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 long acting CNP derivative, a long acting NPRB agonist, a very long acting CNP, a very long acting CNP derivative, a very long acting NPRB agonist, a long acting CNP agonist, a very long acting CNP agonist, or any combination thereof, in the manufacture of a medicament for treating a subject having a lung, liver, and/or kidney injury, or a symptom associated with a lung, liver, and/or kidney injury, wherein the composition is to be administered:

in a therapeutically effective bolus dose,

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

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, 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, and

wherein the lung, liver, and/or kidney injury, or the symptom associated with lung, liver, and/or kidney injury is selected from

i) acute lung injury (ALI),

ii) acute respiratory distress syndrome (ARDS),

iii) pulmonary edema,

iv) elevated level of inflammatory cells in the lung,

v) increased level or expression of inflammatory cytokines in the lung as compared to healthy lung,

vi) increased protein level in lung alveolar space as compared to healthy lung,

vii) low arterial blood oxygenation, wherein low arterial blood oxygenation is a blood PaO2 of below 60 mm Hg and/or a blood hemoglobin oxygen saturation (SpO2) of below 90%,

viii) pneumonia,

ix) fibrosis,

x) kidney injury,

and any combination thereof.

2. The use of Claim 1, 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

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

(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 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 $(polymer)_a$; or

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

3. The use of Claim 2, wherein Y 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 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.

4. 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. 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.

5. The use of Claim 2 or Claim 3, 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.

6. 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],

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.

7. The use of Claim 2 or Claim 3, 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).

8. 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].

9. 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].

10. 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].

11. 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].

12. 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].

13. 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].

14. 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].

15. 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].

16. 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. 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.

17. 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], 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.

18. The use of any one of Claims 1 to 3, wherein the polymer does not include poly(ethylene glycol), MPEG, or both poly(ethylene glycol) and MPEG.

19. The use of any one of Claims 1 to 3, 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.

20. 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, intramuscular, nasal, by inhalation, 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.

21. The use of any one of Claims 1 to 3, wherein the subject has ALI or ARDS associated with pulmonary edema; low arterial blood oxygenation; elevated level of

inflammatory cells in the lung; increase level or expression of inflammatory cytokine in the lung; sepsis; bacteremia; pneumonia, pulmonary fibrosis, or any combination thereof.

22. The use of any one of Claims 1 to 3, wherein inflammatory cytokine comprises IL-6, IL-1b, TNFα , MCP-1, IFNg, or any combination thereof.

23. The use of any one of Claims 1 to 3, wherein the pneumonia comprises bacterial pneumonia, viral pneumonia, aseptic pneumonia,

24. The use of any one of Claims 1 to 3, wherein the ALI or ARDS is caused by:

(i) a systemic insult selected from trauma, sepsis, bacteremia, pancreatitis, shock, multiple transfusions, disseminated intravascular coagulation, burns, drug overdose or toxicity, opioids, aspirin, phenothiazines, tricyclic antidepressant, amiodarone, chemotherapeutic agents, nitrofurantoin, protamine, thrombotic thrombocytopenia purpura, head injury, paraquat, and any combination thereof; or

(ii) a pulmonary insult selected from aspiration of gastric content, lung intubation, embolism, tuberculosis, viral pneumonia, bacterial pneumonia, cytogenic organizing pneumonitis, airway obstruction, smoking free-base cocaine, near-drowning, toxic gas inhalation, oxygen toxicity, lung contusion, radiation exposure, high-altitude exposure, lung re-expansion, reperfusion, and any combination thereof.

25. The use of Claim 24, wherein the embolism is caused by a thrombus, fat, air, or amniotic fluid.

26. The use of Claim 23, wherein the viral pneumonia is SARS caused by a coronavirus or an influenza virus.

27. The use of any one of Claims 1 to 3, wherein:

ALI or ARDS caused by an infectious disease, or

ALI or ARDS caused by PF, or

ALI or ARDS caused by sepsis; or

ALI or ARDS caused by bacteremia; or

ALI or ARDS caused by intubation; or

ALI or ARDS caused by a toxic gas selected from group consisting of chlorine gas, smoke, phosgene, concentrated oxygen, and any combination thereof.

28. The use of Claim 27, wherein the infectious disease is caused by a coronavirus or an influenza virus.

29. The use of any one of Claims 1 to 3, wherein the fibrosis comprises lung or pulmonary fibrosis, cirrhosis, and kidney glomerular sclerosis.

30. 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 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, and/or anionic moieties; wherein the polymer excipient is adapted to sequester or non-covalently bind to any of the CNP or CNP derivatives.

31. 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.

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

33. The use of Claim 32, wherein the polypeptide comprises an antibody.

34. The use of any one of Claims 1 to 3, wherein the long acting NPRB agonist or the very long acting NPRB agonist comprises a molecule of a molecular weight of less than 2kDa.

35. 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,

where x is a natural or unnatural amino acid residue [SEQ ID NO. 11], or any combination thereof, in the manufacture of a medicament for treating a subject having, or at risk of developing ALI or ARDS, wherein the composition is to be administered to the subject in a therapeutically effective bolus dose,

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 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.

36. The use of Claim 35, 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.

37. The use of Claim 35 or Claim 36, 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].

38. The use of any one of Claims 35 to 37, wherein the long acting CNP derivative is $CH_3(CH_2)_{16}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 6].

39. The use of any one of Claims 35 to 37, wherein the long acting CNP derivative is $CH_3(CH_2)_{14}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 5].

40. The use of any one of Claims 35 to 37, wherein the long acting CNP derivative is $CH_3(CH_2)_{18}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 7].

41. The use of any one of Claims 35 to 37, wherein the long acting CNP derivative is $CH_3(CH_2)_{20}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 8].

42. The use of any one of Claims 35 to 37, wherein the long acting CNP derivative is $CH_3(CH_2)_{22}C(=O)$KKKKGGGGLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 9].

43 The use of any one of Claims 35 to 37, 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].

44. The use of any one of Claims 35 to 37, 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].

45. The use of any one of Claims 35 to 44, 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.

46. The use of any one of Claims 1 to 45, wherein administration of the therapeutically effective bolus dose of the composition to the subject decreases a total number of cells and total proteins in a BALF sample from the subject.

47. The use of any one of Claims 1 to 46, wherein administration of the therapeutically effective bolus dose of the composition ti o the subject decreases MPO in a lung tissue from the subject.

48. The use of any one of Claims 1 to 47, wherein administration of the therapeutically effective bolus dose of the composition to the subject decreases inflammatory cytokine expression in the subject.

49. The use of any one of Claims 1 to 48, wherein administration of the therapeutically effective bolus dose of the composition to the subject decreases a fibrotic area in a lung in a subject having idiopathic pulmonary fibrosis.

50. The use of any one of Claims 1 to 49, wherein administration of the therapeutically effective bolus dose of the composition to the subject decreases cell numbers and protein levels, and decreases the expression of any one of IL-6, IL-1b, TNFα, MCP-1, IFNg, or any combination thereof in a subject having idiopathic pulmonary fibrosis.

51. The use of any one of Claims 1 to 49, wherein administration of the therapeutically effective bolus dose of the composition to the subject decreases the expression of any one of IL-6, IL-1b, TNFα, MCP-1, IFNg, or any combination thereof, and decreases lethality in a subject having sepsis.

52. The use of any one of Claims 1 to 51, wherein administration of the therapeutically effective bolus dose of the composition to the subject decreases the expression of any one of AST, ALT, α-SMA, IL-6, IL-1b, TNFα, MCP-1, IFNg, iNOS, Elf-1, Tollip, IRAK-1, P-P38, P-P65, β-act, STAT1, P-STAT1, STAT2, STAT3, STAT6, a fibrotic area, serum creatinine, an albumin/creatinine ratio in urine, hydroxyproline in a lung, or any combination thereof, of the subject.

53. 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):

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

(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 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.

54. The composition of Claim 53, 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.

55. The composition of Claim 53, 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.

56. The composition of Claim 53, 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.

57. The composition of Claim 53, 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.

58. The composition of Claim 53, 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

59. The composition of Claim 53, 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.

60. The composition of Claim 53, 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.

61. The composition of Claim 53, 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.

62. The composition of Claim 53, 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].

63. The composition of Claim 53, 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].