

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 examples, 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 examples, the wild type SIRP- α D1 domain has a sequence according to any one of SEQ ID NOs: 1-10. In some examples, 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 example, there is provided a polypeptide, comprising a signal-regulatory protein α (SIRP- α) D1 variant that comprises the amino acid sequence
EEELQX₁IQPDKSVLVAAGETATLRCTX₂TS LX₃PVGPIQWFRGAGPGRX₄LIYNQX₅X₆GX₇F
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 examples, the SIRP- α D1 variant comprises the amino acid sequence,

EEELQX₁IQPDKSVLVAAGETATLRCTX₂TS LX₃PVGPIQWFRGAGPGRX₄LIYNQX₅X₆GX₇F
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 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 examples, the SIRP- α D1 variant has an amino acid sequence according to any one of SEQ ID NOs: 78-85. In some examples, the SIRP- α D1 variant comprises the amino acid sequence,
EEELQX₁IQPDKSVLVAAGETATLRCTX₂TS LX₃PVGPIQWFRGAGPGRX₄LIYNQX₅X₆GX₇F
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 examples, X₉ is A. In some examples, X₉ is N. In some examples, X₁₀ is I. In some examples, X₉ is N and X₁₀ is P. In some examples, X₉ is N and X₁₁ is any amino acid other than S, T, or C. In some examples, X₁₁ is T. In some examples, X₁₁ is an amino acid other than T. In some examples, X₁₂ is P. In some examples, X₉ is N and X₁₂ is any amino acid other than P. In some examples, the SIRP- α D1 variant comprises the amino acid sequence,

EEELQX₁IQPDKSVLVAAGETATLRCTX₂TSLX₃PVGPIQWFRGAGPGRX₄LIYNQX₅X₆GX₇FPRVTTVSDX₈TKRNNMDFSIRIGX₉ITX₁₀ADAGTYYCX₁₁KFRKGSPDDVEFKSGAGTELSVR 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 example, there is provided a polypeptide comprising a signal-regulatory protein α (SIRP- α) D1 variant that comprises the amino acid sequence

EEELQX₁IQPDKSVLVAAGETATLRCTX₂TSLX₃PVGPIQWFRGAGPGRELIYNQX₄EGX₅FPRVTTVSDX₆TKRNNMDFSIRIGX₇ITPADAGTYYCVKFRKGSPDDVEFKSGAGTELSVR 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 examples, the SIRP- α D1 variant comprises the amino acid sequence,

EEELQX₁IQPDKSVLVAAGETATLRCTX₂TSLX₃PVGPIQWFRGAGPGRELIYNQX₄EGX₅FPRVTTVSDX₆TKRNNMDFSIRIGX₇ITPADAGTYYCVKFRKGSPDDVEFKSGAGTELSVR 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, X₁ is I. In some examples, X₂ is I. In some examples, X₃ is F. In some examples, X₄ is R. In some examples, X₅ is P. In some examples, X₆ is T. In some examples, each of X₁, X₂, X₃, X₄, X₅, and X₆ is not a wild-type amino acid. In some examples, the SIRP- α D1 variant has an amino acid sequence

according to any one of SEQ ID NOs: 81-85. In some examples, the SIRP- α D1 variant comprises the amino acid sequence,

EEELQX₁IQPKSVSVAAGESAILHCTX₂TSLX₃PVGPIQWFRGAGPARELIYNQX₄EG

X₅FPRVTTVSEX₆TKRENMDFSISIX₇ITPADAGTYCYVKFRKGSPDTEFKSGAGTELSVRKPS

(SEQ ID NO: 212), wherein X₁ is V, L, or I; X₂ is V, I, or L; X₃ is I, T, S, or F; X₄ is K or R; X₅ is H, P, or R; X₆ is S, 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 the sequence of SEQ ID NO: 2. In some examples, the polypeptide binds to human CD47 with a K_D less than about 5×10^{-9} M. In some examples, the polypeptide further comprises 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. In some examples, the Fc domain monomer comprises at least one mutation relative to a wild-type human IgG1, IgG2, or IgG4 Fc region. In some examples, the polypeptide has the amino acid sequence of any one of SEQ ID NO: 135, SEQ ID NO: 136, or SEQ ID NO: 137. In some examples, 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. In some examples, 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; and (b) the Fc domain monomer further comprises (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. In some examples, 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 examples, the Fc domain monomer is linked to a second polypeptide comprising a second Fc domain monomer to form an Fc domain dimer. In some examples, the second Fc domain monomer is linked to an additional polypeptide. In some examples, the additional polypeptide comprises an antibody variable domain. In some examples, the antibody variable domain targets an antigen expressed on a cell. In some examples, the cell is a cancer cell. In some examples, the antibody variable domain targets a cell surface protein involved in immune cell regulation. In some examples, the additional polypeptide comprises a therapeutic protein. In some examples, the therapeutic protein is a cytokine, an interleukin, an antigen, a steroid, an anti-inflammatory agent, or an immunomodulatory agent. In some examples, the additional polypeptide comprises a SIRP- α D1 variant. In some examples, the polypeptide further comprises a human serum albumin (HSA) (SEQ ID NO: 12). In some examples, the HSA comprises a C34S or K573P amino acid substitution relative to SEQ ID NO: 12. In some examples, the polypeptide has an amino acid sequence according to any one of SEQ ID NOS: 152-159. In some examples, the polypeptide further comprises an albumin-binding peptide. In some examples, the albumin-binding peptide comprises the amino acid sequence DICLPRWGCLW (SEQ ID NO: 160). In some examples, the polypeptide further comprises a polyethylene glycol (PEG) polymer. In some examples, the PEG polymer is joined to a cysteine substitution in the polypeptide.

[0002c] In another example, 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,

EEX₁X₂QX₃IQPDKX₄VX₅VAAGEX₆X₇X₈LX₉CTX₁₀TS LX₁₁PVGPIQWFRGAGPX₁₂RX₁₃LIYNQX₁₄X₁₅G 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 examples, are polypeptides comprising: a signal-regulatory protein α (SIRP- α) D1 variant, wherein the SIRP- α D1 variant comprises the amino acid sequence,

EEX₁X₂QX₃IQPDKX₄VX₅VAAGEX₆X₇X₈LX₉CTX₁₀TS LX₁₁PVGPIQWFRGAGPX₁₂RX₁₃LIYNQ X₁₄X₁₅GX₁₆FPRVTTVSX₁₇X₁₈TX₁₉RX₂₀NMDFX₂₁IX₂₂IX₂₃X₂₄ITX₂₅ADAGTYCYCX₂₆KX₂₇RKGS PDX₂₈X₂₉EX₃₀KSGAGTELSVRX₃₁KPS (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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, the Fc variant binds to an Fc γ receptor with a K_D greater than about 5 x 10⁻⁶ M.

[0004] In another example, 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 examples, 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 examples, at least one of the Fc domain monomers is a human IgG1 Fc region consisting of mutations L234A, L235A, G237A, and N297A. In some examples, at least one of the Fc domain monomers is a human IgG2 Fc region consisting of mutations A330S, P331S and N297A. In some examples, 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 examples, 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. In some examples, the Fc variant exhibits ablated or reduced binding to C1q compared to the wild-type version of the human IgG Fc fusion. In some examples, at least one of the Fc domain monomers is a human IgG4 Fc region comprising mutations S228P, E233P, F234V, L235A, delG236, and N297A. In some examples, the Fc variant exhibits ablated or reduced binding to a Fcγ receptor compared to the wild-type human IgG4 Fc region. In some examples, 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. In some examples, the Fc variant binds to an Fcγ receptor with a K_D greater than about 5×10^{-6} M. In some examples, the polypeptide further comprises a CD47 binding polypeptide. In some examples, the Fc variant exhibits ablated or reduced binding to an Fcγ receptor compared to a wild-type version of a human IgG Fc region. In some examples, the CD47 binding polypeptide does not cause acute anemia in rodents and non-human primates. In some examples, the CD47 binding polypeptide does not cause acute anemia in humans. In some examples, the CD47 binding polypeptide is a signal-regulatory protein α (SIRP- α) polypeptide or a fragment thereof. In some examples, the SIRP- α polypeptide comprises a SIRP- α D1 variant comprising the amino acid sequence,

EEELQX₁IQPDKSVLVAAGETATLRCTX₂TSLX₃PVGPIQWFRGAGPGRX₄LIYNQX₅EGX₆FPRVTTVS
DX₇TKRNNMDFSIRIGX₈ITPADAGTYXCX₉KFRKGGSPDDVEFKSGAGTELSVRAKPS (SEQ ID NO:
51), 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. In some examples, 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.

[0004a] In an aspect, there is provided a polypeptide, comprising:

(a) a signal-regulatory protein α (SIRP- α) D1 variant comprising an amino acid sequence set forth in any one of SEQ ID NOs: 78-85; and

(b) an Fc variant, wherein the Fc variant is:

(i) a human IgG1 Fc region comprising L234A, L235A, G237A, and N297A mutations, wherein numbering is according to the EU index of Kabat;

(ii) a human IgG2 Fc region comprising A330S, P331S and N297A mutations, wherein numbering is according to the EU index of Kabat;

(iii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, and delG236 mutations, wherein numbering is according to the EU index of Kabat; or

(iv) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, delG236, and N297A mutations, wherein numbering is according to the EU index of Kabat.

[0005] Disclosed herein, in certain examples, are polypeptides comprising: a signal-regulatory protein α (SIRP- α) D1 variant, wherein the SIRP- α D1 variant is a non-naturally occurring high

affinity SIRP- α D1 domain, wherein the SIRP- α D1 variant binds to human CD47 with an affinity that is at least 10-fold greater than the affinity of a naturally occurring D1 domain; and an Fc domain monomer, wherein the Fc domain monomer is linked to a second polypeptide comprising a second Fc domain monomer to form an Fc domain, wherein the Fc domain has ablated or reduced effector function. In some examples, the non-naturally occurring high affinity SIRP- α D1 domain comprises an amino acid mutation at residue 80.

[0006] Disclosed herein, in certain examples, are polypeptides comprising a signal-regulatory protein α (SIRP- α) D1 variant, wherein the SIRP- α D1 variant binds CD47 from a first species with a K_D less than 250 nM; and wherein the SIRP- α D1 variant binds CD47 from a second

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 examples, the SIRP- α D1 variant binds CD47 from at least 3 different species. In some examples, the non-human primate is cynomolgus monkey.

[0007] Disclosed herein, in certain examples, 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 examples, the polypeptide is a non-naturally occurring variant of a human SIRP- α . In some examples, administration of the polypeptide *in vivo* results in hemoglobin reduction by less than 50% during the first week after administration. In some examples, administration of the polypeptide in humans results in hemoglobin reduction by less than 50% during the first week after administration. In some examples, 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 examples, the Fc variant is a human IgG1 Fc region consisting of mutations L234A, L235A, G237A, and N297A. In some examples, the Fc variant is a human IgG2 Fc region consisting of mutations A330S, P331S and N297A. In some examples, 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 a 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 disclosed herein comprising culturing the host cell disclosed herein under appropriate conditions to cause expression of the polypeptide and recovering the polypeptide.

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

[0007f] In another example, 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,

EEX₁X₂QX₃IQPKX₄VX₅VAAGEX₆X₇X₈LX₉CTX₁₀TSLX₁₁PVGPIQWFRGAGPX₁₂RX₁₃LIYNQX₁₄X₁₅GX₁₆FPRVTTVSX₁₇X₁₈TX₁₉RX₂₀NMDFX₂₁IX₂₂IX₂₃X₂₄ITX₂₅ADAGTYYCX₂₆KX₂₇RKGSPDX₂₈X₂₉EX₃₀KSGAGTELSVRX₃₁KPS (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 examples, are methods of treating an individual having a disease or disorder, the method comprising administering to the subject a polypeptide disclosed herein. In some examples, 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 examples, the polypeptide comprises a signal-regulatory protein α (SIRP- α) D1 variant, wherein the SIRP- α D1 variant comprises the amino acid sequence,

EEX₁X₂QX₃IQPDKX₄VX₅VAAGEX₆X₇X₈LX₉CTX₁₀TSLX₁₁PVGPIQWFRGAGPX₁₂RX₁₃LIYNQX₁₄X₁₅GX₁₆FPRVTTVSX₁₇X₁₈TX₁₉RX₂₀NMDFX₂₁IX₂₂IX₂₃X₂₄ITX₂₅ADAGTYCYCX₂₆KX₂₇RKGSPDX₂₈X₂₉EX₃₀KSGAGTELSVRX₃₁KPS (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 examples, the polypeptide comprises 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 examples, the polypeptide comprises a signal-regulatory protein α (SIRP- α) D1 variant, wherein the SIRP- α D1 variant is a non-naturally occurring high affinity SIRP- α D1 domain, wherein the SIRP- α D1 variant binds to human CD47 with an affinity that is at least 10-fold greater than the affinity of a naturally occurring D1 domain; and an Fc domain monomer, wherein the Fc domain monomer is linked to a second polypeptide comprising a second Fc domain monomer to form an Fc domain, wherein the Fc domain has ablated or reduced effector function. In some examples, the non-naturally occurring high affinity SIRP- α D1 domain comprises an amino acid mutation at residue 80. In some examples, the polypeptide comprises a signal-regulatory protein α (SIRP- α) D1 variant, wherein the SIRP- α D1 variant binds CD47 from a first species with a K_D less than 250 nM; and wherein the SIRP- α D1 variant binds CD47 from a second 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 examples, the polypeptide comprises (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 examples, the disease or disorder is a cancer, an autoimmune disease, or an inflammatory disease. In some examples, 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. In some examples, 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. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the method further comprises administering at least one additional agent. In some examples, the at least one additional agent is an antibody, tumor associated antigen, or a non-antibody therapeutic. In some examples, at least two additional agents are administered. In some examples, the at least two additional agents comprise two antibodies. In some examples, the at least two additional agents comprise an antibody and a tumor associated antigen. In some examples, the at least one additional agent is an antibody. In some examples, the antibody is a human IgG1 isotype antibody. In some examples, the antibody is a human IgG2 isotype antibody. In some examples, the antibody is a human IgG4 isotype antibody. In some examples, 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-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. In some examples, 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. In some examples, the at least one additional agent is at least one antibody and the antibody is selected from cetuximab, necitumumab, pembrolizumab, nivolumab, pidilizumab, MEDI0680, MED16469, atezolizumab, avelumab, durvalumab, MEDI6383, RG7888, ipilimumab, tremelimumab, urelumab, PF-05082566, enoblituzumab, vanticumab, varlilumab, mogamalizumab, SAR650984, daratumumab, trastuzumab, trastuzumab emtansine, pertuzumab, elotuzumab, rituximab, ofatumumab, obinutuzumab, RG7155, FPA008, panitumumab, brentuximab vedotin, MSB0010718C, belimumab, bevacizumab, denosumab, panitumumab, ramucirumab, necitumumab, nivolumab, pembrolizumab, avelumab, atezolizumab, durvalumab, MEDI0680, pidilizumab, or BMS-93659. In some examples, the antibody is trastuzumab. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is rituximab. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is cetuximab. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is daratumumab. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is belimumab. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is bevacizumab. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is denosumab. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is pantimumab. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is ramucirumab. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is necitumumab. In some examples, the SIRP- α D1

variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is nivolumab. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is pembrolizumab. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is avelumab. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is atezolizumab. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is durvalumab. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is MEDI0680. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is pidilizumab. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the antibody is BMS-93659. In some examples, the SIRP- α D1 variant has a sequence according to any one of SEQ ID NOs: 78-85, 98-104, 107-113, 116-122, 135-137, or 152-159. In some examples, the at least one additional agent is a tumor associated antigen and the tumor associated antigen elicits an immune response. In some examples, the at least one additional agent is an antibody and the antibody targets a HLA/peptide or MHC/peptide complex. In some examples, the antibody targets a HLA/peptide or MHC/peptide complex comprising NY-ESO-1/LAGE1, SSX-2, MAGE family (MAGE-A3), gp100/pm117, Melan-A/MART-1, 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, BRCA1/2 (mutated), CDK4, CML66, MART-2, p53 (mutated), Ras (mutated), β -catenin (mutated), TGF- β RII (mutated), HPV E6, or E7. In some examples, the antibody is ESK1, RL1B, Pr20, or 3.2G1.

[0008a] In another aspect, there is provided use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating cancer, optionally wherein the cancer is 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, or carcinoma.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

CLAIMS

WHAT IS CLAIMED IS:

1. A polypeptide, comprising:
 - (a) a signal-regulatory protein α (SIRP- α) D1 variant comprising an amino acid sequence set forth in any one of SEQ ID NOs: 78-85; and
 - (b) an Fc variant, wherein the Fc variant is:
 - (i) a human IgG1 Fc region comprising L234A, L235A, G237A, and N297A mutations, wherein numbering is according to the EU index of Kabat;
 - (ii) a human IgG2 Fc region comprising A330S, P331S, and N297A mutations, wherein numbering is according to the EU index of Kabat;
 - (iii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, and delG236 mutations, wherein numbering is according to the EU index of Kabat; or
 - (iv) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, delG236, and N297A mutations, wherein numbering is according to the EU index of Kabat.
2. The polypeptide of claim 1, wherein the Fc variant is a human IgG1 Fc region comprising L234A, L235A, G237A, and N297A mutations.
3. The polypeptide of claim 1 or 2, wherein 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, optionally wherein the Fc γ receptor is CD16a, CD32a, CD32b, CD32c, and CD64.
4. The polypeptide of any one of claims 1-3, wherein the Fc variant exhibits a reduction or ablation of phagocytosis in a phagocytosis assay compared to a wild-type version of the Fc variant.
5. The polypeptide of any one of claims 1-4, wherein the SIRP- α D1 variant binds CD47 with a K_D less than 1×10^{-8} M, optionally less than 1×10^{-9} M, optionally less than 1×10^{-10} M.

6. The polypeptide of any one of claims 1-5, wherein the polypeptide comprises a sequence selected from the group consisting of: SEQ ID NOs: 98-104, 107-113, 116-122, 133, and 135-136.
7. A nucleic acid encoding the polypeptide of any one of claims 1-6.
8. A vector comprising the nucleic acid of claim 7.
9. A host cell comprising the nucleic acid of claim 7 or vector of claim 8.
10. A method of producing a polypeptide of any of claims 1-6 comprising culturing the host cell of claim 9 under appropriate conditions to cause expression of the polypeptide, and recovering the polypeptide.
11. A pharmaceutical composition comprising the polypeptide of any one of claims 1-6 and a pharmaceutically acceptable carrier.
12. Use of the pharmaceutical composition of claim 11 in the manufacture of a medicament for treating cancer, optionally wherein the cancer is 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, or carcinoma.
13. The use according to claim 12, wherein the pharmaceutical composition is to be administered with a therapeutic antibody,

optionally wherein

the therapeutic antibody binds to 4-1BB, 5T4, ALK1, ANG-2, B7-H3, B7-H4, c-Met, CA6, CCR4, CD123, CD19, CD20, CD22, CD27, EpCAM, CD30, CD32b, CD33, CD37, CD38, CD40, CD52, CD70, CD74, CD79b, CD98, CEA, CEACAM5, CLDN18.2, CLDN6, CS1, CTLA-4, CXCR4, DLL-4, EGFR, EGP-1, ENPP3, EphA3, ETBR, FGFR2, fibronectin, FR-alpha, Frizzled receptor, GCC, GD2, glypican-3, GPNMB, HER2, HER3, HLA-DR, ICAM-1, IGF-1R, IL-3R, LIV-1, mesothelin, MUC16, MUC1, NaPi2b, Nectin-4, Notch 2, Notch 1, OX-40, PD-1, PD-L1, PD-L2, PDGFR- α , PS, PSMA, SLTRK6, STEAP1, TEM1, VEGFR, CD25, DKK-1, or CSF-1R, or

wherein the therapeutic antibody is cetuximab, necitumumab, pembrolizumab, nivolumab, pidilizumab, MEDI0680, atezolizumab, avelumab, durvalumab, MEDI6383, MEDI6469, RG7888, ipilimumab, tremelimumab, urelumab, PF-05082566, enoblituzumab, vantictumab, varlilumab, mogamulizumab, SAR650984, daratumumab, trastuzumab, trastuzumab emtansine, pertuzumab, elotuzumab, rituximab, ofatumumab, obinutuzumab, RG7155, FPA008, panitumumab, or brentuximab vedotin.