peptide linker.

28. The modified EphA4 receptor antagonist according to Claim 27, wherein the peptide linker is a tetrapeptide.
29. The modified EphA4 receptor antagonist according to Claim 28, wherein the tetrapeptide is SEQ ID NO: 70.
30. The modified EphA4 receptor antagonist according to Claim 29, wherein the homodimer is



, or



31. The modified EphA4 receptor antagonist according to Claim 25, wherein the heteromultimer is a heterodimer comprising two cyclic peptides each having a different sequence.
32. The modified EphA4 receptor antagonist according to Claim 25 or Claim 31, wherein each of the two cyclic peptides is covalently linked by a peptide linker.
33. The modified EphA4 receptor antagonist according to Claim 32, wherein the peptide linker is a tetrapeptide.
34. The modified EphA4 receptor antagonist according to Claim 33, wherein the tetrapeptide is SEQ ID NO: 70.
35. The modified EphA4 receptor antagonist according to any one of Claims 1-34, wherein the modified EphA4 receptor antagonist has an equilibrium disassociation rate constant for an EphA4 receptor less than 500 nM, less than 450 nM, less than 400 nM, less than 350 nM, less than 300 nM, less than 250 nM, less than 200 nM, less than 150 nM, less than 100 nM, less than 75 nM, less than 50 nM, less than 25 nM, less than 20 nM, less than 15 nM, less than 10 nM, less than 5 nM, less than 1 nM, less than 0.5 nM or less than 0.1 nM.
36. The modified EphA4 receptor antagonist according to any one of Claims 1-35, wherein the modified EphA4 receptor antagonist has an equilibrium disassociation rate constant for an EphA4 receptor of between about 1 nM to about 10 nM, about 1 nM to about 25 nM, about 1 nM to about 75 nM, about 1 nM to about 100 nM, about 1 nM to about 125 nM, about 1 nM to about 150 nM, about 5 nM to about 10 nM, about 5 nM to about 25 nM, about 5 nM to about 75 nM, about 5 nM to about 100 nM, about 5 nM to about 125 nM, about 5 nM to about 150 nM, about 10 nM to about 25 nM, about 10 nM to about 50 nM, about 10 nM to about 75 nM, about 10 nM to about 100 nM, about 10 nM to about 125 nM, about 10 nM to about 150 nM, about 10 nM to about 175 nM or about 10 nM to about 200 nM.
37. The modified EphA4 receptor antagonist according to any one of Claims 1-36, wherein the modified EphA4 receptor antagonist has an equilibrium disassociation rate constant for an ephrin-binding pocket of an ephrin receptor other than an EphA4 receptor of at least 2-fold more, at least 3-fold more, at least 4-fold more, at least 5-fold more, at least 6-fold more, at least 7-fold more, at least 8-fold more, or at least 9-fold more, at least 10-fold more, at least 20-fold more, at least 30-fold more, at least 40-fold more, at least 50-fold more, at least 60-fold more, at least 70-fold more, at least 80-fold more, at least 90-fold more, at least 100-fold more, at least 200-fold more, at least 300-fold more, at least 400-fold more, at least 500-fold more, at least 600-fold more, at least 700-fold more, at least

- 800-fold more, at least 900-fold more, at least 1,000-fold more, at least 2,500-fold more, at least 5,000-fold more, at least 7,500-fold more or at least 10,000-fold more.
38. The modified EphA4 receptor antagonist according to any one of Claims 1-37, wherein the modified EphA4 receptor antagonist reduces EphA4 receptor activity by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100%.
39. The modified EphA4 receptor antagonist according to any one of Claims 1-38, wherein the modified EphA4 receptor antagonist has a plasma half-life of at least 12 hours, at least 18 hours, at least 24 hours, at least 30 hours, at least 36 hours, at least 42 hours, at least 48 hours, at least 54 hours, at least 60 hours, at least 66 hours, at least 72 hours, at least 78 hours, at least 84 hours, at least 90 hours or at least 96 hours.
40. The modified EphA4 receptor antagonist according to any one of embodiments 1-39, wherein the modified EphA4 receptor antagonist has a plasma half-life of about 12 hours to about 24 hours, about 12 hours to about 36 hours, about 12 hours to about 48 hours, about 12 hours to about 60 hours, about 12 hours to about 72 hours, about 12 hours to about 84 hours, about 12 hours to about 96 hours, about 24 hours to about 36 hours, about 24 hours to about 48 hours, about 24 hours to about 60 hours, about 24 hours to about 72 hours, about 24 hours to about 84 hours, about 24 hours to about 96 hours, about 36 hours to about 48 hours, about 36 hours to about 60 hours, about 36 hours to about 72 hours, about 36 hours to about 84 hours, about 36 hours to about 96 hours, about 48 hours to about 60 hours, about 48 hours to about 72 hours, about 48 hours to about 84 hours, about 48 hours to about 96 hours, about 60 hours to about 72 hours, about 60 hours to about 84 hours, about 60 hours to about 96 hours, about 72 hours to about 84 hours, about 72 hours to about 96 hours or about 84 hours to about 96 hours.
41. A pharmaceutical composition comprising one or more EphA4 receptor antagonist according to any one of Claims 1-40.
42. The pharmaceutical composition according to Claim 41, wherein the one or more EphA4 receptor antagonist are each present in an amount of between about 100 ng to about 1,000 µg.
43. The pharmaceutical composition according to Claim 41 or Claim 42, wherein the pharmaceutical composition further comprises one or more pharmaceutical acceptable carriers.
44. Use of a modified EphA4 receptor antagonist as defined in any one of Claims 1-40 or a pharmaceutical composition as defined in any one of Claims 41-43 in the treatment of an EphA4-based disease, disorder or pathology.
45. Use of a modified EphA4 receptor antagonist as defined in any one of Claims 1-41 in the manufacture of a medicament for treating an EphA4-based disease, disorder or pathology.
46. A method of treating an EphA4-based disease, disorder or pathology, the method comprising administering a modified EphA4 receptor antagonist as defined in any one of Claims 1-41 or a pharmaceutical composition as defined in any one of Claims 42-44 to an individual in need thereof, wherein administration reduces one or more symptoms associated with the EphA4-based disease, disorder or pathology.
47. The use according to Claim 44 or Claim 45 or the method according to Claim 46, wherein the EphA4-based disease, disorder or pathology comprises a condition, a disease, a disorder and/or pathology

where a pathophysiology effect is due to dysregulation of EphA4 signaling in a manner that causes EphA4 signaling hyperactivity in cells or spatially or temporally aberrant EphA4 signaling.

48. The use according to any one of Claims 44, 45 or 47 or the method according to Claim 46 or Claim 47, wherein the EphA4-based disease, disorder or pathology is a neurodegenerative disease, a hearing loss, a promotion of nerve regeneration, a promotion of neuroprotection, or a cancer.
49. The use or method according to any one of Claim 48, wherein the neurodegenerative disease is an Alexander disease, an Alper's disease, Alzheimer's disease, an amyotrophic lateral sclerosis, an ataxia telangiectasia, a Canavan disease, a Cockayne syndrome, a corticobasal degeneration, a Creutzfeldt-Jakob disease, a Guillain-Barre Syndrome a HIV-induced neurodegeneration, a Huntington disease, a Kennedy's disease, a Krabbe disease, a Lewy body dementia, a Machado-Joseph disease, a multiple sclerosis, a Parkinson's disease, a Pelizaeus-Merzbacher disease, a Pick's disease, a primary lateral sclerosis, a Refsum's disease, a Sandhoff disease, a Schilder's disease, a spinal cord injury, a Steele-Richardson-Olszewski disease, a stroke, a tabes dorsalis and/or a traumatic brain injury.
50. The method according to any one of Claims 46-49, wherein the one or more symptoms include abnormal movement, abnormal sensation, limb grasping, muscle weakness, atrophy, paralysis, abnormal inhibition of axon growth, abnormal axonal transport, aberrant synaptic function, synaptic transmission loss, impaired synaptic plasticity, synaptic loss, neuronal degeneration, motor neuron degeneration, motor neuron loss, poor neuronal survival, memory loss, impaired learning, dementia, β -amyloid plaque deposits, aberrant neurofilament accumulation, reactive astroglia and/or reactive microglia.
51. The use according to any one of Claims 44, 45 or 47 or the method according to Claim 46 or Claim 47, wherein the cancer is a glioblastoma, a gastric cancer, a pancreatic cancer, a prostate cancer, a breast cancer, a liver cancer, a leukemia or a Sezary syndrome.

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FIG. 1A

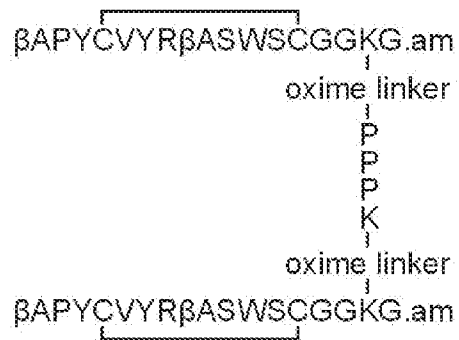


FIG. 1B

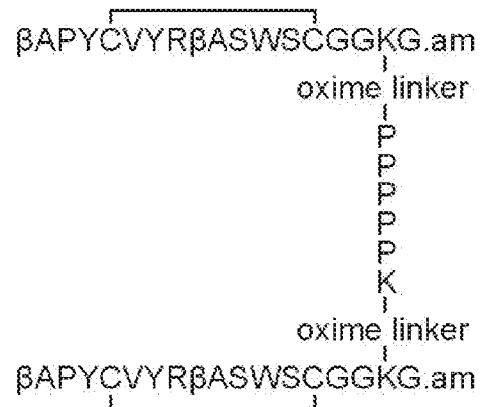
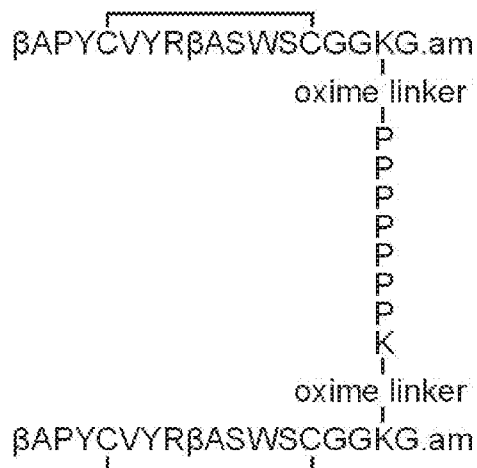


FIG. 1C



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FIG. 2A

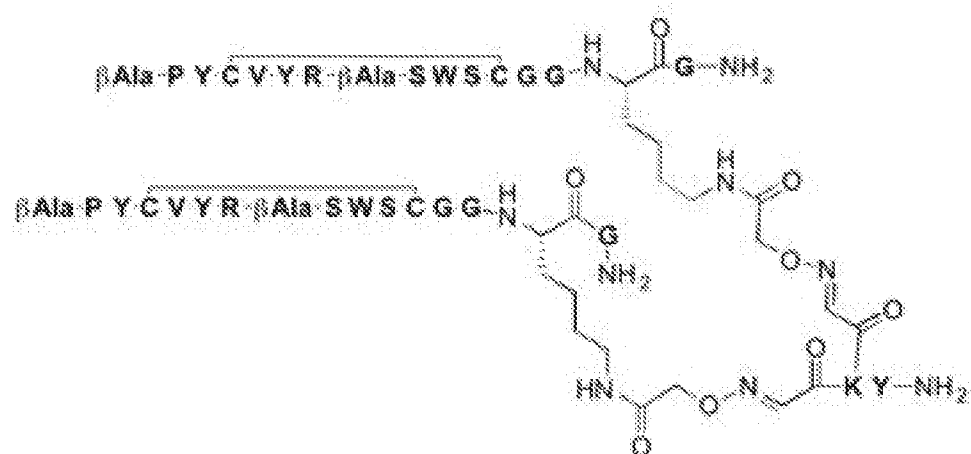
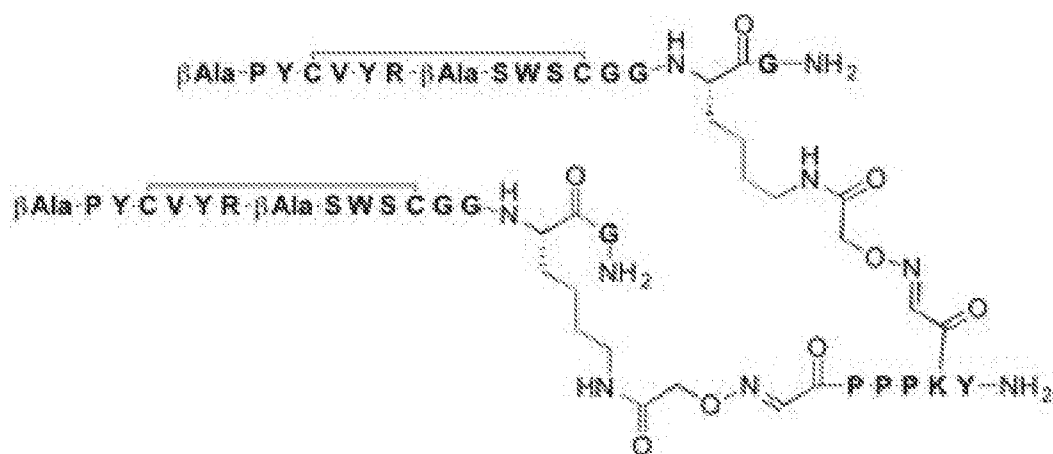


FIG. 2B



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FIG. 2C

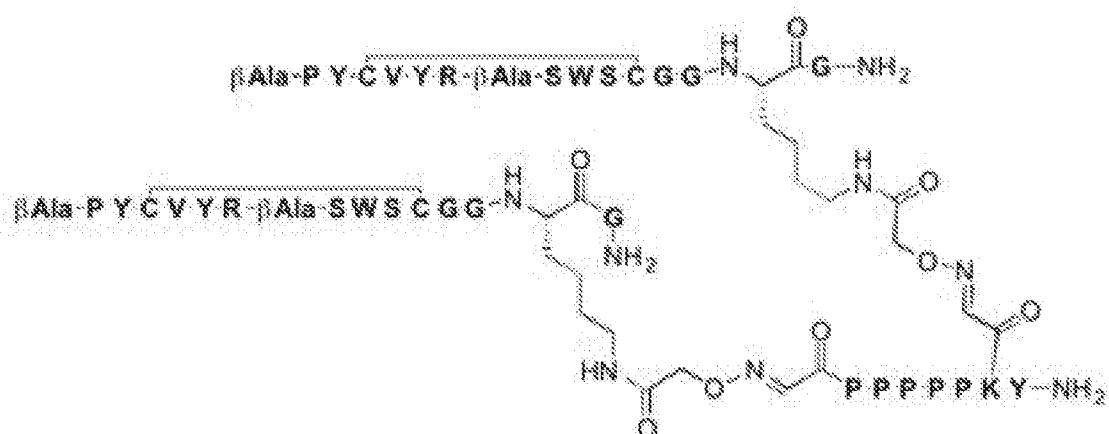
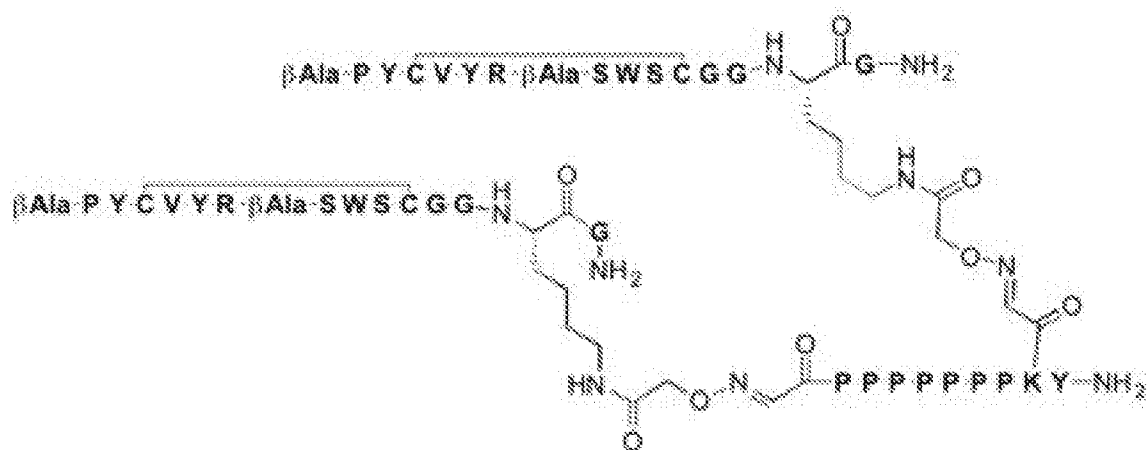


FIG. 2D



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/42669

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A61K 38/00, A61K 38/12, C07K 5/12 (2016.01)
 CPC - A61K 38/00, C07K 7/64

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC(8) - A61K 38/00, A61K 38/12, C07K 5/12 (2016.01)
 CPC - A61K 38/00, C07K 7/64

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 (keyword limited; terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 PatBase, Google Patents, Google Scholar
 Search terms: EphA4, receptor, inhibitor, antagonist, cyclic, peptide, polypeptide, APY, lipoprotein signal peptidase, Lsp, assay, fluorescence resonance energy transfer, FRET

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/0180823 A1 (PASQUALE et al.) 16 September 2004 (16.09.2004) para [0058], [0071], [0131], [0142]	1
A, P	OLSON et al., Modifications of a Nanomolar Cyclic Peptide Antagonist for the EphA4 Receptor To Achieve High Plasma Stability. ACS Med Chem Lett., 25 June 2016, Vol 7, No 9, pp 841-846. Especially abstract	1
A, P	WO 2016/011201 A2 (SANFORD BURNHAM PREBYS MEDICAL DISCOVERY INST et al.) 21 January 2016 (21.01.2016) para [027]	1

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 December 2016

Date of mailing of the international search report

28 DEC 2016

Name and mailing address of the ISA/US

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Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/42669

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 4-51
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-----please see extra sheet-----

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-3, limited to SEQ ID NO: 3, wherein X1 is Ahx; X2 is P; X3 is Y; X5 is V; X6 is Y; X7, X9, X11 is any amino acid; has a modification that increases binding affinity (claim 1).

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/42669

Continuation of Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: Claims 1-3, drawn to a modified EphA4 receptor antagonist comprising a cyclic peptide having a length of 11 to 20 amino acids. The modified EphA4 receptor antagonist will be searched to the extent that the antagonist encompasses

- (claim 1) the sequence X1-X2-X3-C4-X5-X6-X7-.beta.A8-X9-W-X11-C12 (SEQ ID NO: 3), wherein X1 is Ahx;

X2 is P;

X3 is Y;

X5 is V;

X6 is Y;

X7 is any amino acid;

X9 is any amino acid; and

X11 is any amino acid;

wherein C4 and C12 form a disulfide bridge; and

wherein the cyclic peptide has a modification that increase binding affinity to EphA4;

It is believed that claim 1 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass a modified EphA4 receptor antagonist comprising a cyclic peptide having a length of 11 to 20 amino acids and including the sequence X1-X2-X3-C4-X5-X6-X7-.beta.A8-X9-W-X11-C12 (SEQ ID NO: 3), wherein X1 is Ahx; X2 is P; X3 is Y; X5 is V; X6 is Y; X7 is any amino acid; X9 is any amino acid; and X11 is any amino acid; wherein C4 and C12 form a disulfide bridge; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4, increase binding selectivity for EphA4, and/or increase physiological stability of the APY cyclic peptide.

Additional modified EphA4 receptor antagonist sequences will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected modified EphA4 receptor antagonist sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be a modified EphA4 receptor antagonist comprising a cyclic peptide having a length of 11 to 20 amino acids and including the sequence X1-X2-X3-C4-X5-X6-X7-.beta.A8-X9-W-X11-C12 (SEQ ID NO: 3) wherein X1 is Ava; X2 is P; X3 is Y; X5 is V; X6 is Y; X7 is any amino acid; X9 is any amino acid; and X11 is any amino acid; wherein C4 and C12 form a disulfide bridge; and wherein the cyclic peptide has a modification that increase binding affinity to EphA4; i.e. claim 1 limited to this specific modified EphA4 receptor antagonist sequence.

The inventions listed as Group I+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features

The technical feature of each of the inventions listed as Group I+ is the specific modified EphA4 receptor antagonist sequence recited therein. Each invention requires a modified EphA4 receptor antagonist sequence, not required by any of the other inventions

Common Technical Features

The feature shared by the inventions listed as Group I+ is a modified EphA4 receptor antagonist comprising a cyclic peptide having a length of 11 to 20 amino acids.

However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is taught by US 2004/0180823 A1 to Pasquale et al. (hereinafter 'Pasquale').

Pasquale discloses a modified EphA4 receptor antagonist comprising a cyclic peptide having a length of 11 to 20 amino acids (para [0142]) "The Eph receptor binding compounds described herein can also be administered to warm blooded animals, including humans, to modulate Eph receptors in vivo. For example, certain peptides disclosed herein can be used to selectively ... inhibit EphA4"; para [0058] "Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (for example, D-lysine in place of L-lysine) may be used to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated ... for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide"; para [0131] "The compounds may exist in a cyclized form with an intramolecular disulfide bond between the thiol groups of the cysteines"; para [0071] "As used herein, "Eph receptor binding agent" or "Eph receptor binding ligand" is a compound that binds to an Eph receptor. ... Such peptides or peptidomimetics can have a length of ... less than 20").

As the technical feature was known in the art at the time of the invention, it cannot be considered a special technical feature that would otherwise unify the groups.

The inventions listed as Group I+ therefore lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Item 4 (continued)

Claims 4-51 are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).