~~WHAT IS CLAIMED IS:~~

Claims

1. A cationic carrier unit comprising

~~[WP]-L1-[CC]-L2-[AM] (Schema I)~~

~~or~~

~~[WP]-L1-[AM]-L2-[CC] (Schema II)~~

~~wherein~~

~~WP is~~(i) a targeting moiety (A) which targets the transporter LAT1,

(ii) a water- soluble ~~biopolymer moiety;~~polymer which is PEG,

~~CC is~~(iii) a ~~positively charged~~cationic carrier moiety~~;~~ comprising cationic polymer blocks which are lysine, and

~~AM is an~~ (iv) two or more adjuvant ~~moiety; and,~~moieties which are vitamin B3.

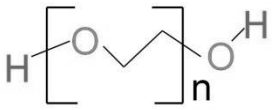
~~L1 and L2 are independently optional linkers, and~~

~~wherein when mixed with a nucleic acid at an ionic ratio of about 1:1, the cationic carrier unit forms a micelle.~~

~~1.~~ The cationic carrier unit of claim 1, wherein the ~~water-soluble polymer comprises poly(alkylene glycols), poly(oxyethylated polyol), poly(olefinic alcohol), poly(vinylpyrrolidone), poly(hydroxyalkylmethacrylamide), poly(hydroxyalkylmethacrylate), poly(saccharides), poly(α-hydroxy acid), poly(vinyl alcohol), polyglycerol, polyphosphazene, polyoxazolines ("POZ") poly(N-acryloylmorpholine), or any combinations thereof.~~

~~2. The cationic carrier unit of claim 1, wherein the water-soluble polymer comprises polyethylene glycol ("PEG"), polyglycerol, or poly(propylene glycol) ("PPG").~~

~~3. The cationic carrier unit of any one of claims 1 to 3, wherein the water-soluble polymer comprises:~~



~~wherein n is 1-1000.~~

~~4. The cationic carrier unit of claim 4, wherein the n is at least about 110, at least about 111, at least about 112, at least about 113, at least about 114, at least about 115, at least about 116, at least about 117, at least about 118, at least about 119, at least about 120, at least about 121, at least about 122, at least about 123, at least about 124, at least about 125, at least about 126, at least about 127, at least about 128, at least about 129, at least about 130, at least about 131, at least about 132, at least about 133, at least about 134, at least about 135, at least about 136, at least about 137, at least about 138, at least about 139, at least about 140, or at least about 141.~~

~~5. The cationic carrier unit of claim 4, wherein the n is about 80 to about 90, about 90 to about 100, about 100 to about 110, about 110 to about 120, about 120 to about 130, about 140 to about 150, about 150 to about 160.~~

~~6. The cationic carrier unit of any one of claims 1 to 6, wherein the water-soluble polymer is linear, branched, or dendritic.~~

~~7. The cationic carrier unit of any one of claims 1 to 7, wherein the cationic carrier~~targeting moiety comprises ~~one or more basic amino acids.~~

~~8. The cationic carrier unit of claim 8, wherein the cationic carrier moiety comprises at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least 11, at least 12, at least 13, at least 14, at last 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, at least 50, at least 51, at least 52, at least 53, at least 54, at least~~

55, at least 56, at least 57, at least 58, at least 59, at least 60, at least 61, at least 62, at least 63, at least 64, at least 65, at least 66, at least 67, at least 68, at least 69, at least 70, at least 71, at least 72, at least 73, at least 74, at least 75, at least 76, at least 77, at least 78, at least 79, or at least 80 basic amino acids.

9. The cationic carrier unit of claim 8, wherein the cationic carrier moiety comprises at least 60, at least about 70, at least about 80, at least about 90, at least about 100, at least about 110, at least about 120, at least about 130, at least about 140, or at least about 150 basic amino acids.

10. The cationic carrier unit of claim 9, wherein the cationic carrier moiety comprises about 30 to about 50 basic amino acids.

11. The cationic carrier unit of claim 10, wherein the cationic carrier moiety comprises about 60 to about 100, e.g., about 70 to about 90, e.g., about 80, basic amino acids.

12. The cationic carrier unit of any one of claims 9 to 12, wherein the basic amino acid comprises arginine, lysine, histidine, or any combination thereof.

13. The cationic carrier unit of any one of claims 1 to 13, wherein the cationic carrier moiety comprises about 40 lysine monomers.

14. cationic carrier unit of any one of claims 1 to 13, wherein the cationic carrier moiety comprises about 70, about 75, about 80, or about 85 lysine monomers.

15. The cationic carrier unit of any one of claims 1 to 15, wherein the adjuvant moiety is capable of modulating an immune response, an inflammatory response, and/or a tissue microenvironment.

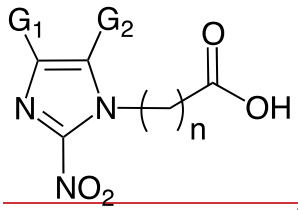
16. The cationic carrier unit of claim 16, wherein the adjuvant moiety is capable of modulating an immune response.

17. The cationic carrier unit of claim 16, wherein the adjuvant moiety is capable of modulating a tumor microenvironment in a subject with a tumor.

18. The cationic carrier unit of claim 16, wherein the adjuvant moiety is capable of inhibiting or reducing hypoxia in the tumor microenvironment.

19. The cationic carrier unit of any one of claims 17 to 18, wherein the adjuvant moiety comprises an imidazole derivative, an amino acid, a vitamin, or any combination thereof.

20. The cationic carrier unit of claim 20, wherein the adjuvant moiety comprises:



,

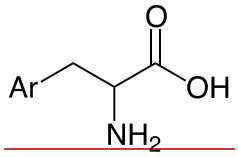
wherein each of G1 and G2 is H, an aromatic ring, or 1-10 alkyl, or G1 and G2 together form an aromatic ring, and wherein n is 1-10.

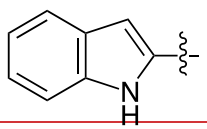
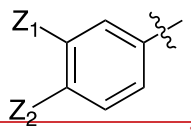
21. The cationic carrier unit of claim 21, wherein the adjuvant moiety comprises nitroimidazole.

22. The cationic carrier unit of claim 22, wherein the adjuvant moiety comprises metronidazole, tinidazole, nimorazole, dimetridazole, pretomanid, ornidazole, megazol, azanidazole, benznidazole, or any combination thereof.

23. The cationic carrier unit of claim 16, wherein the adjuvant moiety comprises an amino acid.

24. The cationic carrier unit of claim 16, wherein the adjuvant moiety comprises



wherein Ar is Ar=  or , and

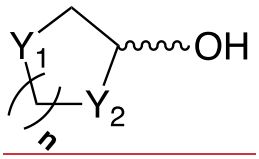
wherein each of Z1 and Z2 is H or OH.

~~25. The cationic carrier unit of claim 16, wherein the adjuvant moiety is capable of inhibiting or reducing an inflammatory response.~~

~~26. The cationic carrier unit of claim 26, wherein the adjuvant moiety is a vitamin.~~

~~27. The cationic carrier unit of claim 27, wherein the vitamin comprises a cyclic ring or cyclic hetero atom ring and a carboxyl group or hydroxyl group.~~

~~28. The cationic carrier unit of claim 28, wherein the vitamin comprises:~~



~~wherein each of Y1 and Y2 is C, N, O, or S, and wherein n is 1 or 2.~~

~~29. The cationic carrier unit of any one of claims 27 to 29, wherein the vitamin is selected from the group consisting of vitamin A, vitamin B1, vitamin B2, vitamin B3, vitamin B6, vitamin B7, vitamin B9, vitamin B12, vitamin C, vitamin D2, vitamin D3, vitamin E, vitamin M, vitamin H, and any combination thereof.~~

~~30. The cationic carrier unit of any one of claims 30, wherein the vitamin is vitamin B3.~~

~~31. The cationic carrier unit of any one of claims 1 to 31, wherein the adjuvant moiety comprises at least about two, at least about three, at least about four, at least about five, at least about six, at least about seven, at least about eight, at least about nine, at least about ten, at least about 11, at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, or at least about 20 vitamin B3.~~

~~32. The cationic carrier unit of any one of claims 1 to 31, wherein the adjuvant moiety comprises at least about 20, at least about 21, at least about 22, at least about 23, at least about 24, at least about 25, at least about 26, at least about 27, at least about 28, at least about 29, at least about 30, at least about 31, at least about 32, at least about 33, at least about 34, at least about 35, at least about 36, at least about 37, at least about 38, at least about 39, or at least about 40 vitamin B3.~~

~~33. The cationic carrier unit of claim 32 or 33, wherein the adjuvant moiety comprises about 10 vitamin B3, about 20 vitamin B3, about 30 vitamin B3, about 40 vitamin B3, or about 50 vitamin B3.~~

~~34. The cationic carrier unit of any one of claims 1 to 34, which comprises about a water-soluble biopolymer moiety with about 120 to about 130 PEG units, a cationic carrier moiety comprising a poly-lysine with about 30 to about 40 lysines, and an adjuvant moiety with about 5 to about 10 vitamin B3.~~

~~35. The cationic carrier unit of any one of claims 1 to 34, which comprises about a water-soluble biopolymer moiety with about 120 to about 130 PEG units, a cationic carrier moiety comprising a poly-lysine with about 70 to about 90 lysines, e.g., about 80 lysines, and an adjuvant moiety with about 20 to about 40 vitamin B3, e.g., about 30 vitamin B3.~~

2. ~~The cationic carrier unit of any one of claims 1 to 36, further comprising an anionic payload, which interacts with the cationic carrier unit via an ionic bond~~phenylalanine.

3. A micelle comprising the cationic carrier unit of ~~any one of claims~~claim 1 ~~to 37~~or 2 and an anionic payload~~, wherein the cationic carrier moiety of the cationic carrier complex and the anionic payload are associated with each other.~~.

4. The micelle of claim ~~38~~3, wherein the ~~association is~~positive charges of the cationic carrier moiety and the negative charges of the anionic payload in the micelle are at a ~~covalent bond.~~charge ratio of between about 1:3 and about 3:1.

~~36.~~ 5. The micelle of claim ~~38~~4, wherein the ~~association is a non-covalent bond.~~

~~37. The micelle of claim 40, wherein the association is an ionic bond.~~

~~38. The micelle of any one of claims 38 to 41, wherein the cationic carrier unit of any one of claims 1 to 36, wherein the positive charge of the cationic carrier moiety of the cationic carrier unit is sufficient to form a micelle when mixed with an anionic payload in a solution, wherein the overall ionic ratio of the~~ positive charges of the cationic carrier moiety ~~of the cationic carrier unit and the negative charges of the anionic payload in the solution is about 1: 1.~~

~~39. The micelle of any one of claims 38 to 41, wherein the cationic carrier unit of any one of claims 1 to 36, wherein the positive charge of the cationic carrier moiety of the cationic carrier unit is sufficient to form a micelle when mixed with an anionic payload in a solution, wherein the overall ionic ratio of the positive charges of the cationic carrier moiety of the cationic carrier unit and the negative charges of the anionic payload in the solution is between about 1:3 and about 3:1.~~

~~40. The micelle of any one of claims 38 to 43, wherein the cationic carrier unit is capable of protecting the anionic payload from degradation by a DNase and/or an RNase.~~

~~41. The micelle of any one of claims 38 to 44, wherein the anionic payload is not conjugated to the cationic carrier unit by a covalent bond and/or the anionic payload interacts with the cationic carrier moiety of the cationic carrier unit only via an ionic interaction.~~

~~42. The micelle of any one of claims 38 to 45, wherein the half-life of the anionic payload is extended compared to the half-life of a free anionic payload not incorporated into a micelle.~~

~~43. The micelle of any one of claims 36 to 46, wherein the positive charges of the cationic carrier moiety of the cationic carrier unit and the negative charges of the anionic payload in the micelle are at an ionic ratio of about 2:1, about 1.9:1, about 1.8:1, about 1.7:1, about 1.6:1, about 1.5:1, about 1.4:1, about 1.3:1, about 1.2:1, about 1:1, about 1:1.1, about 1:1.2, about 1:1.3, about 1:1.4, about 1:1.5, about 1:1.6, about 1:1.7, about 1:1.8, about 1:1.9, or about 1:2.~~

~~The micelle of any one of claims 36 to 46, wherein the positive charges of the cationic carrier moiety of the cationic carrier unit~~ and the negative charges of the anionic payload in the micelle are at ~~an ionic ratio of about 3:1, about 2.9:1, about 2.8:1, about 2.7:1, about 2.6:1, about 2.5:1, about 2.4:1, about 2.3:1, about 2.2:1, about 2.1:1, about 1:2.1, about 1:2.2, about 1:2.3, about 1:2.4, about 1:2.5, about 1:2.6, about 1:2.7, about 1:2.8, about 1:2.9, or about 1:3~~a charge ratio of about 1:1.

~~44. The micelle of claim 48, wherein the positive charges of the cationic carrier moiety of the cationic carrier unit and the negative charges of the anionic payload in the micelle are at a charge ratio of 1: 1.~~

~~45. The micelle of any one of claims 38 to 49, where the diameter of the micelle is between about 1nm and 100nm, between about 10nm and about 100nm, between about 10nm and about 90nm, between about 10nm and about 80nm, between about 10nm and about 70nm, between about 20nm and about 100nm, between about 20nm and about 90nm, between about 20nm and about 80nm, between about 20nm and about 70nm, between about 30nm and about 100nm, between about 30nm and about 90nm, between about 30nm and about 80nm, between about 30nm and about 70nm, between about 40nm and about 100nm, between about 40nm and about 90nm, between about 40nm and about 80nm, or between about 40nm and about 70nm.~~

~~46. The micelle of any one of claims 38 to 50, wherein the anionic payload comprises a nucleic acid.~~

~~The micelle of claim 51, wherein the nucleic acid comprises~~6. The micelle of any one of claims 3 to 5, wherein the anionic payload comprises a nucleic acid selected from the group consisting of mRNA, miRNA, miRNA sponge, tough decoy miRNA, antimir, small RNA, rRNA, siRNA, shRNA, gDNA, cDNA, pDNA, PNA, BNA, antisense oligonucleotide (ASO), aptamer, cyclic dinucleotide, or any combination thereof.

~~47. The micelle of any one of claims 1 to 52, wherein the nucleic acid comprises at least one nucleoside analog.~~

~~48. The micelle of any one of claims 53, wherein the nucleoside analog comprises Locked Nucleic Acid (LNA); 2'-0-alkyl-RNA; 2'-amino-DNA; 2'-fluoro-DNA; arabino nucleic acid (ANA); 2'-fluoro-ANA, hexitol nucleic acid (HNA), intercalating nucleic acid (INA), constrained ethyl nucleoside (cEt), 2'-0-methyl nucleic acid (2'-OMe), 2'-0- methoxyethyl nucleic acid (2'-MOE), or any combination thereof.~~

~~The micelle of any one of claims 51 to 54~~7. The micelle of claim 6, wherein the nucleic acid comprises a nucleotide sequence having 5 to 30 nucleotides in length.

~~49. The micelle of claim 55, wherein the nucleotide sequence is 7,~~ 8~~, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26 nucleotides in length.~~

~~50. The micelle of claim 55 or 56, wherein the nucleotide sequence has a backbone, which comprises a phosphodiester linkage, a phosphotriester linkage, a methylphosphonate linkage, a phosphoramidate linkage, a phosphorothioate linkage, and combinations thereof.~~

. The micelle of any one of claims ~~38~~3 to ~~57~~7, wherein

(a) the water soluble polymer comprises between about 40 and about 1000 ethylene glycol units;

(b) the cationic carrier ~~unit further~~moiety comprises ~~a targeting moiety, which is linked to~~ between about 3 and about 100 lysines; and,

(c) the adjuvant moieties comprise between 1 and 100 vitamin B3.

9. The micelle of any one of claims 3 to 7, wherein

(a) the water soluble polymer ~~optionally via a linker.~~ comprises about 40, 100, 150, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 ethylene glycol units;

(b) the cationic carrier moiety comprises about 3, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 lysines; and,

(c) the adjuvant moieties comprise about 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 vitamin B3.

10. The micelle of ~~claim 58~~any one of claims 3 to 7, wherein

(a) the ~~targeting~~water soluble polymer comprises about 100 to about 120 ethylene glycol units;

~~(a)~~(b) the cationic carrier moiety ~~is capable of targeting~~comprises a ~~tissue.~~poly-lysine with about 30 to about 40 lysines; and,

(c) the adjuvant moieties comprise about 5 to about 10 vitamin B3.

11. The micelle of ~~claim 59~~any one of claims 3 to 7, wherein ~~the tissue is liver, brain, kidney, lung, ovary, pancreas, thyroid, breast, stomach, or any combination thereof.~~

~~51. The micelle of claim 59, wherein the tissue is cancer tissue.~~

(a) the water soluble polymer comprises about 120 to about 130 ethylene glycol units;

(b) the cationic carrier moiety comprising about 70 to about 90 lysines; and,

(c) the adjuvant moieties comprising about 20 to about 50 vitamin B3.

~~52.~~ 12. The micelle of ~~claim 59~~any one of claims 3 to 11, wherein the ~~tissue is liver.~~

~~53. The micelle of claim 62, wherein the targeting moiety comprises cholesterol.~~

~~54. The micelle of claim 59, wherein the tissue is pancreas.~~

~~55. The micelle of claim 59, wherein the targeting moiety comprises a ligand targeting an integrin.~~

~~56. The micelle of claim 59, wherein the targeting~~cationic carrier moiety ~~targets~~and the ~~central nervous system.~~

~~57. The micelle of claim 66, wherein the targeting moiety is capable of being transported~~anionic payload are associated by ~~large neutral amino acid transporter 1 (LAT1).~~

~~58. The micelle of claim 67, wherein the targeting moiety is an amino acid.~~

~~The micelle of claim 68, wherein the targeting moiety comprises~~ a ~~branched-chain~~covalent bond, a non-covalent bond, or ~~aromatic amino acid.~~ an ionic bond.

~~59. The micelle of claim 68, wherein the amino acid is valine, leucine, and/or isoleucine.~~

~~60. The micelle of claim 68, wherein the amino acid is tryptophan and/or tyrosine.~~

~~61. A composition comprising the cationic carrier unit of any one of claims 1 to 37 and a negatively charged molecule.~~

13. A pharmaceutical composition comprising the cationic carrier unit of ~~any one of claims 1 to 37, the composition of~~ claim ~~72,~~1 or 2 or the micelle of any one of claims ~~38~~3 to ~~71,~~12 and a pharmaceutically acceptable carrier.

~~62.~~ 14. A method of preparing the ~~cationic carrier unit of any one of claims 1 to 37 comprising synthesizing the cationic carrier unit.~~

~~63. The method of preparing the~~ micelle of any one of claims ~~38 to 71, comprising mixing the cationic carrier unit with the negatively charged molecule at an ionic ratio of 1:1 in solution.~~

~~The method of preparing the micelle of any one of claims 38 to 71~~3 to 12, comprising mixing the cationic carrier unit with the ~~negatively charged molecule~~anionic payload at an ionic ratio ~~between about~~of 1~~:3 and about 3~~:1 in solution.

~~64.~~ 15. The ~~method of claim 76, further comprising purifying~~ micelle of any one of claims 3 to 12 for use in the ~~micelle.~~

~~A method~~treatment of ~~treating~~ a disease or condition ~~in a subject in need thereof comprising administering~~ .

16. Use of the micelle of any one of claims ~~38 to 71~~3 to 12 in the ~~subject.~~ manufacture of a medicament for the treatment of a disease or condition.

17. The ~~method of claim 78~~micelle of any one of claims 3 to 12 for use in the treatment of a neurodegenerative disease, wherein the ~~anionic payload in the core of the~~ micelle ~~exhibits a longer half-life than a corresponding anionic payload not integrated into a micelle.~~ reduces inflammation.

~~65.~~ 18. The ~~method of claim 78 or 79, wherein the subject is a mammal.~~

~~66. A method of treating cancer in a subject in need thereof comprising administering a therapeutically effective amount of a~~ micelle of any one of claims ~~38~~3 to ~~71 to~~12 for use in the ~~subject.~~

67. The methodtreatment of claim 81a neurodegenerative disease, wherein the cancer is glioma, breast cancer, pancreatic cancer, liver cancer, skin cancermicelle recovers, induces, or cervical cancer.

68. The method of claim 82, wherein the pancreatic cancer is pancreatic adenocarcinoma.

69. A method to reduce inflammation in a subject suffering from a neurodegenerative disease comprising administering a therapeutically effective amount of a micelle of any one of claims 38 to 71 to the subject.

A method to recoverrecovers and/or induce induces neurogenesis in a subject suffering from a neurodegenerative disease comprising administering a therapeutically effective amount of a .

70. 19. The micelle of any one of claims 38 to 71to the subject.

A method to improve3 to 12 for use in the treatment of a neurodegenerative disease, wherein the micelle improves cognitive function in a subject suffering from a neurodegenerative disease comprising administering a therapeutically effective amount of a micelle of any one of claims 38 to 71 to the subject.

The method20. Use of the micelle of any one of claims 843 to 86, wherein12 in the manufacture of a medicament for the treatment of a neurodegenerative disease is.

71. 21. The micelle of any one of claims 3 to 12 for use in the treatment of Alzheimer's disease.

A method to reduce, wherein the micelle reduces amyloid plaque burden in a subject suffering from.

22. Use of the micelle of any one of claims 3 to 12 in the manufacture of a medicament for the treatment of Alzheimer's disease comprising administering a therapeutically effective amount of a micelle of any one of claims 38 to 71 to the subject.

~~72. The method of any one of claims 84 to 88, wherein the micelle comprises a cationic carrier unit targeting LAT1 and a payload comprising an antisense oligonucleotide of SEQ ID NO: 18, or a fragment, variant, or derivative thereof.~~

~~73. The method of claim 89, wherein the fragment comprises 14, 15, 16, 17, 18, 19, 20, or 21 consecutive nucleotides of SEQ ID NO: 18.~~

~~74. The method of claim 89, wherein the variant has at least 70% sequence identity to SEQ ID NO: 18.~~

~~The method of claim 89, wherein the derivative comprises at least one sugar modification and/or at least one backbone modification.~~