CLAIMS

1. A fusion protein comprising, from N-terminus to C-terminus,

a first peptide;

a linker peptide; and

a second peptide,

wherein:

(a) the first peptide comprises an amino acid sequence that differs at 0, 1, 2, 3, 4, or 5 amino acids when compared to the amino acid sequence of SEQ ID NO: 7 and the second peptide comprises an amino acid sequence that differs at 0, 1, 2, 3, 4, or 5 amino acids when compared to the amino acid sequence of SEQ ID NO: 9; or

the first peptide comprises an amino acid sequence that differs at 0, 1, 2, 3, 4, or 5 amino acids when compared to the amino acid sequence of SEQ ID NO: 9 and the second peptide comprises an amino acid sequence that differs at 0, 1, 2, 3, 4, or 5 amino acids when compared to the amino acid sequence of SEQ ID NO: 7,

(b) the linker peptide comprises an amino acid sequence with 12-15 amino acids, comprising 2-5 acidic amino acids and 10-13 non-acidic amino acids, and

(c) the fusion protein has a pI from 6.0 to 8.2.

2. The fusion protein of claim 1, wherein:

the linker peptide comprises an amino acid sequence selected from the group consisting of:

$R_1R_1R_1R_2R_1R_1R_1R_2R_1R_1R_1R_2R_1$;

$R_1R_1R_1R_2R_1R_1R_1R_2R_1R_1R_1R_2R_1R_1R_1$;

$R_1R_1R_2R_1R_1R_1R_2R_2R_1R_1R_1R_2R_1R_1$;

$R_1R_1R_1R_2R_2R_1R_1R_1R_2R_2R_1R_1R_1$; and

$R_1R_1R_2R_1R_2R_1R_1R_2R_1R_2R_1R_1R_1$,

wherein R1 is a non-acidic amino acid and R2 is an acidic amino acid.

3. The fusion protein of claim 1, wherein:

one or more of the acidic amino acid(s) are aspartate or glutamate;

one or more of the acidic amino acid(s) are glutamate;

one or more of the non-acidic amino acid(s) are glycine, proline, or serine;

one or more of the non-acidic amino acid(s) are glycine;

the linker peptide comprises the amino acid sequence of one or more of SEQ ID NO: 14, 15, 16, 17, or 18; and/or

the linker peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 19-23.

4. The fusion protein of any one of the preceding claims, wherein:

the first peptide comprises the amino acid sequence of DSWX$_3$EEVIKLCGRELVRAQIAICGX$_4$ST (SEQ ID NO: 3), wherein X$_3$ is methionine, lysine, or glutamine, and wherein X$_4$ is methionine or lysine;

the first peptide comprises the amino acid sequence of X$_5$QX$_6$YSALANKCCHVGCTKRSLAX$_7$FC (SEQ ID NO: 4), wherein X$_5$ is arginine or absent, wherein X$_6$ is leucine or aspartate, and wherein X$_7$ is arginine, glutamine, or glutamate;

the first peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5-7;

the first peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 8-13;

the second peptide comprises the amino acid sequence of DSWX$_3$EEVIKLCGRELVRAQIAICGX$_4$ST (SEQ ID NO: 3), wherein X$_3$ is methionine, lysine, or glutamine, and wherein X$_4$ is methionine or lysine;

the second peptide comprises the amino acid sequence of X$_5$QX$_6$YSALANKCCHVGCTKRSLAX$_7$FC (SEQ ID NO: 4), wherein X$_5$ is arginine or absent, wherein X$_6$ is leucine or aspartate, and wherein X$_7$ is arginine, glutamine, or glutamate;

the second peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5-7; and/or

the second peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 8-13.

5. The fusion protein of any one of the preceding claims, wherein:

the first peptide comprises the amino acid sequence of SEQ ID NO: 5 and the second peptide comprises the amino acid sequence of SEQ ID NO: 8;

the first peptide comprises the amino acid sequence of SEQ ID NO: 5 and the second peptide comprises the amino acid sequence of SEQ ID NO: 9;

the first peptide comprises the amino acid sequence of SEQ ID NO: 5 and the second peptide comprises the amino acid sequence of SEQ ID NO: 10;

the first peptide comprises the amino acid sequence of SEQ ID NO: 5 and the second peptide comprises the amino acid sequence of SEQ ID NO: 11;

the first peptide comprises the amino acid sequence of SEQ ID NO: 5 and the second peptide comprises the amino acid sequence of SEQ ID NO: 12;

the first peptide comprises the amino acid sequence of SEQ ID NO: 5 and the second peptide comprises the amino acid sequence of SEQ ID NO: 13;

the first peptide comprises the amino acid sequence of SEQ ID NO: 6 and the second peptide comprises the amino acid sequence of SEQ ID NO: 8;

the first peptide comprises the amino acid sequence of SEQ ID NO: 6 and the second peptide comprises the amino acid sequence of SEQ ID NO: 9;

the first peptide comprises the amino acid sequence of SEQ ID NO: 6 and the second peptide comprises the amino acid sequence of SEQ ID NO: 10;

the first peptide comprises the amino acid sequence of SEQ ID NO: 6 and the second peptide comprises the amino acid sequence of SEQ ID NO: 11;

the first peptide comprises the amino acid sequence of SEQ ID NO: 6 and the second peptide comprises the amino acid sequence of SEQ ID NO: 12;

the first peptide comprises the amino acid sequence of SEQ ID NO: 6 and the second peptide comprises the amino acid sequence of SEQ ID NO: 13;

the first peptide comprises the amino acid sequence of SEQ ID NO: 7 and the second peptide comprises the amino acid sequence of SEQ ID NO: 8;

the first peptide comprises the amino acid sequence of SEQ ID NO: 7 and the second peptide comprises the amino acid sequence of SEQ ID NO: 9;

the first peptide comprises the amino acid sequence of SEQ ID NO: 7 and the second peptide comprises the amino acid sequence of SEQ ID NO: 10;

the first peptide comprises the amino acid sequence of SEQ ID NO: 7 and the second peptide comprises the amino acid sequence of SEQ ID NO: 11;

the first peptide comprises the amino acid sequence of SEQ ID NO: 7 and the second peptide comprises the amino acid sequence of SEQ ID NO: 12;

the first peptide comprises the amino acid sequence of SEQ ID NO: 7 and the second peptide comprises the amino acid sequence of SEQ ID NO: 13;

the second peptide comprises the amino acid sequence of SEQ ID NO: 5 and the first peptide comprises the amino acid sequence of SEQ ID NO: 8;

the second peptide comprises the amino acid sequence of SEQ ID NO: 5 and the first peptide comprises the amino acid sequence of SEQ ID NO: 9;

the second peptide comprises the amino acid sequence of SEQ ID NO: 5 and the first peptide comprises the amino acid sequence of SEQ ID NO: 10;

the second peptide comprises the amino acid sequence of SEQ ID NO: 5 and the first peptide comprises the amino acid sequence of SEQ ID NO: 11;

the second peptide comprises the amino acid sequence of SEQ ID NO: 5 and the first peptide comprises the amino acid sequence of SEQ ID NO: 12;

the second peptide comprises the amino acid sequence of SEQ ID NO: 5 and the first peptide comprises the amino acid sequence of SEQ ID NO: 13;

the second peptide comprises the amino acid sequence of SEQ ID NO: 6 and the first peptide comprises the amino acid sequence of SEQ ID NO: 8;

the second peptide comprises the amino acid sequence of SEQ ID NO: 6 and the first peptide comprises the amino acid sequence of SEQ ID NO: 9;

the second peptide comprises the amino acid sequence of SEQ ID NO: 6 and the first peptide comprises the amino acid sequence of SEQ ID NO: 10;

the second peptide comprises the amino acid sequence of SEQ ID NO: 6 and the first peptide comprises the amino acid sequence of SEQ ID NO: 11;

the second peptide comprises the amino acid sequence of SEQ ID NO: 6 and the first peptide comprises the amino acid sequence of SEQ ID NO: 12;

the second peptide comprises the amino acid sequence of SEQ ID NO: 6 and the first peptide comprises the amino acid sequence of SEQ ID NO: 13;

the second peptide comprises the amino acid sequence of SEQ ID NO: 7 and the first peptide comprises the amino acid sequence of SEQ ID NO: 8;

the second peptide comprises the amino acid sequence of SEQ ID NO: 7 and the first peptide comprises the amino acid sequence of SEQ ID NO: 9;

the second peptide comprises the amino acid sequence of SEQ ID NO: 7 and the first peptide comprises the amino acid sequence of SEQ ID NO: 10;

the second peptide comprises the amino acid sequence of SEQ ID NO: 7 and the first peptide comprises the amino acid sequence of SEQ ID NO: 11;

the second peptide comprises the amino acid sequence of SEQ ID NO: 7 and the first peptide comprises the amino acid sequence of SEQ ID NO: 12; or

the second peptide comprises the amino acid sequence of SEQ ID NO: 7 and the first peptide comprises the amino acid sequence of SEQ ID NO: 13.

6. The fusion protein of any one of the preceding claims, wherein the fusion protein comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 25-48.

7. The fusion protein of any one of the preceding claims, wherein the fusion protein further comprises an IgG Fc; optionally wherein:

the IgG Fc comprises the amino acid alanine at EU positions 234 and 235;

the IgG Fc comprises the amino acid alanine at EU position 329;

the IgG Fc comprises the amino acid alanine at EU positions 234, 235, and 329;

the IgG Fc comprises the amino acids alanine, alanine, alanine, leucine, and serine at EU positions 234, 235, 329, 428, and 434, respectively;

the IgG Fc comprises the amino acids lysine, phenylalanine, and tyrosine at EU positions 433, 434, and 436, respectively;

the IgG Fc comprises the amino acids tyrosine, threonine, and glutamate at EU positions 252, 254, and 256, respectively;

the IgG Fc comprises the amino acids leucine and serine at EU positions 428 and 434, respectively;

the IgG Fc comprises an amino acid sequence at least 85% identical to the amino acid sequence of a human IgG1 Fc;

the IgG Fc comprises an amino acid sequence comprising or consisting of the amino acid sequence of SEQ ID NO: 49 or 200;

the IgG Fc comprises an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 50-52 and 201-203; and/or

the IgG Fc is linked to the N-terminus of the first peptide or the IgG Fc is linked to the C-terminus of the second peptide.

8. The fusion protein of any one of the preceding claims, wherein the first and second peptides do not comprise the amino acid sequence of a peptide selected from the group consisting of SEQ ID NOs:187-190.

9. A fusion protein comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 53-118, 204-211, and 214-221.

10. A polynucleotide or an expression vector comprising the polynucleotide, wherein the polynucleotide comprises a nucleotide sequence encoding the fusion protein of any one of the preceding claims, optionally wherein the polynucleotide is an RNA or DNA molecule, optionally wherein the expression vector is a plasmid or a viral vector.

11. A host cell comprising the polynucleotide or the expression vector of claim 10, or a population of host cells comprising two or more of the host cells, wherein:

the host cell is a prokaryotic cell, optionally wherein the prokaryotic cell is an *E. coli* cell or a *Bacillus* cell; or

the host cell is a eukaryotic cell, optionally wherein:

the eukaryotic cell is selected from the group consisting of a yeast cell, an insect cell, and a mammalian cell; or

the eukaryotic cell is a mammalian cell selected from the group consisting of a CHO cell, a HeLa cell, and a 293 cell.

12. A method of producing the fusion protein of any one of claims 1-9 comprising culturing the host cell of claim 11, under conditions such that the fusion protein is produced.

13. A pharmaceutical composition comprising an effective amount of the fusion protein of any one of claims 1-9, or the polynucleotide or the expression vector of claim 10.

14. An *ex vivo* method of enhancing a relaxin-2-related activity in a primary cell, comprising contacting the primary cell with the fusion protein of any one of claims 1-9, thereby enhancing relaxin-2-related activity in the cell, wherein:

the fusion protein activates relaxin-2 receptor (RXFP1) on a cell surface;

the method elevates cAMP levels in the primary cell, inducing vasodilation, inducing the expression of angiogenic factors, inducing the expression of MMPs, and/or inducing collagen degradation; and/or

the primary cell is selected from the group consisting of endothelial cells, vascular smooth muscle cells, other vascular cells, cardiomyocytes, other cardiac cells, and fibroblasts.

15. Use of the fusion protein of any one of claims 1-9, the polynucleotide or the expression vector of claim 10, or the pharmaceutical composition of claim 13, in the manufacture of a medicament for treating a relaxin-associated disorder in a subject in need thereof, wherein:

the relaxin-2-associated disorder is selected from the group consisting of kidney diseases, fibrotic diseases, cardiovascular diseases, focal segmental glomerular sclerosis (FSGS), diabetic nephropathy, hepatorenal syndrome, scleroderma, idiopathic pulmonary fibrosis, renal fibrosis, cardiac fibrosis, NASH, dilated cardiomyopathy, diastolic heart failure, pulmonary arterial hypertension, chronic heart failure, acute heart failure, congestive heart failure, coronary artery disease, hypertension, and pre-eclampsia; and/or

the treating decreases arterial pressure, increases renal artery blood flow, increases cardiac filling at diastole, resolves established fibrosis, or suppresses new fibrosis development.

16. A kit comprising an effective amount of the fusion protein of any one of claims 1-9, the polynucleotide or the expression vector of claim 10, or the pharmaceutical composition of claim 13, and an instruction of use.

17. The fusion protein of any one of claims 1-9, the polynucleotide or the expression vector of claim 10, or the pharmaceutical composition of claim 13, for use as a medicament.

18. The fusion protein of any one of claims 1-9, the polynucleotide or the expression vector of claim 10, or the pharmaceutical composition of claim 13, for use in the treatment of a relaxin-associated disorder in a subject in need thereof, wherein:

the relaxin-2-associated disorder is selected from the group consisting of kidney diseases, fibrotic diseases, cardiovascular diseases, focal segmental glomerular sclerosis (FSGS), diabetic nephropathy, hepatorenal syndrome, scleroderma, idiopathic pulmonary fibrosis, renal fibrosis,

cardiac fibrosis, NASH, dilated cardiomyopathy, diastolic heart failure, pulmonary arterial hypertension, chronic heart failure, acute heart failure, congestive heart failure, coronary artery disease, hypertension, and pre-eclampsia.