

CONSTRUCTS HAVING A SIRP-ALPHA DOMAIN OR VARIANT THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/202,772, filed August 7, 2015; U.S. Provisional Patent Application No. 62/202,775, filed August 7, 2015; U.S. Provisional Patent Application No. 62/202,779, filed August 7, 2015; U.S. Provisional Patent Application No. 62/276,801, filed January 8, 2016; U.S. Provisional Patent Application No. 62/265,887 filed on December 10, 2015; U.S. Provisional Patent Application No. 62/276,796 filed on January 8, 2016; and U.S. Provisional Patent Application No. 62/346,414 filed June 6, 2016 which applications are each incorporated herein in their entireties by reference.

SUMMARY

[0002] Disclosed herein, in certain embodiments, are polypeptides comprising: a signal-regulatory protein α (SIRP- α) D1 variant comprising a SIRP- α D1 domain, or a fragment thereof, having an amino acid mutation at residue 80 relative to a wild-type SIRP- α D1 domain; and at least one additional amino acid mutation relative to a wild-type SIRP- α D1 domain at a residue selected from the group consisting of: residue 6, residue 27, residue 31, residue 47, residue 53, residue 54, residue 56, residue 66, and residue 92. In some embodiments, the wild type SIRP- α D1 domain has a sequence according to any one of SEQ ID NOs: 1-10. In some embodiments, the SIRP- α D1 domain comprises between one and nine additional amino acid mutations relative to a wild-type SIRP- α D1 domain at a residue selected from the group consisting of: residue 6, residue 27, residue 31, residue 47, residue 53, residue 54 residue 56, residue 66, and residue 92.

[0002a] In one aspect, there is provided a polypeptide, comprising a signal-regulatory protein α (SIRP- α) D1 variant that comprises the amino acid sequence
EEELQX₁IQPKSVLVAAGETATLRCTX₂TSX₃PVGPIQWFRGAGPGRX₄LIYNQX₅X₆GX₇F
PRVTTVSDX₈TKRNNMDFSIRIGX₉ITPADAGTYCYX₁₀KFRKGSPDDVEFKSGAGTELSVRA
KPS (SEQ ID NO: 49), wherein X₁ is V, L, or I; X₂ is A, I, V, or L; X₃ is I, F, S, or T; X₄ is E, V, or L; X₅ is K or R; X₆ is E or Q; X₇ is H, P, or R; X₈ is L, T, S, or G; X₉ is A; and X₁₀ is V or I; and comprises at least two amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1. In some embodiments, the SIRP- α D1 variant comprises the amino acid sequence,

EEELQX₁IQPKSVLVAAGETATLRCTX₂TSX₃PVGPIQWFRGAGPGRX₄LIYNQX₅X₆GX₇F
PRVTTVSDX₈TKRNNMDFSIRIGX₉X₁₀X₁₁X₁₂ADAGTYCYX₁₃KFRKGSPDDVEFKSGAGTEL
SVRAKPS (SEQ ID NO: 218), wherein X₁ is V, L, or I; X₂ is A, V, L, or I; X₃ is I, S, T, or F; X₄ is E, L, or V; X₅ is K or R; X₆ is E or Q; X₇ is H, R, or P; X₈ is S, G, L, or T; X₉ is any amino acid;

X₁₀ is any amino acid; X₁₁ is any amino acid; X₁₂ is any amino acid; and X₁₃ is V or I; and wherein the SIRP- α D1 variant has at least two amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1. In some embodiments, X₉ is A. In some embodiments, X₉ is N. In some embodiments, X₁₀ is I. In some embodiments, X₉ is N and X₁₀ is P. In some embodiments, X₉ is N and X₁₁ is any amino acid other than S, T, or C. In some embodiments, X₁₁ is T. In some embodiments, X₁₁ is an amino acid other than T. In some embodiments, X₁₂ is P. In some embodiments, X₉ is N and X₁₂ is any amino acid other than P. In some embodiments, the SIRP- α D1 variant comprises the amino acid sequence, EEELQX₁IQPKSVLVAAGETATLRCTX₂TS LX₃PVGPIQWFRGAGPGRX₄LIYNQX₅X₆GX₇FPRVTTVSDX₈TKRNNMDFSIRIGX₉ITX₁₀ADAGTYYCX₁₁KFRKGSPDDVEFKSGAGTELSVR AKPS (SEQ ID NO: 219), wherein X₁ is V, L, or I; X₂ is A, V, L, or I; X₃ is I, S, T, or F; X₄ is E, L, or V; X₅ is K or R; X₆ is E or Q; X₇ is H, R, or P; X₈ is S, G, L, or T; X₉ is N; X₁₀ is any amino acid other than P; and X₁₁ is V or I; and wherein the SIRP- α D1 variant has at least two amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1.

[0002b] In another aspect, there is provided a polypeptide comprising a signal-regulatory protein α (SIRP- α) D1 variant that comprises the amino acid sequence

EEELQX₁IQPKSVLVAAGETATLRCTX₂TS LX₃PVGPIQWFRGAGPGRELIYNQX₄EGX₅FPRVTTVS DX₆TKRNNMDFSIRIGX₇ITPADAGTYYCVKFRKGSPDDVEFKSGAGTELSVR AKPS (SEQ ID NO: 52), wherein X₁ is V, L, or I; X₂ is A, I, or L; X₃ is I, T, S, or F; X₄ is K or R; X₅ is H, P, or R; X₆ is L, T, or G; and X₇ is A; and comprises at least two amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1. In some embodiments, the SIRP- α D1 variant comprises the amino acid sequence,

EEELQX₁IQPKSVLVAAGETATLRCTX₂TS LX₃PVGPIQWFRGAGPGRELIYNQX₄EGX₅FPR VTTVSDX₆TKRNNMDFSIRIGX₇ITPADAGTYYCVKFRKGSPDDVEFKSGAGTELSVR AKPS (SEQ ID NO: 52), wherein X₁ is V, L, or I; X₂ is A, I, or L; X₃ is I, T, S, or F; X₄ is K or R; X₅ is H, P, or R; X₆ is L, T, or G; and X₇ is A; and wherein the SIRP- α D1 variant has at least two amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1. In some embodiments, X₁ is V or I, X₂ is A or I, X₃ is I or F, X₄ is K or R, X₅ is H or P, X₆ is L or T, and X₇ is A. In some embodiments, the SIRP- α D1 variant has at least three amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1. In some embodiments, the SIRP- α D1 variant has at least four amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1. In some embodiments, the SIRP- α D1 variant has at least five amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1. In some embodiments, the SIRP- α D1 variant has at least six amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1. In some embodiments, the SIRP- α D1 variant has at least seven amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1. In some embodiments, X₁ is I. In some embodiments, X₂ is I. In some embodiments, X₃ is F. In some embodiments, X₄ is R. In some embodiments, X₅ is P. In some embodiments, X₆ is T. In some embodiments, each of X₁, X₂, X₃, X₄, X₅, and X₆ is not a wild-type amino acid. In some embodiments, the SIRP- α D1 variant has an amino acid sequence

G237A, and N297A mutation relative to a human IgG1 Fc region; (iv) a N297A mutation relative to a human IgG2 Fc region; (vi) a A330S, P331S, and N297A mutation relative to a human IgG2 Fc region; (vii) a S228P, E233P, F234V, L235A, and delG236 mutation relative to a human IgG4 Fc region; or (viii) a S228P, E233P, F234V, L235A, delG236, and N297A mutation relative to a human IgG4 Fc region. In some embodiments, the polypeptide exhibits a reduction of phagocytosis in a phagocytosis assay compared to a polypeptide with a wild-type human IgG Fc region. In some embodiments, the Fc domain monomer is linked to a second polypeptide comprising a second Fc domain monomer to form an Fc domain dimer. In some embodiments, the second Fc domain monomer is linked to an additional polypeptide. In some embodiments, the additional polypeptide comprises an antibody variable domain. In some embodiments, the antibody variable domain targets an antigen expressed on a cell. In some embodiments, the cell is a cancer cell. In some embodiments, the antibody variable domain targets a cell surface protein involved in immune cell regulation. In some embodiments, the additional polypeptide comprises a therapeutic protein. In some embodiments, the therapeutic protein is a cytokine, an interleukin, an antigen, a steroid, an anti-inflammatory agent, or an immunomodulatory agent. In some embodiments, the additional polypeptide comprises a SIRP- α D1 variant. In some embodiments, the polypeptide further comprises a human serum albumin (HSA) (SEQ ID NO: 12). In some embodiments, the HSA comprises a C34S or K573P amino acid substitution relative to SEQ ID NO: 12. In some embodiments, the polypeptide has an amino acid sequence according to any one of SEQ ID NOs: 152-159. In some embodiments, the polypeptide further comprises an albumin-binding peptide. In some embodiments, the albumin-binding peptide comprises the amino acid sequence DICLPRWGCLW (SEQ ID NO: 160). In some embodiments, the polypeptide further comprises a polyethylene glycol (PEG) polymer. In some embodiments, the PEG polymer is joined to a cysteine substitution in the polypeptide.

[0002c] In another aspect, there is provided a polypeptide, comprising:

(a) a signal-regulatory protein α (SIRP- α) D1 variant, wherein the SIRP- α D1 variant comprises the amino acid sequence,
EEX₁X₂QX₃IQPDKX₄VX₅VAAGEX₆X₇X₈LX₉CTX₁₀TSLX₁₁PVGPIQWFRGAGPX₁₂RX₁₃LIYNQX₁₄X₁₅G
X₁₆FPRVTTVSX₁₇X₁₈TX₁₉RX₂₀NMDFX₂₁IX₂₂IX₂₃X₂₄ITX₂₅ADAGTYCYCX₂₆KX₂₇RKGSPDX₂₈X₂₉EX₃₀KS
GAGTELSVRX₃₁KPS (SEQ ID NO: 47), wherein X₁ is E, or G; X₂ is L, I, or V; X₃ is V, L, or I; X₄ is S, or F; X₅ is L, or S; X₆ is S, or T; X₇ is A, or V; X₈ is I, or T; X₉ is H, R, or L; X₁₀ is A, V, I, or L; X₁₁ is I, T, S, or F; X₁₂ is A, or G; X₁₃ is E, V, or L; X₁₄ is K, or R; X₁₅ is E, or Q; X₁₆ is H, P, or R; X₁₇ is D, or E; X₁₈ is S, L, T, or G; X₁₉ is K, or R; X₂₀ is E, or N; X₂₁ is S, or P; X₂₂ is S, or R; X₂₃ is S, or G; X₂₄ is A; X₂₅ is any amino acid; X₂₆ is V, or I; X₂₇ is F, L, or V; X₂₈ is D; X₂₉ is T, or V; X₃₀ is F, or V; and X₃₁ is A, or G; and comprises at least two amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to any one of SEQ ID NOs: 1 to 10; and

(b) an Fc variant selected from the group consisting of: (i) a human IgG1 Fc region comprising a N297A mutation; (ii) a human IgG1 Fc region comprising L234A, L235A, and G237A mutations; (iii) a human IgG1 Fc region comprising L234A, L235A, G237A, and N297A mutations; (iv) a human IgG2 Fc region comprising a N297A mutation; (v) a human IgG2 Fc region comprising A330S and P331S mutations; (vi) a human IgG2 Fc region comprising A330S, P331S, and N297A mutations; (vii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, and delG236 mutations; and (viii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, delG236, and N297A mutations, wherein numbering is according to the EU index of Kabat.

[0003] Disclosed herein, in certain embodiments, are polypeptides comprising: a signal-regulatory protein α (SIRP- α) D1 variant, wherein the SIRP- α D1 variant comprises the amino acid sequence,
EEX₁X₂QX₃IQPDKX₄VX₅VAAGEX₆X₇X₈LX₉CTX₁₀TSLX₁₁PVGPIQWFRGAGPX₁₂RX₁₃LIYNQX₁₄X₁₅G
X₁₆FPRVTTVSX₁₇X₁₈TX₁₉RX₂₀NMDFX₂₁IX₂₂IX₂₃X₂₄ITX₂₅ADAGTYCYCX₂₆KX₂₇RKGSPDX₂₈X₂₉EX₃₀KS
GAGTELSVRX₃₁KPS (SEQ ID NO: 47), wherein X₁ is E, or G; X₂ is L, I, or V; X₃ is V, L, or I; X₄ is S, or F; X₅ is L, or S; X₆ is S, or T; X₇ is A, or V; X₈ is I, or T; X₉ is H, R, or L; X₁₀ is A, V, I, or L; X₁₁ is I, T, S, or F; X₁₂ is A, or G; X₁₃ is E, V, or L; X₁₄ is K, or R; X₁₅ is E, or Q; X₁₆ is H, P, or R; X₁₇ is D, or E; X₁₈ is S, L, T, or G; X₁₉ is K, or R; X₂₀ is E, or N; X₂₁ is S, or P; X₂₂ is S, or R; X₂₃ is S, or G; X₂₄ is any amino acid; X₂₅ is any amino acid; X₂₆ is V, or I;

X₂₇ is F, L, or V; X₂₈ is D or absent; X₂₉ is T, or V; X₃₀ is F, or V; and X₃₁ is A, or G; and wherein the SIRP- α D1 variant has at least two amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to any one of SEQ ID NOs: 1 to 10; and an Fc variant comprising an Fc domain dimer having two Fc domain monomers, wherein each Fc domain monomer independently is (i) a human IgG1 Fc region comprising a N297A mutation; (ii) a human IgG1 Fc region comprising L234A, L235A, and G237A mutations; (iii) a human IgG1 Fc region comprising L234A, L235A, G237A, and N297A mutations; (iv) a human IgG2 Fc region comprising a N297A mutation; (v) a human IgG2 Fc region comprising A330S and P331S mutations; (vi) a human IgG2 Fc region comprising A330S, P331S, and N297A mutations; (vii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, and delG236 mutations; or (viii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, delG236, and N297A mutations. In some embodiments, one of the Fc domain monomers in the Fc domain dimer comprises a human IgG1 Fc region comprising L234A, L235A, G237A, and N297A mutations. In some embodiments, the polypeptide comprises an amino acid sequence according to any one of SEQ ID NOs: 98-104, 107-113, 116-122, or 135-137. In some embodiments, the Fc variant exhibits ablated or reduced binding to an Fc γ receptor compared to a wild-type version of a human IgG Fc region. In some embodiments, the IgG1 or IgG2 Fc variant exhibits ablated or reduced binding to CD16a, CD32a, CD32b, CD32c, and CD64 Fc γ receptors compared to a wild-type version of a human IgG1 or IgG2 Fc region. In some embodiments, the IgG4 Fc variant exhibits ablated or reduced binding to CD16a and CD32b Fc γ receptors compared to a wild-type version of the human IgG4 Fc region. In some embodiments, the IgG1 or IgG2 Fc variant exhibits ablated or reduced binding to C1q compared to a wild-type version of a human IgG1 or IgG2 Fc fusion. In some embodiments, the Fc variant binds to an Fc γ receptor with a K_D greater than about 5 x 10⁻⁶ M.

[0004] In another aspect, there is provided a polypeptide, comprising (a) a CD47 binding polypeptide and (b) an Fc variant comprising an Fc domain dimer having two Fc domain monomers, wherein each Fc domain monomer independently is selected from the group consisting of: (i) a human IgG1 Fc region comprising mutations L234A, L235A, G237A, and N297A; (ii) a human IgG2 Fc region comprising mutations A330S, P331S and N297A; or (iii) a human IgG4 Fc region comprising mutations S228P, E233P, F234V, L235A, delG236, and N297A. Disclosed herein, in certain embodiments, are polypeptides comprising an Fc variant, wherein the Fc variant comprises an Fc domain dimer having two Fc domain monomers, wherein each Fc domain monomer independently is selected from (i) a human IgG1 Fc region consisting of mutations L234A, L235A, G237A, and N297A; (ii) a human IgG2 Fc region consisting of mutations A330S, P331S and N297A; or (iii) a human IgG4 Fc region comprising mutations S228P, E233P, F234V, L235A, delG236, and N297A. In some embodiments, at least one of the Fc domain monomers is a human IgG1 Fc region consisting of mutations L234A, L235A, G237A, and N297A. In some embodiments, at least one of the Fc domain monomers is a human IgG2 Fc region consisting of mutations A330S, P331S and N297A. In some embodiments, the Fc variant exhibits ablated or reduced binding to an Fc γ receptor compared to the wild-type version of the human IgG Fc region. In some embodiments, the Fc variant exhibits ablated or

species with a K_D less than 250 nM; and the K_D for CD47 from the first species and the K_D for CD47 from the second species are within 100 fold of each other; wherein the first species and the second species are selected from the group consisting of: human, rodent, and non-human primate. In some embodiments, the SIRP- α D1 variant binds CD47 from at least 3 different species. In some embodiments, the non-human primate is cynomolgus monkey.

[0007] Disclosed herein, in certain embodiments, are polypeptides comprising: (a) a signal-regulatory protein α (SIRP- α) D1 domain that binds human CD47 with a K_D less than 250 nM; and (b) an Fc domain monomer linked to the N-terminus or the C-terminus of the SIRP- α D1 domain, wherein the polypeptide does not cause acute anemia in rodents and non-human primates. In some embodiments, the polypeptide is a non-naturally occurring variant of a human SIRP- α . In some embodiments, administration of the polypeptide *in vivo* results in hemoglobin reduction by less than 50% during the first week after administration. In some embodiments, administration of the polypeptide in humans results in hemoglobin reduction by less than 50% during the first week after administration. In some embodiments, the polypeptide further comprises at least one Fc variant, wherein the Fc variant is selected from (i) a human IgG1 Fc region consisting of mutations L234A, L235A, G237A, and N297A; (ii) a human IgG2 Fc region consisting of mutations A330S, P331S and N297A; or (iii) a human IgG4 Fc region comprising mutations S228P, E233P, F234V, L235A, delG236, and N297A. In some embodiments, the Fc variant is a human IgG1 Fc region consisting of mutations L234A, L235A, G237A, and N297A. In some embodiments, the Fc variant is a human IgG2 Fc region consisting of mutations A330S, P331S and N297A. In some embodiments, the Fc variant is a human IgG4 Fc region comprising mutations S228P, E233P, F234V, L235A, delG236, and N297A.

[0007a] In another aspect, there is provided an isolated nucleic acid encoding the polypeptide disclosed herein.

[0007b] In another aspect, there is provided a vector comprising the nucleic acid disclosed herein.

[0007c] In another aspect, there is provided a host cell comprising the nucleic acid disclosed herein or the vector disclosed herein.

[0007d] In another aspect, there is provided a method of producing a polypeptide comprising culturing the host cell disclosed herein under appropriate conditions to cause expression of the polypeptide and recovering the polypeptide.

[0007e] In another aspect, there is provided a composition comprising the polypeptide disclosed herein, wherein the polypeptide is a dimer.

[0007f] In another aspect, there is provided use of a polypeptide comprising:

(a) a signal-regulatory protein α (SIRP- α) D1 variant, wherein the SIRP- α D1 variant comprises the amino acid sequence,
EEX₁X₂QX₃IQPDKX₄VX₅VAAGEX₆X₇X₈LX₉CTX₁₀TSLX₁₁PVGPIQWFRGAGPX₁₂RX₁₃LIYN
QX₁₄X₁₅GX₁₆FPRVTTVSX₁₇X₁₈TX₁₉RX₂₀NMDFX₂₁IX₂₂IX₂₃X₂₄ITX₂₅ADAGTYCYCX₂₆KX₂₇RK
GSPDX₂₈X₂₉EX₃₀KSGAGTELSVRX₃₁KPS (SEQ ID NO: 47), wherein X₁ is E, or G; X₂ is L, I, or

V; X₃ is V, L, or I; X₄ is S, or F; X₅ is L, or S; X₆ is S, or T; X₇ is A, or V; X₈ is I, or T; X₉ is H, R, or L; X₁₀ is A, V, I, or L; X₁₁ is I, T, S, or F; X₁₂ is A, or G; X₁₃ is E, V, or L; X₁₄ is K, or R; X₁₅ is E, or Q; X₁₆ is H, P, or R; X₁₇ is D, or E; X₁₈ is S, L, T, or G; X₁₉ is K, or R; X₂₀ is E, or N; X₂₁ is S, or P; X₂₂ is S, or R; X₂₃ is S, or G; X₂₄ is A; X₂₅ is any amino acid; X₂₆ is V, or I; X₂₇ is F, L, or V; X₂₈ is D; X₂₉ is T, or V; X₃₀ is F, or V; and X₃₁ is A, or G; and comprises at least two amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to any one of SEQ ID NOs: 1 to 10; and

(b) an Fc variant selected from the group consisting of: (i) a human IgG1 Fc region comprising a N297A mutation; (ii) a human IgG1 Fc region comprising L234A, L235A, and G237A mutations; (iii) a human IgG1 Fc region comprising L234A, L235A, G237A, and N297A mutations; (iv) a human IgG2 Fc region comprising a N297A mutation; (v) a human IgG2 Fc region comprising A330S and P331S mutations; (vi) a human IgG2 Fc region comprising A330S, P331S, and N297A mutations; (vii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, and delG236 mutations; and (viii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, delG236, and N297A mutations, wherein numbering is according to the EU index of Kabat

in the manufacture of a medicament for treating a disease or disorder in a patient.

[0007g] In another aspect, there is provided a pharmaceutical composition comprising the polypeptide disclosed herein and a pharmaceutically acceptable carrier.

[0008] Disclosed herein, in certain embodiments, are methods of treating an individual having a disease or disorder, the method comprising administering to the subject a polypeptide disclosed herein. In some embodiments, the polypeptide comprises a signal-regulatory protein α (SIRP- α) D1 variant comprising a SIRP- α D1 domain, or a fragment thereof, having an amino acid mutation at residue 80 relative to a wild-type SIRP- α D1 domain; and at least one additional amino acid mutation relative to a wild-type SIRP- α D1 domain at a residue selected from the group consisting of: residue 6, residue 27, residue 31, residue 47, residue 53, residue 54, residue 56, residue 66, and residue 92. In some embodiments, the polypeptide comprises a signal-regulatory protein α (SIRP- α) D1 variant, wherein the SIRP- α D1 variant comprises the amino acid sequence, EEX₁X₂QX₃IQPKX₄VX₅VAAGEX₆X₇X₈LX₉CTX₁₀TSLX₁₁PVGPIQWFRGAGPX₁₂RX₁₃LIYNQX₁₄X₁₅GX₁₆FPRVTTVSX₁₇X₁₈TX₁₉RX₂₀NMDFX₂₁IX₂₂IX₂₃X₂₄ITX₂₅ADAGTYCYCX₂₆KX₂₇RKGSPDX₂₈X₂₉EX₃₀KSGAGTELSVRX₃₁KPS (SEQ ID NO: 47), wherein X₁ is E, or G; X₂ is L, I, or

CLAIMS

WHAT IS CLAIMED IS:

1. A polypeptide, comprising a signal-regulatory protein α (SIRP- α) D1 variant that comprises the amino acid sequence
EEELQX₁IQPDKSVLVAAGETATLRCTX₂TSLX₃PVGPIQWFRGAGPGRX₄LIYNQX₅X₆GX₇
FPRVTTVSDX₈TKRNNMDFSIRIGX₉ITPADAGTYYCX₁₀KFRKGSPDDVEFKSGAGTELSV
RAKPS (SEQ ID NO: 49), wherein X₁ is V, L, or I; X₂ is A, I, V, or L; X₃ is I, F, S, or T; X₄ is E, V, or L; X₅ is K or R; X₆ is E or Q; X₇ is H, P, or R; X₈ is L, T, S, or G; X₉ is A; and X₁₀ is V or I; and comprises at least two amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1.
2. The polypeptide of claim 1, wherein the SIRP- α D1 variant comprises an amino acid sequence according to any one of SEQ ID NOs: 78-85.
3. A polypeptide comprising a signal-regulatory protein α (SIRP- α) D1 variant that comprises the amino acid sequence
EEELQX₁IQPDKSVLVAAGETATLRCTX₂TSLX₃PVGPIQWFRGAGPGRELIYNQX₄EGX₅F
PRVTTVSDX₆TKRNNMDFSIRIGX₇ITPADAGTYYCVKFRKGSPDDVEFKSGAGTELSVR
AKPS (SEQ ID NO: 52), wherein X₁ is V, L, or I; X₂ is A, I, or L; X₃ is I, T, S, or F; X₄ is K or R; X₅ is H, P, or R; X₆ is L, T, or G; and X₇ is A; and comprises at least two amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1.
4. The polypeptide of claim 3, wherein X₁ is V or I, X₂ is A or I, X₃ is I or F, X₄ is K or R, X₅ is H or P, X₆ is L or T, and X₇ is A.
5. The polypeptide of claim 3, wherein the SIRP- α D1 variant comprises at least three amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1.

6. The polypeptide of claim 3, wherein the SIRP- α D1 variant comprises at least four amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1.
7. The polypeptide of claim 3, wherein the SIRP- α D1 variant comprises at least five amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1.
8. The polypeptide of claim 3, wherein the SIRP- α D1 variant comprises at least six amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1.
9. The polypeptide of claim 3, wherein the SIRP- α D1 variant comprises at least seven amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to SEQ ID NO: 1.
10. The polypeptide of claim 3, wherein X_1 is I.
11. The polypeptide of claim 3, wherein X_2 is I.
12. The polypeptide of claim 3, wherein X_3 is F.
13. The polypeptide of claim 3, wherein X_4 is R.
14. The polypeptide of claim 3, wherein X_5 is P.
15. The polypeptide of claim 3, wherein X_6 is T.
16. The polypeptide of claim 3, wherein each of X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 is not a wild-type amino acid.

17. The polypeptide of claim 3, wherein the SIRP- α D1 variant comprises an amino acid sequence according to any one of SEQ ID NOs: 81-85.
18. The polypeptide of claim 1 or 3, wherein the polypeptide binds to human CD47 with a K_D less than about 5×10^{-9} M.
19. The polypeptide of claim 1 or 3, further comprising an Fc domain monomer linked to the N-terminus or the C-terminus of the polypeptide, wherein the Fc domain monomer is a human IgG1, IgG2, or IgG4 Fc region.
20. The polypeptide of claim 19, wherein the Fc domain monomer comprises at least one mutation relative to a wild-type human IgG1, IgG2, or IgG4 Fc region.
21. The polypeptide of claim 20, wherein the polypeptide comprises the amino acid sequence of any one of SEQ ID NO: 135, SEQ ID NO: 136, or SEQ ID NO: 137.
22. The polypeptide of claim 20, wherein the Fc domain monomer comprises:
- (a) one of the following amino acid substitutions relative to wild type human IgG1: T366W, T366S, L368A, Y407V, T366Y, T394W, F405W, Y349T, Y349E, Y349V, L351T, L351H, L351N, L351K, P353S, S354D, D356K, D356R, D356S, E357K, E357R, E357Q, S364A, T366E, L368T, L368Y, L368E, K370E, K370D, K370Q, K392E, K392D, T394N, P395N, P396T, V397T, V397Q, L398T, D399K, D399R, D399N, F405T, F405H, F405R, Y407T, Y407H, Y407I, K409E, K409D, K409T, or K409I; or
 - (b) (i) a N297A mutation relative to a human IgG1 Fc region; (ii) a L234A, L235A, and G237A mutation relative to a human IgG1 Fc region; (iii) a L234A, L235A, G237A, and N297A mutation relative to a human IgG1 Fc region; (iv) a N297A mutation relative to a human IgG2 Fc region; (v) a A330S and P331S mutation relative to a human IgG2 Fc region; (vi) a A330S, P331S, and N297A mutation relative to a human IgG2 Fc region; (vii) a S228P, E233P, F234V, L235A, and delG236 mutation relative to a human IgG4 Fc region; or (viii) a S228P, E233P, F234V, L235A, delG236, and N297A mutation relative to a human IgG4 Fc region,
- wherein numbering is according to the EU index of Kabat.

23. The polypeptide of claim 20, wherein the polypeptide exhibits a reduction of phagocytosis in a phagocytosis assay compared to a polypeptide with a wild-type human IgG Fc region.
24. The polypeptide of claim 20, wherein the Fc domain monomer is linked to a second polypeptide comprising a second Fc domain monomer to form an Fc domain dimer.
25. The polypeptide of claim 24, wherein the second Fc domain monomer is linked to an additional polypeptide.
26. The polypeptide of claim 25, wherein the additional polypeptide comprises an antibody variable domain.
27. The polypeptide of claim 26, wherein the antibody variable domain targets an antigen expressed on a cell.
28. The polypeptide of claim 27, wherein the cell is a cancer cell.
29. The polypeptide of claim 28, wherein the antibody variable domain targets a cell surface protein involved in immune cell regulation.
30. The polypeptide of claim 25, wherein the additional polypeptide comprises a therapeutic protein.
31. The polypeptide of claim 30, wherein the therapeutic protein is a cytokine, an interleukin, an antigen, a steroid, an anti-inflammatory agent, or an immunomodulatory agent.
32. The polypeptide of claim 30, wherein the additional polypeptide comprises a SIRP- α D1 variant.

33. A polypeptide, comprising:

(a) a signal-regulatory protein α (SIRP- α) D1 variant, wherein the SIRP- α D1 variant comprises the amino acid sequence,

EE_{X1}X₂QX₃IQPD_{KX4}VX₅VAAGEX₆X₇X₈LX₉CTX₁₀TSLX₁₁PVGPIQWFRGAGPX₁₂RX₁₃LIY
NQX₁₄X₁₅GX₁₆FPRVTTVSX₁₇X₁₈TX₁₉RX₂₀NMDFX₂₁IX₂₂IX₂₃X₂₄ITX₂₅ADAGTYCYCX₂₆KX₂₇
RKGSPDX₂₈X₂₉EX₃₀KSGAGTELSVRX₃₁KPS (SEQ ID NO: 47), wherein X₁ is E, or G; X₂ is
L, I, or V; X₃ is V, L, or I; X₄ is S, or F; X₅ is L, or S; X₆ is S, or T; X₇ is A, or V; X₈ is I, or T;
X₉ is H, R, or L; X₁₀ is A, V, I, or L; X₁₁ is I, T, S, or F; X₁₂ is A, or G; X₁₃ is E, V, or L; X₁₄ is
K, or R; X₁₅ is E, or Q; X₁₆ is H, P, or R; X₁₇ is D, or E; X₁₈ is S, L, T, or G; X₁₉ is K, or R; X₂₀
is E, or N; X₂₁ is S, or P; X₂₂ is S, or R; X₂₃ is S, or G; X₂₄ is A; X₂₅ is any amino acid; X₂₆ is V,
or I; X₂₇ is F, L, or V; X₂₈ is D; X₂₉ is T, or V; X₃₀ is F, or V; and X₃₁ is A, or G; and comprises
at least two amino acid substitutions relative to a wild-type SIRP- α D1 domain having a
sequence according to any one of SEQ ID NOs: 1 to 10; and

(b) an Fc variant selected from the group consisting of: (i) a human IgG1 Fc region comprising a N297A mutation; (ii) a human IgG1 Fc region comprising L234A, L235A, and G237A mutations; (iii) a human IgG1 Fc region comprising L234A, L235A, G237A, and N297A mutations; (iv) a human IgG2 Fc region comprising a N297A mutation; (v) a human IgG2 Fc region comprising A330S and P331S mutations; (vi) a human IgG2 Fc region comprising A330S, P331S, and N297A mutations; (vii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, and delG236 mutations; and (viii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, delG236, and N297A mutations, wherein numbering is according to the EU index of Kabat.

34. The polypeptide of claim 33, wherein the Fc variant comprises a human IgG1 Fc region comprising L234A, L235A, G237A, and N297A mutations, wherein numbering is according to the EU index of Kabat.

35. The polypeptide of claim 33, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.

36. The polypeptide of claim 33, wherein the polypeptide exhibits ablated or reduced binding to an Fcγ receptor compared to a wild-type version of a human IgG Fc region.
37. The polypeptide of claim 33, wherein the polypeptide comprises an IgG1 or IgG2 Fc variant, and wherein the polypeptide exhibits ablated or reduced binding to CD16a, CD32a, CD32b, CD32c, and CD64 Fcγ receptors compared to a polypeptide comprising a wild-type version of a human IgG1 or IgG2 Fc region.
38. The polypeptide of claim 33, wherein the polypeptide comprises an IgG4 Fc variant, and wherein the polypeptide exhibits ablated or reduced binding to CD16a and CD32b Fcγ receptors compared to a polypeptide comprising a wild-type version of the human IgG4 Fc region.
39. The polypeptide of claim 33, wherein the polypeptide comprises an IgG1 or IgG2 Fc variant, and wherein the polypeptide exhibits ablated or reduced binding to C1q compared to a wild-type version of a human IgG1 or IgG2 Fc fusion.
40. The polypeptide of claim 33, wherein the polypeptide binds to an Fcγ receptor with a K_D greater than about 5×10^{-6} M.
41. The polypeptide of claim 33, wherein the SIRP-α D1 variant comprises the amino acid sequence set forth in SEQ ID NO: 78.
42. The polypeptide of claim 33, wherein the SIRP-α D1 variant comprises the amino acid sequence set forth in SEQ ID NO: 82.
43. The polypeptide of claim 33, wherein the SIRP-α D1 variant comprises the amino acid sequence set forth in SEQ ID NO: 85.
44. The polypeptide of claim 33, wherein the polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 101.

45. The polypeptide of claim 33, wherein the polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 110.
46. The polypeptide of claim 33, wherein the polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 136.
47. A composition comprising the polypeptide of claim 33, wherein the polypeptide is a dimer.
48. A polypeptide, comprising:
(a) a CD47 binding polypeptide and
(b) an Fc variant comprising an Fc domain dimer having two Fc domain monomers, wherein each Fc domain monomer independently is selected from the group consisting of: (i) a human IgG1 Fc region comprising mutations L234A, L235A, G237A, and N297A; (ii) a human IgG2 Fc region comprising mutations A330S, P331S and N297A; or (iii) a human IgG4 Fc region comprising mutations S228P, E233P, F234V, L235A, delG236, and N297A.
49. The polypeptide of claim 48, wherein the two Fc domain monomers are identical.
50. The polypeptide of claim 48, wherein the two Fc domain monomers are different.
51. The polypeptide of claim 48, wherein at least one of the Fc domain monomers is a human IgG1 Fc region comprising mutations L234A, L235A, G237A, and N297A.
52. The polypeptide of claim 48, wherein at least one of the Fc domain monomers is a human IgG2 Fc region comprising mutations A330S, P331S, and N297A.

53. The polypeptide of claim 48, wherein the Fc variant exhibits ablated or reduced binding to an Fcγ receptor compared to the wild-type version of the human IgG Fc region.
54. The polypeptide of claim 53, wherein the Fc variant exhibits ablated or reduced binding to CD16a, CD32a, CD32b, CD32c, and CD64 Fcγ receptors compared to the wild-type version of the human IgG Fc region.
55. The polypeptide of claim 48, wherein the Fc variant exhibits ablated or reduced binding to C1q compared to the wild-type version of the human IgG Fc fusion.
56. The polypeptide of claim 48, wherein at least one of the Fc domain monomers is a human IgG4 Fc region comprising mutations S228P, E233P, F234V, L235A, delG236, and N297A.
57. The polypeptide of claim 56, wherein the Fc variant exhibits ablated or reduced binding to a Fcγ receptor compared to the wild-type human IgG4 Fc region.
58. The polypeptide of claim 57, wherein the Fc variant exhibits ablated or reduced binding to CD16a and CD32b Fcγ receptors compared to the wild-type version of its human IgG4 Fc region.
59. The polypeptide of claim 48, wherein the Fc variant binds to an Fcγ receptor with a K_D greater than about 5×10^{-6} M.
60. The polypeptide of claim 48, wherein the CD47 binding polypeptide does not cause acute anemia in rodents and non-human primates.

61. The polypeptide of claim 48, wherein the CD47 binding polypeptide does not cause acute anemia in humans.
62. The polypeptide of claim 48, wherein the CD47 binding polypeptide is a signal-regulatory protein α (SIRP- α) polypeptide or a fragment thereof.
63. The polypeptide of claim 62, wherein the SIRP- α polypeptide comprises a SIRP- α D1 variant comprising the amino acid sequence,
EEELQX₁IQPDKSVLVAAGETATLRCTX₂TSLX₃PVGPIQWFRGAGPGRX₄LIYNQX₅EGX₆FPRVTTVSDX₇TKRNNMDFSIRIGX₈ITPADAGTYYCX₉KFRKGSPDDVEFKSGAGTELSVRAKPS (SEQ ID NO: 221), wherein X₁ is V or I; X₂ is A or I; X₃ is I or F; X₄ is E or V; X₅ is K or R; X₆ is H or P; X₇ is L or T; X₈ is any amino acid other than N; and X₉ is V or I.
64. The polypeptide of claim 63, wherein the SIRP- α polypeptide comprises a SIRP- α D1 variant wherein X₁ is V or I; X₂ is A or I; X₃ is I or F; X₄ is E; X₅ is K or R; X₆ is H or P; X₇ is L or T; X₈ is not N; and X₉ is V.
65. Use of a polypeptide comprising:
(a) a signal-regulatory protein α (SIRP- α) D1 variant, wherein the SIRP- α D1 variant comprises the amino acid sequence,
EEX₁X₂QX₃IQPDKX₄VX₅VAAGEX₆X₇X₈LX₉CTX₁₀TSLX₁₁PVGPIQWFRGAGPX₁₂RX₁₃LIYNQX₁₄X₁₅GX₁₆FPRVTTVSX₁₇X₁₈TX₁₉RX₂₀NMDFX₂₁IX₂₂IX₂₃X₂₄ITX₂₅ADAGTYYCX₂₆KX₂₇RKGSPDX₂₈X₂₉EX₃₀KSGAGTELSVRX₃₁KPS (SEQ ID NO: 47), wherein X₁ is E, or G; X₂ is L, I, or V; X₃ is V, L, or I; X₄ is S, or F; X₅ is L, or S; X₆ is S, or T; X₇ is A, or V; X₈ is I, or T; X₉ is H, R, or L; X₁₀ is A, V, I, or L; X₁₁ is I, T, S, or F; X₁₂ is A, or G; X₁₃ is E, V, or L; X₁₄ is K, or R; X₁₅ is E, or Q; X₁₆ is H, P, or R; X₁₇ is D, or E; X₁₈ is S, L, T, or G; X₁₉ is K, or R; X₂₀ is E, or N; X₂₁ is S, or P; X₂₂ is S, or R; X₂₃ is S, or G; X₂₄ is A; X₂₅ is any amino acid; X₂₆ is V, or I; X₂₇ is F, L, or V; X₂₈ is D; X₂₉ is T, or V; X₃₀ is F, or V; and X₃₁ is A, or G; and comprises at least two amino acid substitutions relative to a wild-type SIRP- α D1 domain having a sequence according to any one of SEQ ID NOs: 1 to 10; and

(b) an Fc variant selected from the group consisting of: (i) a human IgG1 Fc region comprising a N297A mutation; (ii) a human IgG1 Fc region comprising L234A, L235A, and G237A mutations; (iii) a human IgG1 Fc region comprising L234A, L235A, G237A, and N297A mutations; (iv) a human IgG2 Fc region comprising a N297A mutation; (v) a human IgG2 Fc region comprising A330S and P331S mutations; (vi) a human IgG2 Fc region comprising A330S, P331S, and N297A mutations; (vii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, and delG236 mutations; and (viii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, delG236, and N297A mutations, wherein numbering is according to the EU index of Kabat

in the manufacture of a medicament for treating a disease or disorder in a patient.

66. The use according to claim 65, wherein the disease or disorder is a cancer, an autoimmune disease, or an inflammatory disease.

67. The use according to claim 66, wherein the disease or disorder is a cancer, and the cancer is selected from solid tumor cancer, hematological cancer, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, bladder cancer, pancreatic cancer, cervical cancer, endometrial cancer, lung cancer, bronchus cancer, liver cancer, ovarian cancer, colon and rectal cancer, stomach cancer, gastric cancer, gallbladder cancer, gastrointestinal stromal tumor cancer, thyroid cancer, head and neck cancer, oropharyngeal cancer, esophageal cancer, melanoma, non-melanoma skin cancer, Merkel cell carcinoma, virally induced cancer, neuroblastoma, breast cancer, prostate cancer, renal cancer, renal cell cancer, renal pelvis cancer, leukemia, lymphoma, sarcoma, glioma, brain tumor, and carcinoma.

68. The use according to claim 66, wherein the disease or disorder is an autoimmune disease or an inflammatory disease, and the autoimmune disease or the inflammatory disease is selected from multiple sclerosis, rheumatoid arthritis, a spondyloarthropathy, systemic lupus erythematosus, an antibody-mediated inflammatory or autoimmune disease, graft versus host disease, sepsis, diabetes, psoriasis, atherosclerosis, Sjogren's syndrome, progressive systemic sclerosis, scleroderma, acute coronary syndrome, ischemic reperfusion, Crohn's Disease,

endometriosis, glomerulonephritis, myasthenia gravis, idiopathic pulmonary fibrosis, asthma, acute respiratory distress syndrome (ARDS), vasculitis, and inflammatory autoimmune myositis.

69. The use according to claim 65, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.

70. The use according to claim 65, wherein the SIRP- α D1 variant comprises the amino acid sequence set forth in SEQ ID NO: 78.

71. The use according to claim 65, wherein the SIRP- α D1 variant comprises the amino acid sequence set forth in SEQ ID NO: 82.

72. The use according to claim 65, wherein the SIRP- α D1 variant comprises the amino acid sequence set forth in SEQ ID NO: 85.

73. The use according to claim 65, wherein the polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 101.

74. The use according to claim 65, wherein the polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 110.

75. The use according to claim 65, wherein the polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 136.

76. The use according to claim 65, wherein the medicament is formulated for administration in combination with at least one additional agent.

77. The use according to claim 76, wherein the at least one additional agent is an antibody, tumor associated antigen, or a non-antibody therapeutic.

78. The use according to claim 77, wherein the medicament is formulated for administration in combination with at least two additional agents.
79. The use according to claim 78, wherein the at least two additional agents comprise two antibodies.
80. The use according to claim 78, wherein the at least two additional agents comprise an antibody and a tumor associated antigen.
81. The use according to claim 77, wherein the at least one additional agent is an antibody.
82. The use according to claim 81, wherein the antibody is a human IgG1 isotype antibody.
83. The use according to claim 81, wherein the antibody is a human IgG2 isotype antibody.
84. The use according to claim 81, wherein the antibody is a human IgG4 isotype antibody.
85. The use according to claim 81, wherein the antibody is selected from an anti-HER2 antibody, anti-CD20 antibody, anti-CD19 antibody, anti-CS1 antibody, anti-CD38 antibody, anti-EGFR antibody, anti-PD1 antibody, anti-OX40 antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-RANKL antibody, anti-CD274 antibody, anti-CTLA-4 antibody, anti-CD137 antibody, anti-4-1BB antibody, anti-B7-H3 antibody, anti-FZD7 antibody, anti-CD27 antibody, anti-CCR4 antibody, anti-CD38 antibody, anti-CSF1R antibody, anti-CSF antibody, anti-CD30 antibody, anti-BAFF antibody, anti-VEGF antibody, or anti-VEGFR2 antibody.

86. The use according to claim 85, wherein the antibody is selected from an anti-HER2 antibody, anti-CD20 antibody, anti-CD19 antibody, anti-CS1 antibody, anti-CD38 antibody, anti-PD-1 antibody, anti-RANKL antibody, or anti-PD-L1 antibody.
87. The use according to claim 81, wherein the at least one additional agent is at least one antibody and the antibody is cetuximab, necitumumab, pembrolizumab, nivolumab, pidilizumab, ipilimumab, tremelimumab, urelumab, daratumumab, trastuzumab, trastuzumab emtansine, pertuzumab, elotuzumab, rituximab, ofatumumab, obinutuzumab, panitumumab, brentuximab vedotin, MSB0010718C, belimumab, bevacizumab, denosumab, ramucirumab, or atezolizumab.
88. The use according to claim 87, wherein the antibody is trastuzumab.
89. The use according to claim 88, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.
90. The use according to claim 87, wherein the antibody is rituximab.
91. The use according to claim 90, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.
92. The use according to claim 87, wherein the antibody is cetuximab.
93. The use according to claim 92, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.
94. The use according to claim 87, wherein the antibody is daratumumab.

95. The use according to claim 94, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.

96. The use according to claim 87, wherein the antibody is belimumab.

97. The use according to claim 96, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.

98. The use according to claim 87, wherein the antibody is bevacizumab.

99. The use according to claim 98, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.

100. The use according to claim 87, wherein the antibody is denosumab.

101. The use according to claim 100, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.

102. The use according to claim 87, wherein the antibody is panitumumab.

103. The use according to claim 102, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.

104. The use according to claim 87, wherein the antibody is ramucirumab.

105. The use according to claim 104, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.
106. The use according to claim 87, wherein the antibody is necitumumab.
107. The use according to claim 106, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.
108. The use according to claim 87, wherein the antibody is nivolumab.
109. The use according to claim 108, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.
110. The use according to claim 87, wherein the antibody is pembrolizumab.
111. The use according to claim 110, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.
112. The use according to claim 87, wherein the antibody is MSB0010718C.
113. The use according to claim 112, herein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.
114. The use according to claim 87, wherein the antibody is atezolizumab.

115. The use according to claim 114, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.
116. The use according to claim 87, wherein the antibody is durvalumab.
117. The use according to claim 116, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.
118. The use according to claim 87, wherein the antibody is MEDI0680.
119. The use according to claim 118, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.
120. The use according to claim 87, wherein the antibody is pidilizumab.
121. The use according to claim 120, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.
122. The use according to claim 87, wherein the antibody is BMS-93659.
123. The use according to claim 122, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, and 135-137.
124. The use according to claim 77, wherein the at least one additional agent is a tumor associated antigen and the tumor associated antigen elicits an immune response.

125. The use according to claim 77, wherein the at least one additional agent is an antibody and the antibody targets a HLA/peptide or MHC/peptide complex.
126. The use according to claim 125, wherein the antibody targets a HLA/peptide or MHC/peptide complex comprising a peptide derived from NY-ESO-1/LAGE1, SSX-2, a member of the MAGE protein family, gp100/pmel17, MelanA/MART1, gp75/TRP1, tyrosinase, TRP2, CEA, PSA, TAG-72, Immature laminin receptor, MOK/RAGE-1, WT-1, Her2/neu, EphA3, SAP-1, BING-4, Ep-CAM, MUC1, PRAME, survivin, Mesothelin, BRCA1, BRCA2, CDK4, CML66, MART-2, p53, Ras, β -catenin, TGF- β RII, HPV E6, or HPV E7.
127. An isolated nucleic acid encoding the polypeptide of claim 33.
128. A vector comprising the nucleic acid of claim 127.
129. A host cell comprising the nucleic acid of claim 127 or the vector of claim 128.
130. A method of producing a polypeptide comprising culturing the host cell of claim 129 under appropriate conditions to cause expression of the polypeptide and recovering the polypeptide.
131. A pharmaceutical composition comprising the polypeptide of claim 33 and a pharmaceutically acceptable carrier.