~~What is claimed is:~~

CLAIMS

1. A polypeptide that binds to human serum albumin (HSA) with a K_d of $1x10^{-6}$ M or less at pH 7.4, and at pH 6 binds to HSA with a K_d that is at least half a log less than the K_d for binding to HSA at pH 7.4.

~~2. The polypeptide of claim 1, wherein the polypeptide binds to HSA with a K_d of $1x10^{-7}$ M or less at pH 7.4, a K_d of $1x10^{-8}$ M or less at pH 7.4, or K_d of $1x10^{-9}$ M or less at pH 7.4.~~

~~3~~2. The polypeptide of claim 1 ~~or 2~~, wherein the polypeptide at pH 6 binds to HSA with a K_d that is at least one log less than the K_d for binding to HSA at pH 7.4~~, at least 1.5 logs less than the K_d for binding to HSA at pH 7.4, at least 2 logs less than the K_d for binding to HSA at pH 7.4, or at least 2.5 log less than the K_d for binding to HSA at pH 7.4~~.

~~4~~3. The polypeptide of claim 1 ~~any one of claim 1-3~~, wherein the polypeptide has a serum half-life in human patients of greater than 10 hours~~, greater than 24 hours, greater than 48 hours, greater than 72 hours, greater than 96 hours, greater than 120 hours, greater than 144 hours, greater than 168 hours, greater than 192 hours, greater than 216 hours, greater than 240 hours, greater than 264 hours, greater than 288 hours, greater than 312 hours, greater than 336 hours or, greater than 360 hours~~.

~~5~~4. The polypeptide of claim 1 ~~any one of claims 1-4~~, wherein the polypeptide has a serum half-life in human patients of greater than 50%~~, greater than 60%, greater than 70%, or greater than 80%~~ of the serum half-life of HSA.

~~6~~5. The polypeptide of claim 1 ~~any one of claims 1-5~~ comprising an amino acid sequence represented in general formula (I)

$$FR1\text{-}(Xaa)_n\text{-}FR2\text{-}(Xaa)_m\text{-}FR3 \quad (I),$$

wherein

FR1 is an amino acid sequence having at least ~~70%~~90% identity to MIPGGLSEAK PATPEIQEIV DKVKPQLEEK TNETYGKLEA VQYKTQVLA (SEQ ID NO: 1);

FR2 is an amino acid sequence having at least ~~70%~~90% identity to GTNYYIKVRA GDNKYMHLKV FKSL (SEQ ID NO: 2);

FR3 is an amino acid sequence having at least ~~70%~~90% identity to EDLVLTGYQV DKNKDDELTG F (SEQ ID NO: 3); and

Xaa, individually for each occurrence, is an amino acid,

n is an integer from 3 to 20, and m is an integer from 3 to 20.

~~7. The polypeptide of claim 6, wherein:~~

~~FR1 has at least 80%, at least 82%, at least 84%, at least 86%, at least 88%, at least 90%, at least 92%, at least 94%, at least 96%, or at least 98% identity to SEQ ID NO: 1;~~

~~FR2 has at least 80%, at least 84%, at least 88%, at least 92%, or at least 96% identity to SEQ ID NO: 2; and/or.~~

~~FR3 has at least 80%, at least 85%, at least 90%, or at least 95% identity to SEQ ID NO: 3.~~

~~8~~6. The polypeptide of claim ~~5~~7, wherein:

FR1 comprises the amino acid sequence of SEQ ID NO: 1;

FR2 comprises the amino acid sequence of SEQ ID NO: 2; and/or

FR3 comprises the amino acid sequence of SEQ ID NO: 3.

~~9~~7. The polypeptide of claim ~~6~~ 5, wherein the amino acid sequence is represented in general formula (II)

MIP-Xaa1-GLSEAKPATPEIQEIVDKVKPQLEEKTNETYGKLEAVQYKTQVLA-$(Xaa)_n$-Xaa2-TNYYIKVRAGDNKYMHLKVF-Xaa3-Xaa4-Xaa5-$(Xaa)_m$-Xaa6-D-Xaa7-VLTGYQVDKNKDDELTGF (SEQ ID NO: 166) (II),

wherein

Xaa, individually for each occurrence, is an amino acid;

n is an integer from 3 to 20, and m is an integer from 3 to 20;

Xaa1 is Gly, Ala, Val, Arg, Lys, Asp, or Glu;

Xaa2 is Gly, Ala, Val, Ser or Thr;

Xaa3 is Arg, Lys, Asn, Gln, Ser, Thr;

Xaa4 is Gly, Ala, Val, Ser or Thr;

Xaa5 is Ala, Val, Ile, Leu, Gly or Pro;

Xaa6 is Gly, Ala, Val, Asp or Glu; and

Xaa7 is Ala, Val, Ile, Leu, Arg or Lys.

~~10~~8. The polypeptide of claim ~~9~~ 7, wherein the amino acid sequence is represented in general formula (III)

MIPRGLSEAKPATPEIQEIVDKVKPQLEEKTNETYGKLEAVQYKT
QVLA-(Xaa)n-STNYYIKVRAGDNKYMHLKVFNGP-(Xaa)m-ADR
VLTGYQVDKNKDDELTGF (SEQ ID NO: 167) (III),

wherein

Xaa, individually for each occurrence, is an amino acid; n is an integer from 3 to 20; and m is an integer from 3 to 20.

~~11. The polypeptide of any one of claims 6-10, wherein (Xaa)$_n$ is represented by formula (IV)~~

~~aa1-aa2-aa3-aa4-aa5-aa6-aa7-aa8-aa9 (SEQ ID NO: 180) (IV),~~

~~wherein~~

~~aa1 is an amino acid selected from D, G, N, and V;~~

~~aa2 is an amino acid selected from W, Y, H, and F;~~

~~aa3 is an amino acid selected from W, Y, G, W, and F;~~

~~aa4 is an amino acid selected from Q, A, and P;~~

~~aa5 is an amino acid selected from A, Q, E, R, and S;~~

~~aa6 is an amino acid selected from K, R, and Y;~~

~~aa7 is an amino acid selected from W and Q;~~

~~aa8 is an amino acid selected from P and H; and~~

~~aa9 is an amino acid selected from H, G, and Q.~~

~~12~~9. The polypeptide of claim 5 ~~any one of claims 6-11,~~ wherein

(a) (Xaa)$_n$ is an amino acid sequence having ~~at least 80% or~~ at least 90% identity to the amino acid sequence of any one of SEQ ID NOS: 4-55; and/or

(b) (Xaa)$_m$ is an amino acid sequence having at least 90% identity to the amino acid sequence of any one of SEQ ID NOS: 57-108.

~~13~~10. The polypeptide of claim ~~12~~9, wherein

(a) (Xaa)$_n$ is the amino acid sequence of any one of SEQ ID NOS: 4-55; and/or

(b) $(Xaa)_m$ is the amino acid sequence of any one of SEQ ID NOS: 57-108.

~~14. The polypeptide of any one of claims 6-13, wherein $(Xaa)_n$ is an amino acid sequence having at least 80% or at least 90% identity to the amino acid sequence of any one of SEQ ID NOS: 22, 24, 26, 35, 40, 41, and 45.~~

~~15~~11. The polypeptide of claim 10~~14~~, wherein

(a) $(Xaa)_n$ is an amino acid sequence of any one of SEQ ID NOS: 22, 24, 26, 35, 40, 41, and 45; and/or

(b) $(Xaa)_m$ is an amino acid sequence of any one of SEQ ID NOS: 75, 77, 79, 88, 93, 94, and 98.

~~16. The polypeptide of any one of claims 6-15, wherein $(Xaa)_m$ is represented by formula (IV)~~

~~aa1-aa2-aa3-aa4-aa5-aa6-aa7-aa8-aa9 (SEQ ID NO: 181) (IV),~~

~~wherein~~

~~aa1 is an amino acid selected from Y, F, W, and N;~~

~~aa2 is an amino acid selected from K, P, H, A, and T;~~

~~aa3 is an amino acid selected from V, N, G, Q, A, and F;~~

~~aa4 is an amino acid selected from H, T, Y, W, K, V, and R;~~

~~aa5 is an amino acid selected from Q, S, G, P, and N;~~

~~aa6 is an amino acid selected from S, Y, E, L, K, and T;~~

~~aa7 is an amino acid selected from S, D, V, and K;~~

~~aa8 is an amino acid selected from G, L, S, P, H, D, and R; and~~

~~aa9 is an amino acid selected from G, Q, E, and A.~~

~~17. The polypeptide of any one of claims 6-16, wherein $(Xaa)_m$ is an amino acid sequence having at least 80% or at least 90% identity to the amino acid sequence of any one of SEQ ID NOS: 57-108.~~

~~18. The polypeptide of claim 17, wherein $(Xaa)_m$ is the amino acid sequence of any one of SEQ ID NOS: 57-108.~~

~~19. The polypeptide of any one of claims 6-16, wherein (Xaa)$_m$ is an amino acid sequence having at least 80% or at least 90% identity to the amino acid sequence of any one of SEQ ID NOS: 75, 77, 79, 88, 93, 94, and 98.~~

~~20. The polypeptide of claim 19, wherein (Xaa)$_m$ is an amino acid sequence of any one of SEQ ID NOS: 75, 77, 79, 88, 93, 94, and 98.~~

~~21~~12. The polypeptide of claim 1 ~~any one of any one of claims 1-20~~, wherein the polypeptide comprises an amino acid sequence that has ~~at least 70%, at least 80%, or~~ at least 90% identity to an amino acid sequence of any one of SEQ ID NOS: 110-116 and 138.

~~22~~13. The polypeptide of claim ~~21~~ 12, wherein the polypeptide comprises an amino acid sequence of any one of SEQ ID NOS: 110-116 and 138.

~~23. The polypeptide of any one of claims 6-10, wherein (Xaa)$_n$ is represented by formula (IV)~~

~~aa1-aa2-aa3-aa4-aa5-aa6-aa7-aa8-aa9 (IV),~~

~~wherein~~

~~aa1 is an amino acid with a neutral polar hydrophilic side chain;~~
~~aa2 is an amino acid with a neutral nonpolar hydrophobic side chain;~~
~~aa3 is an amino acid with a neutral nonpolar hydrophobic side chain;~~
~~aa4 is an amino acid with a neutral polar hydrophilic side chain;~~
~~aa5 is an amino acid with a positively charged polar hydrophilic side chain;~~
~~aa6 is an amino acid with a positively charged polar hydrophilic side chain;~~
~~aa7 is an amino acid with a neutral nonpolar hydrophobic side chain;~~
~~aa8 is an amino acid with a neutral nonpolar hydrophobic side chain; and~~
~~aa9 is an amino acid with a neutral nonpolar hydrophilic side chain.~~

~~24. The polypeptide of any one of claims 6-10, wherein (Xaa)$_m$ is represented by formula (IV)~~

~~aa1-aa2-aa3-aa4-aa5-aa6-aa7-aa8-aa9 (IV)~~

~~wherein~~

~~aa1 is an amino acid with a neutral nonpolar hydrophobic side chain;~~
~~aa2 is an amino acid with a positively charged polar hydrophilic side chain;~~

~~aa3 is an amino acid with a neutral nonpolar hydrophobic side chain;~~

~~aa4 is an amino acid with a positively charged polar hydrophilic side chain;~~

~~aa5 is an amino acid with a neutral polar hydrophilic side chain;~~

~~aa6 is an amino acid with a neutral polar hydrophilic side chain;~~

~~aa7 is an amino acid with a negatively charged polar hydrophilic side chain;~~

~~aa8 is an amino acid with a positively charged polar hydrophilic side chain; and~~

~~aa9 is an amino acid with a neutral nonpolar hydrophilic side chain.~~

~~25. The polypeptide of claim 23 or 24, wherein~~

~~the amino acid with the neutral nonpolar hydrophilic side chain is selected from cysteine (C) and glycine (G);~~

~~the amino acid with the neutral nonpolar hydrophobic side chain is selected from alanine (A), isoleucine (I), leucine (L), methionine (M), phenylalanine (F), proline (P), tryptophan (W), and valine (V);~~

~~the amino acid with the neutral polar hydrophilic side chain is selected from asparagine (N), glutamine (Q), serine (S), threonine (T), and tyrosine (Y);~~

~~the amino acid with the positively charged polar hydrophilic side chain is selected from arginine (R), histidine (H), and lysine (K); and~~

~~the amino acid with the negatively charged polar hydrophilic side chain is selected from aspartate (D) and glutamate (E).~~

~~26. The polypeptide of any one of claims 1-25, wherein the polypeptide comprises an amino acid sequence that comprises a cysteine.~~

~~27~~14. The polypeptide of claim 1~~26~~, wherein the polypeptide comprises an amino acid sequence that comprises a cysteine ~~the cysteine is available for chemical conjugation, and optionally wherein the cysteine is~~ located at the C-terminal end or the N-terminal end of the polypeptide~~, and optionally wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 138~~.

~~28~~15. The polypeptide of claim 1 ~~any one of claims 1-27~~ further comprising a heterologous polypeptide covalently linked through an amide bond to form a contiguous fusion protein.

~~29. The polypeptide of claim 28, wherein the heterologous polypeptide comprises a therapeutic polypeptide.~~

~~30~~16. The polypeptide of claim 15~~29~~, wherein the heterologous polypeptide ~~therapeutic polypeptide~~ is

(a) selected from the group consisting of polypeptide hormones, polypeptide cytokines, polypeptide chemokines, growth factors, hemostasis active polypeptides, enzymes, and toxins;

(b) selected from the group consisting of receptor traps and receptor ligands;

(c) selected from the group consisting of angiogenic agents and anti-angiogenic agents;

(d) a neurotransmitter;

(e) an erythropoiesis-stimulating agent; or

(f) an incretin.

~~31. The polypeptide of claim 29, wherein the therapeutic polypeptide is selected from the group consisting of receptor traps and receptor ligands.~~

~~32. The polypeptide of claim 29, wherein the therapeutic polypeptide sequence is selected from the group consisting of angiogenic agents and anti-angiogenic agents.~~

~~33. The polypeptide of claim 29, wherein the therapeutic polypeptide sequence is a neurotransmitter, and optionally wherein the neurotransmitter is Neuropeptide Y.~~

~~34. The polypeptide of claim 29, wherein the therapeutic polypeptide sequence is an erythropoiesis-stimulating agent, and optionally wherein the erythropoiesis-stimulating agent is erythropoietin or an erythropoietin mimetic.~~

~~35. The polypeptide of claim 29, wherein the therapeutic polypeptide is an incretin, and optionally wherein the incretin is selected from the group consisting of glucagon, gastric inhibitory peptide (GIP), glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), peptide YY (PYY), and oxyntomodulin (OXM).~~

~~36~~17. A pharmaceutical composition suitable for therapeutic use in a human patient, comprising a polypeptide of claim 1 ~~any of claim 1-35,~~ and a pharmaceutically acceptable excipient.

~~37~~18. A polynucleotide comprising a sequence encoding the polypeptide of claim 1 ~~any of claims 1-36~~.

~~38. The polynucleotide of claim 37, wherein the sequence encoding the polypeptide is operably linked to a transcriptional regulatory sequence.~~

~~39. The polynucleotide of claim 38, wherein the transcriptional regulatory sequence is selected from the group consisting of promoters and enhancers.~~

~~40. The polynucleotide of claim 38 or 39, further comprising an origin of replication, a minichromosome maintenance element (MME), and/or a nuclear localization element.~~

~~41. The polynucleotide of any of claims 38-40, further comprising a polyadenylation signal sequence operably linked and transcribed with the sequence encoding the polypeptide.~~

~~42. The polynucleotide of any of claims 38-41, wherein the sequence encoding the polypeptide comprises at least one intronic sequence.~~

~~43. The polynucleotide of any of claims 38-42, further comprising at least one ribosome binding site transcribed with the sequence encoding the polypeptide.~~

~~44. The polynucleotide of any of claims 38-43, wherein the polynucleotide is a deoxyribonucleic acid (DNA).~~

~~45. The polynucleotide of any of claims 38-43, wherein the polynucleotide is a ribonucleic acid (RNA).~~

~~46~~19. A viral vector, a plasmid or minicircle comprising the polynucleotide of claim 18 ~~any of claims 38-45~~.

~~47. A plasmid or minicircle comprising the polynucleotide of any of claims 38-46.~~

~~48~~20. A fusion protein comprising a polypeptide of claim 1 ~~any one of the preceding claims~~.

~~49. The fusion protein of claim 48 further comprising a linker.~~

~~50. The fusion protein of claim 49, wherein the linker is a rigid linker.~~

~~51. The fusion protein of claim 50, wherein the rigid linker comprises the sequence of SEQ ID NO: 161.~~

~~52. The fusion protein of claim 49, wherein the linker is a flexible linker.~~

~~53. The fusion protein of claim 50, wherein the flexible linker comprises the sequence of SEQ ID NO: 165.~~

~~54. The fusion protein of any one of claims 48-53 comprising two polypeptides of any one of the preceding claims.~~

~~55. The fusion protein of any one of claims 48-54 further comprising a therapeutic molecule.~~

~~56. The fusion protein of claim 55, wherein the therapeutic molecule is a therapeutic polypeptide.~~

~~57. The fusion protein of claim 56, wherein the therapeutic polypeptide is selected from hormones, cytokines, chemokines, growth factors, hemostasis active polypeptides, enzymes, and toxins, or is selected from antagonists of hormones, cytokines, chemokines, growth factors, hemostasis active polypeptides, enzymes, and toxins.~~

~~58. The fusion protein of any one of claims 48-57, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 110.~~

~~59. The fusion protein of any one of claims 48-57, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 113.~~

~~60. The fusion protein of any one of claims 48-57, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 116.~~