CLAIMS

The embodiments of the disclosure in which an exclusive property or privilege is claimed are defined as follows:

1. Use of a composition comprising a long acting CNP, a very long acting CNP, a long acting CNP derivative, a very long acting CNP derivative, a long acting NPRB agonist, a very long acting NPRB agonist, or any combination thereof, in the manufacture of a medicament for treating a subject having an abnormal vasculature, in any tissue or organ, wherein the composition is to be administered in a therapeutically effective bolus dose to the subject,

wherein administration of the therapeutically effective bolus dose of the composition provides a vasculature normalization or an increase in pericyte coating index by at least 10%,

wherein the composition does not decrease blood pressure by more than 20% of a baseline blood pressure measurement, and

wherein the composition increases plasma cyclic-GMP level at from 1 hour to 12 hours after administration to above 1.5x of a baseline plasma cyclic-GMP level, and the baseline plasma cyclic-GMP level is an average plasma cyclic-GMP level prior to administration of the composition or the average plasma cyclic-GMP level of a healthy subject.

2. Use of a composition comprising a long acting CNP, a very long acting CNP, a long acting CNP derivative, a very long acting CNP derivative, a long acting NPRB agonist, a very long acting NPRB agonist, or any combination thereof, in the manufacture of a medicament for increasing a number of cytotoxic T-cells and/or a number of activated NK cells, wherein the composition is to be administered to a subject in a therapeutically effective bolus dose,

wherein the therapeutically effective bolus dose of the composition provides an increase in the number of cytotoxic T cells and/or NK cells of at least 15% above the level prior to administration of the composition or above the level in a healthy subject,

wherein administration of the therapeutically effective bolus dose of the composition does not decrease blood pressure by more than 20% of a baseline blood pressure measurement, and

wherein the composition increases plasma cyclic-GMP level at from 1 hour to 12 hours after administration to above 1.5x of a baseline plasma cyclic-GMP level, and the baseline plasma cyclic-GMP level is an average plasma cyclic-GMP level prior to administration of the composition or the average plasma cyclic-GMP level of a healthy subject.

3. The use of Claim 1 or Claim 2, wherein:

the subject has a condition (i) to (viii):

(i) a low number of cytotoxic T cells,

(ii) a low number of activated NK cells,

(iii) a high number of Treg cells,

(iv) a high level of expression of TGFβ,

(v) a high level or expression of Foxp3,

(vi) a high number of myeloid-derived suppressor cells or MDSCs,

(vii) a high level or expression of Bv8; or

(viii) any combination thereof; or

the subject is in need of (ix) to (xvi):

(ix) an increase in a number of cytotoxic T-cells;

(x) an increase in activated NK cells;

(xi) a decrease in a number of Treg cells;

(xii) a decrease in TGF-β expression;

(xiii) a decrease in Foxp3 expression;

(xiv) a decrease in a number of myeloid-derived suppressor cells (MDSCs);

(xv)a decrease in Bv8 expression, or

(xvi) any combination thereof,

wherein administration of the therapeutically effective bolus dose of the composition provides a reduction in tumor size when present, an increase in the number of cytotoxic T-cells, an increase in the number of activated NK cells, a reduction in the number of Treg cells, a decrease in the level or expression of TGFβ, a decrease in the level or expression of Foxp3, a decrease in the number of myeloid-derived suppressor cells (MDSCs), a decrease in the level or expression of Bv8, an improvement in survival/lifespan, or a combination thereof.

4. Use of a composition comprising a long acting CNP derivative or a very long acting CNP derivative comprising U-GLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 2], U-GLSKGCFGLK(U)LDRIGSMSGLGC [SEQ ID NO. 3], GLSKGCFGLK(U)LDRIGSMSGLGC [SEQ ID NO. 4], U-CFGLKLDRIGSxSGLGC, in the manufacture of a medicament for treating a subject having cancer, wherein the composition is to be administered to the subject in need thereof in a therapeutically effective bolus dose, where x is a natural or unnatural amino acid residue [SEQ ID NO. 11], or any combination thereof,

wherein:

U is a moiety of Formula (I) or (II), where Formula (I) is

$$(\text{aliphatic})_a\text{-}(X)\text{-};$$

(I)

wherein

a is 1;

aliphatic is an optionally substituted $C_{4\text{-}24}$ chain (*e.g.*, an optionally substituted $C_{10\text{-}24}$ chain, an optionally substituted $C_{12\text{-}18}$ chain), covalently bound to X via a chemical linkage, such as a carbonyl (*e.g.*, as part of an amide or an ester linkage), a thioether, an ether, a thioether, a carbamate moiety, a bond, or the like with X; preferably via a carbonyl as part of an amide or an ester linkage; or more preferably via a carbonyl as part of an amide linkage with X;

X is a 1-10 amino acid residue or peptide sequence, wherein each amino acid residue is independently selected from lysine (K), arginine (R), glycine (G), alanine (A), glutamic acid (E), and aspartic acid (D); or

X is a linker $(\gamma E)_m\text{-}(B)_n$ wherein B is 1-8 amino acid residue or peptide sequence wherein each amino acid residue is independently selected from 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, Gly, Ala, Leu, Ser, Arg, and Lys; m is 0, 1, 2, or 3; n is 0, 1, 2, or 3; and the sum of m and n is at least 1;

and Formula (II) is

$$(\text{polymer})_a\text{-}(Y)\text{-};$$

(II)

wherein

a is 1;

polymer is cellulose, poly(ethylene glycol) (PEG), methoxy poly(ethylene glycol) (MPEG), poly(lactic-co-glycolic acid), poly(N-vinyl pyrrolidone), or a derivative thereof;

Y is:

a 1-10 amino acid residue or peptide sequence, wherein each amino acid residue is independently selected from lysine (K), arginine (R), glycine (G), alanine (A), glutamic acid (E), and aspartic acid (D);

a non-amino acid linker comprising an ester, an amide, a thioether, an ether, a thioether, a carbamate moiety, or a combination thereof;

an amino acid residue-containing linker, wherein the amino acid residue is covalently attached to $(polymer)_a$; or

a peptide linker different from the 1-10 amino acid residue or peptide sequence;

wherein the composition does not decrease blood pressure by more than 15% of a baseline blood pressure measurement; and

wherein the composition increases plasma cyclic-GMP level at from 1 hour to 12 hours to above 1.5x of a baseline plasma cyclic-GMP level, and the baseline plasma cyclic-GMP level is an average plasma cyclic-GMP level prior to administration of the composition or the average plasma cyclic-GMP level of a healthy subject.

5. The use of Claim 4, wherein Y is a linker $(\gamma E)_m$-$(B)_n$, wherein B is 1-8 amino acid residue or peptide sequence wherein each amino acid residue is independently selected from 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, Gly, Ala, Leu, Ser, Arg, and Lys; m is 0, 1, 2, or 3; n is 0, 1, 2, or 3; and the sum of m and n is at least 1.

6. The use of Claim 4 or Claim 5, wherein the long acting CNP derivative is selected from

$CH_3(CH_2)_{16}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 6];

$CH_3(CH_2)_{14}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 5];

$CH_3(CH_2)_{18}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 7];

$CH_3(CH_2)_{20}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 8];

$CH_3(CH_2)_{22}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 9];

$HOC(=O)(CH_2)_{16}C(=O)$-γE-Aeea-Aeea-GCFGLKLDRIGShomoQSGLGC comprising a disulfide bond between the cysteine residues [SEQ ID NO. 20]; and

$HOC(=O)(CH_2)_{16}C(=O)$-Aeea-Aeea-GCFGLKLDRIGShomoQSGLGC comprising a disulfide bond between the cysteine residues [SEQ ID NO. 21].

7. The use of any one of Claims 4 to 6, wherein the long acting CNP derivative is $CH_3(CH_2)_{16}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 6].

8. The use of any one of Claims 4 to 6, wherein the long acting CNP derivative is $CH_3(CH_2)_{14}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 5].

9. The use of any one of Claims 4 to 6, wherein the long acting CNP derivative is $CH_3(CH_2)_{18}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 7].

10. The use of any one of Claims 4 to 6, wherein the long acting CNP derivative is $CH_3(CH_2)_{20}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 8].

11. The use of any one of Claims 4 to 6, wherein the long acting CNP derivative is $CH_3(CH_2)_{22}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 9].

12. The use of any one of Claims 4 to 6, wherein the long acting CNP derivative is $HOC(=O)(CH_2)_{16}C(=O)$-γE-Aeea-Aeea-GCFGLKLDRIGShomoQSGLGC comprising a disulfide bond between the cysteine residues [SEQ ID NO. 20].

13. The use of any one of Claims 4 to 6, wherein the long acting CNP derivative is $HOC(=O)(CH_2)_{16}C(=O)$-Aeea-Aeea-GCFGLKLDRIGShomoQSGLGC comprising a disulfide bond between the cysteine residues [SEQ ID NO. 21].

14. The use of any one of Claims 1 to 3, wherein the subject further has a low number of cytotoxic T cells, a low number of activated NK cells, or both a low number of cytotoxic T cells and a low number of activated NK cells prior to administering the therapeutically effective bolus dose of the composition.

15. The use of any one of Claims 1 to 3, wherein the long acting CNP derivative or the very long acting CNP derivative comprises U-GLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 2], U-GLSKGCFGLK(U)LDRIGSMSGLGC [SEQ ID NO. 3], GLSKGCFGLK(U)LDRIGSMSGLGC [SEQ ID NO. 4], U-CFGLKLDRIGSxSGLGC, where x is a natural or unnatural amino acid residue [SEQ ID NO. 11], or any combination thereof,

wherein:

U is a moiety of Formula (I) or (II), where Formula (I) is

$$(\text{aliphatic})_a\text{-(X)-};$$

(I)

wherein

a is 1;

aliphatic is an optionally substituted $C_{4\text{-}24}$ chain (*e.g.*, an optionally substituted $C_{10\text{-}24}$ chain, an optionally substituted $C_{12\text{-}18}$ chain), covalently bound to X via a chemical linkage, such as a carbonyl (*e.g.*, as part of an amide or an ester linkage), a thioether, an ether, a thioether, a carbamate moiety, a bond, or the like with X; preferably via a carbonyl as part of an amide or an ester linkage; or more preferably via a carbonyl as part of an amide linkage with X;

X is a 1-10 amino acid residue or peptide sequence, wherein each amino acid residue is independently selected from lysine (K), arginine (R), glycine (G), alanine (A), glutamic acid (E), and aspartic acid (D); or

X is a linker $(\gamma E)_m\text{-}(B)_n$,

wherein B is a 1-8 amino acid residue sequence wherein each amino acid residue is independently selected from 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, Gly, Ala, Leu, Ser, Arg, and Lys;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3; and

the sum of m and n is at least 1,

and Formula (II) is

$$(\text{polymer})_a\text{-}(Y)\text{-};$$

(II)

wherein

a is 1;

polymer is cellulose, poly(ethylene glycol) (PEG), methoxy poly(ethylene glycol) (MPEG), poly(lactic-co-glycolic acid), poly(N-vinyl pyrrolidone), or a derivative thereof;

Y is:

a 1-10 amino acid residue or peptide sequence, wherein each amino acid residue is independently selected from lysine (K), arginine (R), glycine (G), alanine (A), glutamic acid (E), and aspartic acid (D);

a non-amino acid linker comprising an ester, an amide, a thioether, an ether, a thioether, a carbamate moiety, or a combination thereof;

an amino acid residue-containing linker, wherein the amino acid residue is covalently attached to $(\text{polymer})_a$; or

a peptide linker different from the 1-10 amino acid residue or peptide sequence.

16. The use of Claim 15, wherein Y is a linker $(\gamma E)_m\text{-}(B)_n$, wherein B is a 1-8 amino acid residue or peptide sequence wherein each amino acid residue is independently selected from a 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, Gly, Ala, Leu, Ser, Arg, and Lys; m is 0, 1, 2, or 3; n is 0, 1, 2, or 3; and the sum of m and n is at least 1.

17. The use of Claim 15, wherein the long acting CNP derivative or the very long acting CNP derivative comprises U-GLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 2], U-GLSKGCFGLK(U)LDRIGSMSGLGC [SEQ ID NO. 3], GLSKGCFGLK(U)LDRIGSMSGLGC [SEQ ID NO. 4], U-CFGLKLDRIGSxSGLGC, where x is a natural or unnatural amino acid residue [SEQ ID NO. 12], or any combination thereof; and;

wherein:

U is a moiety of Formula (I), where Formula (I) is

$(aliphatic)_a$-(X)-;

(I)

wherein

a is 1;

aliphatic is an optionally substituted C_{10-24} chain (*e.g.*, an optionally substituted C_{12-18} chain), covalently bound to X via a chemical linkage, such as a carbonyl (*e.g.*, as part of an amide or an ester linkage), a thioether, an ether, a thioether, a carbamate moiety, a bond, or the like with X; preferably via a carbonyl as part of an amide or an ester linkage; or more preferably via a carbonyl as part of an amide linkage with X;

X is a 1-10 amino acid residue or peptide sequence, wherein each amino acid residue is independently selected from lysine (K), arginine (R), glycine (G), alanine (A), glutamic acid (E), and aspartic acid (D); or

X is a linker $(\gamma E)_m$-$(B)_n$,

wherein B is a 1-8 amino acid residue or peptide sequence wherein each amino acid residue is independently selected from 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, Gly, Ala, Leu, Ser, Arg, and Lys;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3; and

the sum of m and n is at least 1.

18. The use of Claim 15, wherein X is a 4-7 amino acid sequence, wherein each amino acid residue is independently selected from lysine (K), arginine (R), and glycine (G), or

X is a linker $(\gamma E)_m$-$(B)_n$ wherein B is a 1-8 amino acid residue sequence wherein each amino acid residue is independently selected from 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, Gly, Ala, Leu, Ser, Arg, and Lys; m is 0, 1, 2, or 3; n is 0, 1, 2, or 3; and the sum of m and n is at least 1.

19. The use of Claim 15, wherein the long acting CNP derivative or the very long acting CNP derivative comprises U-GLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 2],

wherein:

U is $(aliphatic)_a$-(X)-;

wherein

a is 1;

aliphatic is an optionally substituted C_{4-24} chain (*e.g.*, an optionally substituted C_{10-24} chain, an optionally substituted C_{12-18} chain), covalently bound to X via a chemical linkage, such as a carbonyl (*e.g.*, as part of an amide or an ester linkage), a thioether, an ether, a thioether, a carbamate moiety, a bond, or the like with X; preferably via a carbonyl as part of an amide or an ester linkage; or more preferably via a carbonyl as part of an amide linkage with X;

X is a 1-10 amino acid residue or peptide sequence, wherein each amino acid residue is independently selected from lysine (K), arginine (R), glycine (G), alanine (A), glutamic acid (E), and aspartic acid (D); or

X is a linker $(\gamma E)_m$-$(B)_n$ wherein B is a 1-8 amino acid residue sequence wherein each amino acid residue is independently selected from 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, Gly, Ala, Leu, Ser, Arg, and Lys; m is 0, 1, 2, or 3; n is 0, 1, 2, or 3; and the sum of m and n is at least 1.

20. The use of Claim 15, wherein aliphatic does not comprise a straight or branched optionally substituted C_{4-9} chain (*e.g.*, an optionally substituted C_{3-8} alkyl-C(=O)- moiety, and/or an optionally substituted C_{4-9} chain that is covalently bound to the peptide via a linkage such as a thioether, an ether, a thioether, a carbamate moiety, a bond, or the like).

21. The use of any one of Claims 1 to 3, wherein the long acting CNP derivative is selected from

$CH_3(CH_2)_{16}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 6];

$CH_3(CH_2)_{14}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 5];

$CH_3(CH_2)_{18}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 7];

$CH_3(CH_2)_{20}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 8];

$CH_3(CH_2)_{22}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 9];

$HOC(=O)(CH_2)_{16}C(=O)$-γE-Aeea-Aeea-GCFGLKLDRIGShomoQSGLGC comprising a disulfide bond between the cysteine residues [SEQ ID NO. 20]; and

$HOC(=O)(CH_2)_{16}C(=O)$-Aeea-Aeea-GCFGLKLDRIGShomoQSGLGC comprising a disulfide bond between the cysteine residues [SEQ ID NO. 21].

22. The use of any one of Claims 1 to 3, wherein the long acting CNP derivative is $CH_3(CH_2)_{16}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 6].

23. The use of any one of Claims 1 to 3, wherein the long acting CNP derivative is $CH_3(CH_2)_{14}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 5].

24. The use of any one of Claims 1 to 3, wherein the long acting CNP derivative is $CH_3(CH_2)_{18}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 7].

25. The use of any one of Claims 1 to 3, wherein the long acting CNP derivative is $CH_3(CH_2)_{20}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 8].

26. The use of any one of Claims 1 to 3, wherein the long acting CNP derivative is $CH_3(CH_2)_{22}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 9].

27. The use of any one of Claims 1 to 3, wherein the long acting CNP derivative is $HOC(=O)(CH_2)_{16}C(=O)$-γE-Aeea-Aeea-GCFGLKLDRIGShomoQSGLGC comprising a disulfide bond between the cysteine residues [SEQ ID NO. 20]

28. The use of any one of Claims 1 to 3, wherein the long acting CNP derivative is $HOC(=O)(CH_2)_{16}C(=O)$-Aeea-Aeea-GCFGLKLDRIGShomoQSGLGC comprising a disulfide bond between the cysteine residues [SEQ ID NO. 21]

29. The use of Claim 15, wherein the long acting CNP derivative or the very long acting CNP derivative comprises U-GLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 2], U-GLSKGCFGLK(U)LDRIGSMSGLGC [SEQ ID NO. 3], GLSKGCFGLK(U)LDRIGSMSGLGC [SEQ ID NO. 4], U-CFGLKLDRIGSxSGLGC,

where x is a natural or unnatural amino acid residue [SEQ ID NO. 27], or any combination thereof;

wherein:

U is a moiety of Formula (II), where Formula (II) is

$(polymer)_a$-(Y)-;

(II)

wherein

a is 1;

polymer is cellulose, poly(ethylene glycol) (PEG), methoxy poly(ethylene glycol) (MPEG), poly(lactic-co-glycolic acid), or poly(N-vinyl pyrrolidone);

Y is:

a 4-10 amino acid residue or peptide sequence, wherein each amino acid residue is independently selected from lysine (K), arginine (R), and glycine (G);

a non-amino acid linker comprising an ester, an amide, a thioether, an ether, a thioether, a carbamate moiety, or a combination thereof; or

a linker $(\gamma E)_m$-$(B)_n$, wherein B is 1-8 amino acid residue sequence wherein each amino acid residue is independently selected from 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, Gly, Ala, Leu, Ser, Arg, and Lys; m is 0, 1, 2, or 3; n is 0, 1, 2, or 3; and the sum of m and n is at least 1.

30. The use of Claim 29, wherein the long acting CNP derivative or the very long acting CNP derivative comprises U-GLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 2], U-GLSKGCFGLK(U)LDRIGSMSGLGC [SEQ ID NO. 3], or any combination thereof;

wherein:

U is a moiety of Formula (II), where Formula (II) is

$(polymer)_a$-(Y)-;

(II)

wherein

a is 1;

polymer is cellulose, poly(ethylene glycol) (PEG), methoxy poly(ethylene glycol) (MPEG), poly(lactic-co-glycolic acid), poly(N-vinyl pyrrolidone), or a derivative thereof;

Y is:

a 1-10 amino acid residue or peptide sequence, wherein each amino acid residue is independently selected from lysine (K), arginine (R), glycine (G), alanine (A), glutamic acid (E), and aspartic acid (D);

a non-amino acid linker comprising an ester, an amide, a thioether, an ether, a thioether, a carbamate moiety, or a combination thereof;

an amino acid residue-containing linker, wherein the amino acid residue is covalently attached to $(polymer)_a$;

a peptide linker different from the 1-10 amino acid residue or peptide sequence; or

a linker $(\gamma E)_m$-$(B)_n$, wherein B is 1-8 amino acid residue sequence wherein each amino acid residue is independently selected from a 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, Gly, Ala, Leu, Ser, Arg, and Lys; m is 0, 1, 2, or 3; n is 0, 1, 2, or 3; and the sum of m and n is at least 1.

31. The use of Claim 29, wherein the polymer does not include poly(ethylene glycol), MPEG, or both poly(ethylene glycol) and MPEG.

32. The use of Claim 15, wherein Y is:

a 4-10 amino acid residue or peptide sequence, wherein each amino acid residue is independently selected from lysine (K), arginine (R), and glycine (G); or

a linker $(\gamma E)_m$-$(B)_n$, wherein B is 1-8 amino acid residue or peptide sequence wherein each amino acid residue is independently selected from 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, Gly, Ala, Leu, Ser, Arg, and Lys; m is 0, 1, 2, or 3; n is 0, 1, 2, or 3; and the sum of m and n is at least 1.

33. The use of any one of Claims 1 to 3, wherein the bolus dose administration occurs at most twice a day and the route of administration comprises subcutaneous, intravenous, by inhalation, intramuscular, nasal, enteral, or any combination thereof, or

wherein the route of administration is subcutaneous; or

wherein the route of administration is intravenous; or

wherein the route of administration is intramuscular; or

wherein the route of administration is by inhalation; or

wherein the route of administration is nasal; or

wherein the enteral route of administration is oral.

34. The use of any one of Claims 1 to 3, wherein the subject has cancer.

35. The use of Claim 34, wherein the cancer is selected from breast cancer; bone cancer; prostate cancer; colon cancer, head cancer, neck cancer, liver cancer, kidney cancer, cervical cancer, lung cancer, stomach cancer, urethra cancer, bladder cancer, cancer of the ureter, renal pelvic cancer, cancer of the rectum, esophageal cancer, cancer of the lymph node, pancreatic cancer, stomach cancer, ovarian cancer; cancer of the central nervous system, soft tissue cancer, endocrine gland cancer; or any combination thereof, or

wherein the subject has skin cancer; or

wherein the subject has colon cancer; or

wherein the subject has breast cancer; or

wherein the subject has bone cancer; or

wherein the subject has prostate cancer.

36. The use of Claim 34, wherein the cancer is responsive to a cytotoxic cell immunostimulant.

37. The use of Claim 34, wherein the cancer is selected from head and neck cancer, skin cancer, liver cancer, kidney cancer, cervical cancer, lung cancer, breast cancer, stomach cancer, colon cancer, lymph node cancer, pancreatic cancer, ovary such as dMMR, cancer of the urethra, bladder, ureters, renal pelvis, and surrounding organs.

38. The use of Claim 35, wherein

the skin cancer comprises Merkel cell carcinoma, squamous cell carcinoma, melanoma, or any combination thereof;

the liver cancer comprises hepatocellular carcinoma;

the kidney cancer comprises renal cell carcinoma;

the lung cancer comprises small cell or non-small cell lung carcinoma;

the breast cancer comprises triple negative breast cancer;

the stomach cancer comprises gastric cancer, adenocarcinoma of esophageal junction, or dMMR);

the lymph node cancer comprises Hodgkin or non-Hodgkin PMBCL;

the pancreatic cancer and ovarian cancer each independent comprises dMMR; and

the cancer of the surrounding organs to the renal pelvic area comprises urothelial cancer.

39. The use of Claim 34, wherein the subject is to be further administered

an immune adjuvant, wherein the immune adjuvant modulates a toll-like receptor, or a cytotoxic cell immunostimulant comprising therapeutic agents or antibodies targeting an immune checkpoint protein selected from CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), PD1 (programmed cell death protein 1 or CD279), PD-L1 (programmed death-ligand 1), PD-L2 (programmed death-ligand 2), LAG-3 (lymphocyte-activation gene 3 protein), BTLA (B- and T-lymphocyte attenuator), B7H3 ((CD276, an immune checkpoint member of the B7 and CD28 families), B7H4 (a molecule of the B7 family, negatively regulates T cell immunity), and TIM-3 (a co-inhibitory receptor that is expressed on IFN-γ-producing T cells); wherein the cytotoxic cell immunostimulant inhibits an immune checkpoint protein; or

wherein cytotoxic cell immunostimulant comprises an antibody or portion of an antibody against an immune checkpoint protein, a soluble ligand of an immune checkpoint protein, pembrolizumab, Nivolumab, Ipilimumab, Atezolizumab, Avelumab, Durvalumab, Cemiplimab, tremelimumab, lambrolizumab, and/or pidilizumab; or

wherein the immune adjuvant comprises a toll-like receptor 9 agonist; or

wherein the immune adjuvant comprises a CpG oligodeoxynucleotide.

40. The use of Claim 34, wherein the subject is to be further administered CAR T-cells.

41. The use of any one of Claims 1 to 3, wherein the composition comprises a long acting CNP composition or a very long acting CNP derivative composition comprising a CNP, a CNP derivative, or a long acting CNP derivative and a polymer excipient, the polymer excipient comprising a poly(amino acid) grafted with polyethylene glycol, fatty

acid, anionic moieties, or any combination thereof; wherein the polymer excipient is adapted to sequester or non-covalently bind to any of the CNP or CNP derivatives..

42. The use of any one of Claims 1 to 3, wherein the composition comprises a very long acting CNP derivative composition comprising a long acting CNP derivative and a polymer excipient, the polymer excipient comprising a poly(amino acid) grafted with polyethylene glycol, fatty acid, anionic moieties, or any combination thereof; and wherein the polymer excipient is adapted to sequester or non-covalently bind to the long acting CNP derivative.

43. The uae of any one of Claims 1 to 3, wherein the long acting NPRB agonist or the very long acting NPRB agonist comprises a polypeptide.

44. The use of Claim 43, wherein the polypeptide comprises an antibody.

45. The use of 43, wherein the long acting NPRB agonist or the very long acting NPRB agonist comprises a molecule of a molecular weight of less than 2kDa.

46. The use of any one of Claims 1 to 3, wherein the composition does not decrease blood pressure by more than 15% of a baseline blood pressure measurement.

47. The use of any one of Claims 1 to 3, wherein the composition does not decrease blood pressure by more than 10% of a baseline blood pressure measurement.

48. The use of any one of Claims 4 to 13 and 44 to 47, wherein the composition comprises a very long acting CNP derivative composition comprising a long acting CNP derivative and a polymer excipient, the polymer excipient comprising a poly(amino acid) grafted with polyethylene glycol, fatty acid, anionic moieties, or any combination thereof; wherein the polymer excipient is adapted to sequester or non-covalently bind to the long acting CNP derivative.

49. The use of any one of Claims 1 to 48, wherein the subject has a tumor and administration of the therapeutically effective bolus dose of the composition to the subject increases vasculature normalization or an increase in pericyte coating index by at least 20% within a tumor tissue.

50. The use of any one of Claims 1 to 49, wherein the subject has a tumor and administration of the therapeutically effective bolus dose of the composition to the subject decreases the tumor size.

51. The use of any one of Claims 1 to 50, wherein the subject has a tumor and administration of the therapeutically effective bolus dose of the composition to the subject improves survival of the subject.

52. The use of any one of Claims 1 to 51, wherein the subject has a tumor and administration of the therapeutically effective bolus dose of the composition to the subject increases the number of cytotoxic T-cells within the tumor.

53. The use of any one of Claims 1 to 52, wherein the subject has a tumor and administration of the therapeutically effective bolus dose of the composition to the subject increases the number of activated NK cells within the tumor.

54. The use of any one of Claims 1 to 53, wherein the subject has a tumor and administration of the therapeutically effective bolus dose of the composition to the subject increases vascular normalization within the tumor, decreases the tumor size, improves survival, increases the number of cytotoxic T-cells within the tumor and/or increases number of activated NK cells within the tumor.

55. A composition comprising a long acting CNP derivative of comprising a formula U-CFGLKLDRIGSxSGLGC [SEQ ID NO. 30], wherein

x is a natural or unnatural amino acid residue, provided that x is not a methionine residue; and

U has is a moiety of Formula (I):

$$(\text{aliphatic})_a\text{-(X)-};$$

(I)

wherein a is 1;

aliphatic is an optionally substituted $C_{4\text{-}24}$ chain (*e.g.*, an optionally substituted $C_{10\text{-}24}$ chain, an optionally substituted $C_{12\text{-}18}$ chain), covalently bound to X via a chemical linkage, such as a carbonyl (*e.g.*, as part of an amide or an ester linkage), a thioether, an

ether, a thioether, a carbamate moiety, a bond, or the like with X; preferably via a carbonyl as part of an amide or an ester linkage; or more preferably via a carbonyl as part of an amide linkage with X;

X is a linker $(\gamma E)_m$-$(B)_n$ wherein B is 1-8 amino acid residue or peptide sequence wherein each amino acid residue is independently selected from 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, Gly, Ala, Leu, Ser, Arg, and Lys; m is 0, 1, 2, or 3; n is 0, 1, 2, or 3; and the sum of m and n is at least 1.

56. The composition of Claim 55, wherein x is homoglutamine, aliphatic is a branched or straight optionally substituted C_{18} chain covalently bound to X via a carbonyl (*e.g.*, $CH_3(CH_2)_{16}C(=O)$) or a C_{18} chain covalently bound to X via a chemical linkage, such a thioether, an ether, a thioether, a carbamate moiety, a bond, or the like with X; preferably aliphatic is a branched or straight optionally substituted C_{18} chain covalently bound to X via a carbonyl (*e.g.*, $CH_3(CH_2)_{16}C(=O)$) as part of an amide or ester linkage with X; or more preferably aliphatic is a branched or straight optionally substituted C_{18} chain covalently bound to X via a carbonyl (*e.g.*, $CH_3(CH_2)_{16}C(=O)$) as part of an amide linkage with X, or aliphatic is $HOC(=O)(CH_2)_{16}C(=O)$); a is 1; B is Gly; m is 0, 1, or 2; and n is 1.

57. The composition of Claim 55, wherein x is homoglutamine, aliphatic is a branched or straight optionally substituted C_{18} chain covalently bound to X via a carbonyl (*e.g.*, $CH_3(CH_2)_{16}C(=O)$) or a C_{18} chain covalently bound to X via a chemical linkage, such a thioether, an ether, a thioether, a carbamate moiety, a bond, or the like with X; preferably aliphatic is a branched or straight optionally substituted C_{18} chain covalently bound to X via a carbonyl (*e.g.*, $CH_3(CH_2)_{16}C(=O)$) as part of an amide or ester linkage with X; or more preferably aliphatic is a branched or straight optionally substituted C_{18} chain covalently bound to X via a carbonyl (*e.g.*, $CH_3(CH_2)_{16}C(=O)$) as part of an amide linkage with X, or aliphatic is $HOC(=O)(CH_2)_{16}C(=O)$); a is 1; B is Gly; m is 1; and n is 1.

58. The composition of Claim 55, wherein x is homoglutamine, aliphatic is a branched or straight optionally substituted C_{18} chain covalently bound to X via a carbonyl (*e.g.*, $CH_3(CH_2)_{16}C(=O)$) or a C_{18} chain covalently bound to X via a chemical linkage,

such a thioether, an ether, a thioether, a carbamate moiety, a bond, or the like with X; preferably aliphatic is a branched or straight optionally substituted C_{18} chain covalently bound to X via a carbonyl (*e.g.*, $CH_3(CH_2)_{16}C(=O)$) as part of an amide or ester linkage with X; or more preferably aliphatic is a branched or straight optionally substituted C_{18} chain covalently bound to X via a carbonyl (*e.g.*, $CH_3(CH_2)_{16}C(=O)$) as part of an amide linkage with X, or aliphatic is $HOC(=O)(CH_2)_{16}C(=O)$); a is 1; m is 1; and n is 0.

59. The composition of Claim 55, wherein x is homoglutamine (homoQ) [SEQ ID NO. 16], U is $(aliphatic)_a$-(X)-; wherein a is 0 or 1 (preferably a is 1); aliphatic is a branched or straight optionally substituted C_{18} chain covalently bound to X via a carbonyl (*e.g.*, $CH_3(CH_2)_{16}C(=O)$) or a C_{18} chain covalently bound to X via a chemical linkage, such a thioether, an ether, a thioether, a carbamate moiety, a bond, or the like with X; preferably aliphatic is a branched or straight optionally substituted C_{18} chain covalently bound to X via a carbonyl (*e.g.*, $CH_3(CH_2)_{16}C(=O)$) as part of an amide or ester linkage with X; or more preferably aliphatic is a branched or straight optionally substituted C_{18} chain covalently bound to X via a carbonyl (*e.g.*, $CH_3(CH_2)_{16}C(=O)$) as part of an amide linkage with X, or aliphatic is $HOC(=O)(CH_2)_{16}C(=O)$); X is a linker $(\gamma E)_m$-$(B)_n$; B is 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, m is 0, and n is 2.

60. The composition of Claim 55, wherein x is homoglutamine (homoQ) [SEQ ID NO. 17], U is $(aliphatic)_a$-(X)-; wherein a is 0 or 1 (preferably a is 1); aliphatic is a branched or straight optionally substituted C_{18} chain covalently bound to X via a carbonyl (*e.g.*, $CH_3(CH_2)_{16}C(=O)$) or a C_{18} chain covalently bound to X via a chemical linkage, such a thioether, an ether, a thioether, a carbamate moiety, a bond, or the like with X; preferably aliphatic is a branched or straight optionally substituted C_{18} chain covalently bound to X via a carbonyl (*e.g.*, $CH_3(CH_2)_{16}C(=O)$) as part of an amide or ester linkage with X; or more preferably aliphatic is a branched or straight optionally substituted C_{18} chain covalently bound to X via a carbonyl (*e.g.*, $CH_3(CH_2)_{16}C(=O)$) as part of an amide linkage with X, or aliphatic is $HOC(=O)(CH_2)_{16}C(=O)$); X is a linker $(\gamma E)_m$-$(B)_n$; B is 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, m is 1, and n is 2.

61. The composition of Claim 55, wherein x is homoglutamine, aliphatic is a $CH_3(CH_2)_{16}C(=O)$ or $HOC(=O)(CH_2)_{16}C(=O)$; B is a 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, m is 0, and n is 2.

62. The composition of Claim 55, wherein x is homoglutamine, aliphatic is a $CH_3(CH_2)_{16}C(=O)$ or $HOC(=O)(CH_2)_{16}C(=O)$; B is a 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, m is 1, and n is 2.

63. The composition of Claim 55, wherein x is homoglutamine, aliphatic is a $CH_3(CH_2)_{16}C(=O)$ or $HOC(=O)(CH_2)_{16}C(=O)$; B is (2-[2-(2-aminoethoxy)ethoxy]acetic acid)-(2-[2-(2-aminoethoxy)ethoxy]acetic acid)-(Gly), m is 1, and n is 1.

64. The composition of Claim 55, wherein the long acting CNP derivative is $HOC(=O)(CH_2)_{16}C(=O)$-γE-Aeea-Aeea-GCFGLKLDRIGShomoQSGLGC with a disulfide bond between the cysteine residues [SEQ ID NO. 20] .

65. The composition of Claim 55, wherein the long acting CNP derivative is $HOC(=O)(CH_2)_{16}C(=O)$-Aeea-Aeea-GCFGLKLDRIGShomoQSGLGC with a disulfide bond between the cysteine residues [SEQ ID NO. 21].