WHAT IS CLAIMED IS:

1. A relaxin polypeptide comprising one or more non-naturally encoded amino acids.

2. The relaxin polypeptide of claim 1, wherein the relaxin polypeptide comprises one or more post-translational modifications.

3. The relaxin polypeptide of claim 1, wherein the polypeptide is linked to a linker, polymer, or biologically active molecule.

4. The relaxin analog polypeptide of claim 3, wherein the polypeptide is linked to a water soluble polymer.

5. The relaxin polypeptide of claim 1, wherein the polypeptide is linked to a bifunctional polymer, bifunctional linker, or at least one additional relaxin polypeptide.

6. The relaxin polypeptide of claim 5, wherein the bifunctional linker or polymer is linked to a second polypeptide.

7. The relaxin polypeptide of claim 6, wherein the second polypeptide is a relaxin polypeptide.

8. The relaxin polypeptide of claim 4, wherein the water soluble polymer comprises a poly(ethylene glycol) moiety.

9. The relaxin polypeptide of claim 4, wherein said water soluble polymer is linked to a non-naturally encoded amino acid present in said relaxin polypeptide.

10. The relaxin polypeptide of claim 1, wherein the non-naturally encoded amino acid is substituted at a position selected from the group consisting of residues before position 1 (i.e. at the N-terminus), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54(i.e., at the carboxyl terminus of the protein), and any combination thereof (SEQ ID NO: 1 or the corresponding amino acids in SEQ ID NO: 2 or 3).

11. The relaxin polypeptide of claim 10, wherein the non-naturally encoded amino acid is substituted at a position selected from the group consisting of residues: 1, 2, 5, 13, 18, 29, 31, 52, and any combination thereof, of SEQ ID NO: 1 or the corresponding amino acids in SEQ ID NOs: 2 and 3.

12. The relaxin polypeptide of claim 10, wherein the non-naturally encoded amino acid is substituted at a position selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 (i.e., at the carboxyl terminus of the protein), and any combination thereof, of SEQ ID NO: 4 or the corresponding amino acids in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3.

13. The relaxin polypeptide of claim 10, wherein the non-naturally encoded amino acid is substituted at a position selected from the group consisting of 2, 5, 18, and any combination thereof, of S EQ ID NO: 4 or the corresponding amino acids in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3.

14. The relaxin polypeptide of claim 1, wherein the non-naturally encoded amino acid is substituted at a position selected from the group consisting of 5, 7, 18, 28, and any combination thereof, of SEQ ID NO: 5 or the corresponding amino acids in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:6.

15. The relaxin polypeptide of claim 10, wherein the non-naturally encoded amino acid is substituted at position 1 (SEQ ID NO: 1 or the corresponding amino acid of SEQ ID NO: 2 or 3).

16. The relaxin polypeptide of claim 4, wherein the non-naturally encoded amino acid is substituted at a position selected from the group consisting of residues before position 1 (i.e. at the N-terminus), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54 (i.e., at the carboxyl terminus of the protein), and any combination thereof (SEQ ID NO: 1 or the corresponding amino acids in SEQ ID NO: 2 or 3).

17. The relaxin polypeptide of claim 16, wherein the non-naturally encoded amino acid is substituted at a position selected from the group consisting of residues 1, 2, 5, 13, 18, 29, 31, 52, and any combination thereof of SEQ ID NO: 1 or the corresponding amino acids in SEQ ID NO: 2 or 3.

18. The relaxin polypeptide of claim 16, wherein the non-naturally encoded amino acid is substituted at a position selected from the group consisting of residues 1, 2, 5, 13, 18, 29, and any combination thereof (SEQ ID NO: 1 or the corresponding amino acids in SEQ ID NO: 2 or 3).

19. The relaxin polypeptide of claim 16, wherein the non-naturally encoded amino acid is substituted at a position selected from the group consisting of residues 1, 25, and any combination thereof (SEQ ID NO: 1 or the corresponding amino acids in SEQ ID NO: 2 or 3).

20. The relaxin polypeptide of claim 16, wherein the non-naturally encoded amino acid is substituted at position 1 (SEQ ID NO: 1 or the corresponding amino acid of SEQ ID NO: 2 or 3).

21. The relaxin polypeptide of claim 4, wherein the non-naturally encoded amino acid is substituted at position 1, 2, 5, 13, 18, 25, 29, 31, 52 (SEQ ID NO: 1 or the corresponding amino acid of SEQ ID NO: 2).

22. The relaxin polypeptide of claim 1, wherein the relaxin polypeptide comprises one or more amino acid substitution, addition or deletion that modulates affinity of the relaxin polypeptide for a relaxin receptor.

23. The relaxin polypeptide of claim 1, wherein the relaxin polypeptide comprises one or more amino acid substitution, addition or deletion that increases the stability or solubility of the relaxin polypeptide.

24. The relaxin polypeptide of claim 1, wherein the relaxin polypeptide comprises one or more amino acid substitution, addition or deletion that increases the expression of the relaxin polypeptide in a recombinant host cell or synthesized in vitro.

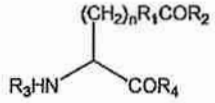
25. The relaxin polypeptide of claim 1, wherein the relaxin polypeptide comprises one or more amino acid substitution, addition or deletion that increases protease resistance of the relaxin polypeptide.

26. The relaxin polypeptide of claim 1, wherein the non-naturally encoded amino acid is reactive toward a linker, polymer, or biologically active molecule that is otherwise unreactive toward any of the 20 common amino acids in the polypeptide.

27. The relaxin polypeptide of claim 1, wherein the non-naturally encoded amino acid comprises a carbonyl group, an aminooxy group, a hydrazine group, a hydrazide group, a semicarbazide group, an azide group, or an alkyne group.

28. The relaxin polypeptide of claim 27, wherein the non-naturally encoded amino acid comprises a carbonyl group.

29. The relaxin polypeptide of claim 28, wherein the non-naturally encoded amino acid has the structure:



wherein n is 0-10; R1 is an alkyl, aryl, substituted alkyl, or substituted aryl; R2 is H, an alkyl, aryl, substituted alkyl, and substituted aryl; and R3 is H, an amino acid, a polypeptide, or an amino terminus modification group, and R4 is H, an amino acid, a polypeptide, or a carboxy terminus modification group.

30. The relaxin polypeptide of claim 27, wherein the non-naturally encoded amino acid comprises an aminooxy group.

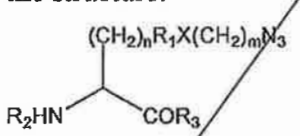
31. The relaxin polypeptide of claim 27, wherein the non-naturally encoded amino acid comprises a hydrazide group.

32. The relaxin polypeptide of claim 27, wherein the non-naturally encoded amino acid comprises a hydrazine group.

33. The relaxin polypeptide of claim 27, wherein the non-naturally encoded amino acid residue comprises a semicarbazide group.

34. The relaxin polypeptide of claim 27, wherein the non-naturally encoded amino acid residue comprises an azide group.

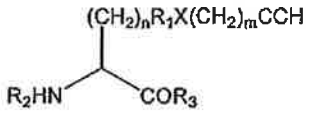
35. The relaxin polypeptide of claim 34, wherein the non-naturally encoded amino acid has the structure:



wherein n is 0-10; R1 is an alkyl, aryl, substituted alkyl, substituted aryl or not present; X is O, N, S or not present; m is 0-10; R2 is H, an amino acid, a polypeptide, or an amino terminus modification group, and R3 is H, an amino acid, a polypeptide, or a carboxy terminus modification group.

36. The relaxin polypeptide of claim 27, wherein the non-naturally encoded amino acid comprises an alkyne group.

37. The relaxin polypeptide of claim 36, wherein the non-naturally encoded amino acid has the structure:



wherein n is 0-10; R1 is an alkyl, aryl, substituted alkyl, or substituted aryl; X is O, N, S or not present; m is 0-10, R2 is H, an amino acid, a polypeptide, or an amino terminus modification group, and R3 is H, an amino acid, a polypeptide, or a carboxy terminus modification group.

38. The relaxin polypeptide of claim 4, wherein the water soluble polymer has a molecular weight of between about 0.1 kDa and about 100 kDa.

39. The relaxin polypeptide of claim 38, wherein the water soluble polymer has a molecular weight of between about 0.1 kDa and about 50 kDa.

40. The relaxin polypeptide of claim 4, which is made by reacting a relaxin polypeptide comprising a carbonyl-containing amino acid with a water soluble polymer comprising an aminooxy, hydrazine, hydrazide or semicarbazide group.

41. The relaxin polypeptide of claim 40, wherein the aminooxy, hydrazine, hydrazide or semicarbazide group is linked to the water soluble polymer through an amide linkage.

42. The relaxin polypeptide of claim 4, which is made by reacting a water soluble polymer comprising a carbonyl group with a polypeptide comprising a non-naturally encoded amino acid that comprises an aminooxy, a hydrazine, a hydrazide or a semicarbazide group.

43. The relaxin polypeptide of claim 4, which is made by reacting a relaxin polypeptide comprising an alkyne-containing amino acid with a water soluble polymer comprising an azide moiety.

44. The relaxin polypeptide of claim 4, which is made by reacting a relaxin polypeptide comprising an azide-containing amino acid with a water soluble polymer comprising an alkyne moiety.

45. The relaxin polypeptide of claim 27, wherein the azide or alkyne group is linked to a water soluble polymer through an amide linkage.

46. The relaxin polypeptide of claim 4, wherein the water soluble polymer is a branched or multiarmed polymer.

47. The relaxin polypeptide of claim 46, wherein each branch of the water soluble polymer has a molecular weight of between about 1 kDa and about 100 kDa.

48. The relaxin polypeptide of claim 1, wherein the polypeptide is a relaxin antagonist.

49. The relaxin polypeptide of claim 48, wherein the polypeptide comprises one or more post-translational modification, linker, polymer, or biologically active molecule.

50. The relaxin polypeptide of claim 49, wherein the polymer comprises a moiety selected from a group consisting of a water soluble polymer and poly(ethylene glycol).

51. The relaxin polypeptide according to claim 48, wherein the polypeptide prevents activation of the relaxin receptor.

52. The relaxin polypeptide of claim 1, wherein the non-naturally encoded amino acid comprises a saccharide moiety.

53. The relaxin polypeptide of claim 3, wherein the linker, polymer, or biologically active molecule is linked to the polypeptide via a saccharide moiety.

54. An isolated nucleic acid comprising a polynucleotide that hybridizes under stringent conditions to SEQ ID NO: 12 or a polynucleotide sequence encoding SEQ ID NO: 1 or 2 or 3, wherein the polynucleotide comprises at least one selector codon.

55. The isolated nucleic acid of claim 54, wherein the selector codon is selected from the group consisting of an amber codon, ochre codon, opal codon, a unique codon, a rare codon, and a four-base codon.

56. A method of making the relaxin polypeptide of claim 3, the method comprising contacting an isolated relaxin polypeptide comprising a non-naturally encoded amino acid with a linker, polymer, or biologically active molecule comprising a moiety that reacts with the non-naturally encoded amino acid.

57. The method of claim 56, wherein the polymer comprises a moiety selected from a group consisting of a water soluble polymer and poly(ethylene glycol).

58. The method of claim 56, wherein the non-naturally encoded amino acid comprises a carbonyl group, an aminooxy group, a hydrazide group, a hydrazine group, a semicarbazide group, an azide group, or an alkyne group.

59. The method of claim 56, wherein the non-naturally encoded amino acid comprises a carbonyl moiety and the linker, polymer, or biologically active molecule comprises an aminooxy, a hydrazine, a hydrazide or a semicarbazide moiety.

60. The method of claim 59, wherein the aminooxy, hydrazine, hydrazide or semicarbazide moiety is linked to the linker, polymer, or biologically active molecule through an amide linkage.

61. The method of claim 56, wherein the non-naturally encoded amino acid comprises an alkyne moiety and the linker, polymer, or biologically active molecule comprises an azide moiety.

62. The method of claim 56, wherein the non-naturally encoded amino acid comprises an azide moiety and the linker, polymer, or biologically active molecule comprises an alkyne moiety.

63. The method of claim 58, wherein the azide or alkyne moiety is linked to a linker, polymer, or biologically active molecule through an amide linkage.

64. The method of claim 57, wherein the poly(ethylene glycol) moiety has an average molecular weight of between about 0.1 kDa and about 100 kDa.

65. The method of claim 57, wherein the poly(ethylene glycol) moiety is a branched or multiarmed polymer.

66. A composition comprising the relaxin polypeptide of claim 1 and a pharmaceutically acceptable carrier.

67. The composition of claim 66, wherein the non-naturally encoded amino acid is linked to a water soluble polymer.

68. A method of treating a patient having a disorder modulated by relaxin comprising administering to the patient a therapeutically-effective amount of the composition of claim 66.

69. A cell comprising the nucleic acid of claim 54.

70. The cell of claim 69, wherein the cell comprises an orthogonal tRNA synthetase or an orthogonal tRNA.

71. A method of making a relaxin polypeptide comprising a non-naturally encoded amino acid, the method comprising, culturing cells comprising a polynucleotide or polynucleotides encoding a relaxin polypeptide comprising a selector codon, an orthogonal RNA synthetase and an orthogonal tRNA under conditions to permit expression of the relaxin polypeptide comprising a non-naturally encoded amino acid; and purifying the relaxin polypeptide.

72. A method of modulating serum half-life or circulation time of a relaxin polypeptide, the method comprising substituting one or more non-naturally encoded amino acids for any one or more naturally occurring amino acids in the relaxin polypeptide.

73. A relaxin polypeptide encoded by a polynucleotide having a sequence shown in SEQ ID NO: 12 or encoding a polypeptide shown as SEQ ID NO: 1, 2 or 3, wherein said

polynucleotide comprises a selector codon, and wherein said polypeptide comprises at least one non-naturally encoded amino acid.

74. The relaxin polypeptide of claim 73, wherein the non-naturally encoded amino acid is linked to a linker, polymer, water soluble polymer, or biologically active molecule.

75. The relaxin polypeptide of claim 74, wherein the water soluble polymer comprises a poly(ethylene glycol) moiety.

76. The relaxin polypeptide of claim 73, wherein the non-naturally encoded amino acid is substituted at a position selected from the group consisting of residues before position 1 (i.e. at the N-terminus), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54 (i.e., at the carboxyl terminus of the protein), and any combination thereof (SEQ ID NO: 1 or the corresponding amino acids in SEQ ID NO: 2).

77. The relaxin polypeptide of claim 76, wherein the non-naturally encoded amino acid is substituted at a position selected from the group consisting of residues 1, 2, 5, 13, 18, 29, 31, 52, and any combination thereof of SEQ ID NO: 1 or the corresponding amino acids in SEQ ID NO: 2 or 3.

78. The relaxin polypeptide of claim 76, wherein the non-naturally encoded amino acid is substituted at a position selected from the group consisting of residues 2, 5, 13, 18, 29, 31, 52, and any combination thereof (SEQ ID NO: 1 or the corresponding amino acids in SEQ ID NO: 2).

79. The relaxin polypeptide of claim 76, wherein the non-naturally encoded amino acid is substituted at a position selected from the group consisting of residues 1, 2, 5, 13, 18, and any combination thereof (SEQ ID NO: 1 or the corresponding amino acids in SEQ ID NO: 2 ior 3).

80. The relaxin polypeptide of claim 76, wherein the non-naturally encoded amino acid is substituted at position 1 (SEQ ID NO: 1 or the corresponding amino acid of SEQ ID NO: 2 or 3).

81. The relaxin polypeptide of claim 73, wherein the non-naturally encoded amino acid is substituted at position 2 (SEQ ID NO: 1 or the corresponding amino acid of SEQ ID NO: 2 or 3).

82. The relaxin polypeptide of claim 73, wherein the non-naturally encoded amino acid comprises a carbonyl group, an aminooxy group, a hydrazide group, a hydrazine group, a semicarbazide group, an azide group, or an alkyne group.

83. The relaxin polypeptide of claim 75, wherein the poly(ethylene glycol) moiety has a molecular weight of between about 0.1 kDa and about 100 kDa.

84. The relaxin polypeptide of claim 75, wherein the poly(ethylene glycol) moiety is a branched or multiarmed polymer.

85. The relaxin polypeptide of claim 84, wherein the poly(ethylene glycol) moiety has a molecular weight of between about 1 kDa and about 100 kDa.

86. A composition comprising the relaxin polypeptide of claim 73 and a pharmaceutically acceptable carrier.

87. A relaxin polypeptide comprising one or more amino acid substitution, addition or deletion that increases the expression of the relaxin polypeptide in a recombinant host cell.

88. A relaxin polypeptide comprising a water soluble polymer linked by a covalent bond to the relaxin polypeptide at a single amino acid.

89. The relaxin polypeptide of claim 88, wherein the water soluble polymer comprises a poly(ethylene glycol) moiety.

90. The relaxin polypeptide of claim 88, wherein the amino acid covalently linked to the water soluble polymer is a non-naturally encoded amino acid.

91. The relaxin polypeptide of claim 10 wherein said non-naturally encoded amino acid is linked to a poly(ethylene glycol) molecule.

92. A relaxin polypeptide comprising at least one linker, polymer, or biologically active molecule, wherein said linker, polymer, or biologically active molecule is attached to the polypeptide through a functional group of a non-naturally encoded amino acid ribosomally incorporated into the polypeptide.

93. The relaxin polypeptide of claim 92, wherein said relaxin polypeptide is monoPEGylated.

94. A relaxin polypeptide comprising a linker, polymer or biologically active molecule that is attached to one or more non-naturally encoded amino acids wherein said non-naturally encoded amino acid is ribosomally incorporated into the polypeptide at pre-selected sites.

95. The relaxin polypeptide of claim 94, wherein the relaxin polypeptide comprises one said linker, polymer, or biologically active molecule.

96. The relaxin polypeptide of claim 1, wherein the relaxin polypeptide comprises one or more amino acid substitution, addition, or deletion that modulates angiogenesis in a patient after administration of the polypeptide.

97. The relaxin polypeptide of claim 1, wherein the relaxin polypeptide comprises one or more amino acid substitution, addition, or deletion that modulates serum half-life or circulation time of the relaxin polypeptide.

98. The relaxin polypeptide of claim 1, wherein the relaxin polypeptide comprises one or more amino acid substitution, addition, or deletion that modulates vasoconstriction in a patient after administration of the polypeptide.

99. The relaxin polypeptide of claim 1, wherein the polypeptide also comprises a naturally encoded amino acid substitution.

WHAT IS CLAIMED IS:

1. A modified relaxin polypeptide comprising a non-naturally encoded amino acid, wherein:

(a) the relaxin polypeptide comprises a relaxin A chain polypeptide having at least 90% identity to SEQ ID NO: 4 and a relaxin B chain polypeptide having at least 90% identity to SEQ ID NO: 5 or SEQ ID NO: 6, substituted with a non-naturally encoded amino acid at a position selected from the group consisting of: A chain residue 1, A chain residue 2, A chain residue 5, A chain residue 13, A chain residue 18, B chain residue 5, and B chain residue 7; and

(b) said non-naturally encoded amino acid comprises a functional group selected from the group consisting of: a carbonyl group, an aminooxy group, a hydrazide group, a hydrazine group, a semicarbazide group, an azide group, and an alkyne group.

2. A modified relaxin polypeptide comprising a non-naturally encoded amino acid, wherein:

(a) the relaxin polypeptide comprises the relaxin A chain polypeptide of SEQ ID NO: 4 and the relaxin B chain polypeptide of SEQ ID NO: 5 or SEQ ID NO: 6, substituted with a non-naturally encoded amino acid at a position selected from the group consisting of: A chain residue 1, A chain residue 2, A chain residue 5, A chain residue 13, A chain residue 18, B chain residue 5, and B chain residue 7, wherein said A chain and said B chain each contain up to one further amino acid substitution; and

(b) said non-naturally encoded amino acid comprises a functional group selected from the group consisting of: a carbonyl group, an aminooxy group, a hydrazide group, a hydrazine group, a semicarbazide group, an azide group, and an alkyne group.

3. A modified relaxin polypeptide comprising a non-naturally encoded amino acid, wherein:

(a) the relaxin polypeptide comprises a relaxin A chain polypeptide having at least 90% identity to SEQ ID NO: 4 and a relaxin B chain polypeptide having at least 90% identity to SEQ ID NO: 5 or SEQ ID NO: 6, substituted with a non-naturally encoded amino acid at a position

selected from the group consisting of: A chain residue 1, A chain residue 2, A chain residue 5, A chain residue 13, A chain residue 18, B chain residue 5, and B chain residue 7; and

(b) said non-naturally encoded amino acid comprises a para-substituted, ortho-substituted, or meta-substituted phenylalanine.

4. A modified relaxin polypeptide comprising a non-naturally encoded amino acid, wherein:

(a) the relaxin polypeptide comprises the relaxin A chain polypeptide of SEQ ID NO: 4 and the relaxin B chain polypeptide of SEQ ID NO: 5 or SEQ ID NO: 6 substituted with a non-naturally encoded amino acid at a position selected from the group consisting of: A chain residue 1, A chain residue 2, A chain residue 5, A chain residue 13, A chain residue 18, B chain residue 5, and B chain residue 7, wherein said A chain and said B chain each contain up to one further amino acid substitution; and

(b) said non-naturally encoded amino acid comprises a para-substituted, ortho-substituted, or meta-substituted phenylalanine.

5. The modified relaxin polypeptide of claim 3 or 4, wherein said para-substituted, ortho-substituted, or meta-substituted phenylalanine comprises a functional group selected from the group consisting of: a carbonyl group, an aminooxy group, a hydrazide group, a hydrazine group, a semicarbazide group, an azide group, and an alkyne group.

6. The modified relaxin polypeptide of any one of claims 1-5, wherein said relaxin A chain polypeptide comprises the polypeptide of SEQ ID NO: 4 substituted with said non-naturally encoded amino acid at residue 1.

7. The modified relaxin polypeptide of any one of claims 1–6, wherein said non-naturally encoded amino acid comprises para-acetyl-L-phenylalanine.

8. The modified relaxin polypeptide of any one of claims 1–6, wherein said non-naturally encoded amino acid comprises para-azido-L-phenylalanine.

9. The modified relaxin polypeptide of any one of claims 1-8, wherein said non-naturally encoded amino acid is linked to a linker, polymer, or biologically active molecule.

10. The modified relaxin polypeptide of any one of claims 1-8, wherein said non-naturally encoded amino acid is linked to a polymer.

11. A modified relaxin polypeptide comprising a non-naturally encoded amino acid, wherein:

(a) the relaxin polypeptide comprises the relaxin A chain polypeptide of SEQ ID NO: 4 and the relaxin B chain polypeptide of SEQ ID NO: 5 or SEQ ID NO: 6 substituted with a non-naturally encoded amino acid at a position selected from the group consisting of: A chain residue 1, A chain residue 2, A chain residue 5, A chain residue 13, A chain residue 18, B chain residue 5, and B chain residue 7, wherein said A chain and said B chain each contain up to one further amino acid substitution;

(b) said non-naturally encoded amino acid comprises a para-substituted, ortho-substituted, or meta-substituted phenylalanine; and

(c) said non-naturally encoded amino acid is linked to a linker, polymer, or biologically active molecule.

12. A modified relaxin polypeptide comprising a non-naturally encoded amino acid, wherein:

(a) the relaxin polypeptide comprises the relaxin A chain polypeptide of SEQ ID NO: 4 substituted with a non-naturally encoded amino acid at residue 1 and the relaxin B chain polypeptide of ID NO: 6;

(b) said non-naturally encoded amino acid comprises a para-substituted, ortho-substituted, or meta-substituted phenylalanine; and

(c) said non-naturally encoded amino acid is linked to a linker, polymer, or biologically active molecule.

13. The modified relaxin polypeptide of any one of claims 9-12, wherein said polymer comprises a poly(ethylene glycol) moiety.

14. The modified relaxin polypeptide of any one of claims 9-12, wherein said polymer comprises a water soluble polymer.

15. The modified relaxin polypeptide of claim 13, wherein said poly(ethylene glycol) moiety has an average molecular weight of between about 0.1 kDa and about 100 kDa, between about 0.1 kDa and about 50 kDa, between about 1 kDa and about 50 kDa, between about 1 kDa and about 40 kDa, between about 10 kDa and about 40 kDa, or about 20 kDa.

16. The modified relaxin polypeptide of any one of claims 9-15, wherein said non-naturally encoded amino acid is linked to said linker, polymer, or biologically active molecule by an oxime linkage or a triazole linkage.

17. The modified relaxin polypeptide of claim 16, wherein said oxime linkage has the structure resulting from by the reaction of a carbonyl moiety and aminooxy moiety, or wherein said triazole linkage has the structure resulting from the reaction of an azide moiety and an alkyne moiety.

18. A modified relaxin polypeptide comprising a non-naturally encoded amino acid, wherein:

(a) the relaxin polypeptide comprises the relaxin A chain polypeptide of SEQ ID NO: 4 and the relaxin B chain polypeptide of SEQ ID NO: 6 substituted with a non-naturally encoded amino acid at the position A chain residue 1; and

(b) the non-naturally encoded amino acid comprises para-acetyl-L-phenylalanine linked to a polymer comprising a poly(ethylene glycol) moiety having an average molecular weight of about 20 kDa.

19. The modified relaxin polypeptide of claim 18, wherein said non-naturally encoded amino acid is linked to said polymer by an oxime linkage produced by the reaction of a carbonyl moiety and aminooxy (hydroxylamine) moiety.

20. The modified relaxin polypeptide of any one of claims 9-19, wherein the modified relaxin polypeptide exhibits an increased *in vivo* half-life relative to the human relaxin consisting of SEQ ID NO: 4 and SEQ ID NO: 5.

21. The modified relaxin polypeptide of claim 20, wherein the half-life is increased by at least 2-fold, at least 5-fold or at least 10-fold.

22. The modified relaxin polypeptide of any one of claims 1–21, wherein said modified relaxin polypeptide is recombinant, is produced in a eukaryotic host cell, is produced in a non-eukaryotic host cell, or is produced by *in vitro* translation.

23. The modified relaxin polypeptide of any one of claims 1–22, wherein said modified relaxin polypeptide is biologically active.

24. A composition comprising a modified relaxin polypeptide of any one of claims 1-23 and a pharmaceutically acceptable carrier.

25. An isolated nucleic acid encoding at least one of: a relaxin polypeptide comprising the relaxin A chain polypeptide of SEQ ID NO: 4 and a relaxin B chain polypeptide of SEQ ID NO: 5 or SEQ ID NO: 6 substituted with a non-naturally encoded amino acid at a position selected from the group consisting of: A chain residue 1, A chain residue 2, A chain residue 5, A chain residue 13, A chain residue 18, B chain residue 5, and B chain residue 7, wherein the nucleic acid comprises at least one selector codon that encodes said non-naturally encoded amino acid.

26. The isolated nucleic acid of claim 25, wherein said selector codon is selected from the group consisting of an amber codon, ochre codon, opal codon, a unique codon, a rare codon, and a four-base codon.

27. An isolated cell comprising the nucleic acid of claim 25 or 26.

28. A method of manufacturing the modified relaxin polypeptide of any one of claims 1 to 23 comprising: expressing a polynucleotides encoding said relaxin A chain polypeptide and said relaxin B chain polypeptide comprising a selector codon that encodes said non-naturally encoded amino acid in the presence of an orthogonal tRNA comprising said non-naturally encoded amino acid under conditions to permit expression of the relaxin polypeptide comprising said non-naturally encoded amino acid.

29. Use of the modified relaxin polypeptide of any one of claims 1–23 or the composition of claim 24 for the manufacture of a medicament.

30. Use of the modified relaxin polypeptide of any one of claims 1–23 or the composition of claim 24 for the preparation of a medicament for the treatment of a disease, condition, or disorder selected from the group consisting of: atherosclerosis; Type 1 diabetes; Type 2 diabetes; coronary artery disease; scleroderma; stroke; diastolic dysfunction; familial hypercholesterolemia; isolated systolic hypertension; primary hypertension; secondary hypertension; left ventricular hypertrophy; arterial stiffness associated with long-term tobacco smoking; arterial stiffness associated with obesity; arterial stiffness associated with age; systemic lupus erythematosus; preeclampsia; hypercholesterolemia; or for use in increasing arterial compliance in perimenopausal, menopausal, and post-menopausal women at risk of the afore-mentioned disorders; or to modulate vasoconstriction, NO production, or platelet aggregation; or for use in treatment of angiotensin-II (AngII)-mediated vasoconstriction or endothelin-1 (ET-1)-mediated vasoconstriction; or for use in treatment of heart failure, congestive heart failure, loss or damage of myocardial tissue, increase in ventricular filling pressure, ventricular wall stress, and impaired integration of arterial and venous vasodilation.

31. Use of the modified relaxin polypeptide of claim 18 for the preparation of a medicament for the treatment of a disease, condition, or disorder selected from the group consisting of: atherosclerosis; Type 1 diabetes; Type 2 diabetes; coronary artery disease; scleroderma; stroke; diastolic dysfunction; familial hypercholesterolemia; isolated systolic hypertension; primary hypertension; secondary hypertension; left ventricular hypertrophy; arterial stiffness associated with long-term tobacco smoking; arterial stiffness associated with obesity; arterial stiffness associated with age; systemic lupus erythematosus; preeclampsia; hypercholesterolemia; or for use in increasing arterial compliance in perimenopausal, menopausal, and post-menopausal women at risk of the afore-mentioned disorders; or to modulate vasoconstriction, NO production, or platelet aggregation; or for use in treatment of angiotensin-II (AngII)-mediated vasoconstriction or endothelin-1 (ET-1)-mediated vasoconstriction; or for use in treatment of heart failure, congestive heart failure, loss or damage of myocardial tissue, increase in ventricular filling pressure, ventricular wall stress, and impaired integration of arterial and venous vasodilation.