

SUMMARY OF THE INVENTION

[0007] Described herein are methods and compositions for targeting tumor cells with an immunoglobulin fusion protein specific for both a tumor cell antigen and CD47.

Specifically, the immunoglobulin fusion protein includes an immunoglobulin moiety that is specific for a tumor cell antigen and has a second moiety that is specific for CD47.

[0007a] In one aspect, there is provided a SIRP α immunoglobulin fusion protein comprising: an IgV extracellular domain of SIRP α or a SIRP α variant comprising an amino acid sequence at least 80% identical to residues 3-115 of SEQ ID NO:6 or to residues 3-114 of SEQ ID NO:8; and an immunoglobulin molecule or portion thereof that binds to a surface antigen on a disease promoting cell.

[0008] Also disclosed are SIRP α immunoglobulin fusion proteins. The fusion protein includes an IgV extracellular domain of SIRP α or a SIRP α variant having an amino acid sequence at least 80% identical to residues 3-115 of SEQ ID NO:6 or to 3-114 of SEQ ID NO:8. The fusion protein also includes an immunoglobulin molecule or portion thereof that binds to a surface antigen on a disease promoting cell. In one example, the disease promoting cell is a tumor cell and the surface antigen is a tumor antigen.

[0009] In certain examples, the immunoglobulin fusion protein includes a SIRP α variant with an amino acid sequence at least 85%, at least 90%, or at least 95% identical to residues 3-115 of SEQ ID NO:6 or to 3-114 of SEQ ID NO:8.

[0010] In certain examples, the immunoglobulin fusion protein includes a SIRP α variant with an amino acid sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to residues 1-115 of SEQ ID NO:6 or to 1-114 of SEQ ID NO:8.

[0011] In some examples, the IgV extracellular domain is residues 1-115 of SEQ ID NO: 6, while in other examples, the IgV extracellular domain is residues 1-114 of SEQ ID NO:8. In some examples, the IgV extracellular domain is residues 3-115 of SEQ ID NO: 6 while in other examples, the IgV extracellular domain is residues 3-114 of SEQ ID NO:8. In yet other examples, the IgV extracellular domain is residues 1-114 of SEQ ID NO:193 or residues 1-115 of SEQ ID NO:194 or residues 1-115 of SEQ ID NO:195 or residues 1-115 of SEQ ID NO:196 or

residues 1-114 of SEQ ID NO:197 or residues 1-114 of SEQ ID NO:198 or residues 1-115 of SEQ ID NO:199 or residues 1-114 of SEQ ID NO:200 or residues 1-115 of SEQ ID NO: 190.

[0012] In other examples, the SIRP α variant has an amino acid sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to residues 1-343 of SEQ ID NO:6. In other examples, the IgV extracellular domain of SIRP α is a wild-type human SIRP α IgV extracellular domain.

[0013] In other examples, the SIRP α variant has an amino acid sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to residues 1-114 of SEQ ID NO:193 or residues 1-115 of SEQ ID NO:194 or residues 1-115 of SEQ ID NO:195 or residues 1-115 of SEQ ID NO:196 or residues 1-114 of SEQ ID NO:197 or residues 1-114 of SEQ ID NO:198 or residues 1-115 of SEQ ID NO:199 or residues 1-114 of SEQ ID NO:200 or residues 1-115 of SEQ ID NO: 190.

[0014] In certain examples, the SIRP α variant of the immunoglobulin fusion protein has a modification to an amino acid at one or more of positions 6, 27, 31, 37, 54, 56, 66, or 72 corresponding to SEQ ID NO:6 or to SEQ ID NO:8. The modification may be a substitution, deletion, or insertion of an amino acid. In a preferred example, the modification is a substitution.

[0015] In certain examples, the SIRP α variant of the immunoglobulin fusion protein includes one or more substitutions at positions corresponding to positions 6, 27, 31, 37, 54, 56, 66, or 72 of SEQ ID NO:6 or of SEQ ID NO:8 selected from the group consisting of: V6I, V27I, A27I, I31R, I31T, Q37W, Q37H, E54P, H56P, S66Q, L66A, and M72R. In one example, the substitution corresponds to V6I. In another example, the substitution corresponds to V27I or A27I. In another example, the substitution corresponds to I31R. In another example, the substitution corresponds to I31T. In another example, the substitution corresponds to Q37W. In another example the substitution corresponds to Q37H. In another example, the substitution corresponds to E54P. In another example, the substitution corresponds to H56P. In another example, the substitution corresponds to S66Q or L66Q. In another example, the substitution corresponds to M72R.

[0016] In certain examples, the SIRP α variant of the immunoglobulin fusion protein has a modification to an amino acid at one or more of positions corresponding to positions 4, 6, 27, 31, 35, 37, 47, 52, 53, 54, 56, 66, 67, 68, 72, 92 or 94 of SEQ ID NO:6 or of SEQ ID NO:8. The modification may be a substitution, deletion, or insertion of an amino acid. In a preferred example, the modification is a substitution.

[0017] In certain examples, the SIRP α variant of the immunoglobulin fusion protein includes one or more of the following substitutions:

L66T, L66V, L66W, or L66Y; or S66A, S66C, S66D, S66E, S66F, S66G, S66H, S66I, S66K, S66L, S66M, S66N, S66P, S66Q, S66T, S66V, S66W, or S66Y;

- m. a substitution at a position corresponding to position 67 selected from T67A, T67C, T67D, T67E, T67F, T67G, T67H, T67I, T67L, T67M, T67N, T67Q, T67R, T67S, T67V, T67W, or T67Y;
- n. a substitution at a position corresponding to position 68 wherein the substitution is K68R
- o. a substitution at a position corresponding to position 72 selected from M72A, M72C, M72D, M72E, M72F, M72G, M72H, M72I, M72K, M72L, M72N, M72Q, M72R, M72S, M72T, M72V, M72W, or M72Y;
- p. a substitution at a position corresponding to position 92 selected from V92A, V92C, V92D, V92E, V92G, V92I, V92M, V92N, V92Q, V92R, V92S, or V92T; and/or
- q. a substitution at a position corresponding to position 94 wherein the substitution is F94L.

[0018] In some examples, the SIRP α variant has a modification, preferably a substitution, that decreases the binding affinity of the SIRP α variant for CD47 as compared to wild-type SIRP α . In yet other examples, the SIRP α variant has a modification, preferably a substitution, that increases the binding affinity of the SIRP α variant for CD47 as compared to wild-type SIRP α .

[0019] In certain examples, the immunoglobulin molecule is an intact antibody, while in other examples, the immunoglobulin molecule is an antigen binding portion of an antibody. In yet another example, the immunoglobulin molecule is a portion of an antibody that is an antibody variable domain. In some examples, the antibody variable domain is an antigen-binding fragment such as an Fab, Fab', F(ab')₂, Fv, scFv, single chain antibody, minibody, diabody, or single-domain antibody (nanobody). In one example, the intact antibody is an anti-EGFR antibody, such as cetuximab.

[0020] In other examples, immunoglobulin molecule is an antigen binding portion of an antibody that is an Fc region, wherein the Fc region is engineered to contain an antigen binding site, for example, an Fcab moiety. In some examples, when the immunoglobulin

molecule is an Fcab, the SIRP α or SIRP α variant is connected by its N-terminus to the immunoglobulin molecule, whereas in other examples the SIRP α or SIRP α variant is connected to the immunoglobulin molecule via its C-terminus.

[0021] In some examples, the SIRP α or SIRP α variant is connected by its N-terminus to the immunoglobulin molecule, whereas in other examples the SIRP α or SIRP α variant is connected via its C-terminus to the immunoglobulin molecule. In other examples, when the immunoglobulin molecule is an intact antibody, the SIRP α or SIRP α variant is connected to the C-terminus of the heavy chain, or the C-terminus of the light chain, and optionally, via a linker. In other examples, when the immunoglobulin molecule is an intact antibody, the SIRP α or SIRP α variant is connected to the N-terminus of the heavy chain, or the N-terminus of the light chain, and optionally, via a linker.

[0022] In yet other examples, the immunoglobulin molecule or portion thereof is connected to the SIRP α or SIRP α variant via a linker moiety. The linker moiety may be fused to the SIRP α or SIRP α variant at either the N-terminus or C-terminus of the SIRP α moiety.

[0023] In yet other examples, the immunoglobulin molecule or portion thereof is connected via its N-terminus to the SIRP α or SIRP α variant, optionally via a linker moiety, while in other examples, the immunoglobulin molecule or portion thereof is connected via its C-terminus to the SIRP α or SIRP α variant, optionally via a linker moiety. In other examples, the SIRP α or SIRP α variant is connected to the N-terminus of an antibody light chain or a portion thereof, while in another examples, the SIRP α or SIRP α variant is connected to the C-terminus of an antibody light chain or a portion thereof. In other examples, the SIRP α or SIRP α variant is connected to the N-terminus of an antibody heavy chain or a portion thereof, while in another example, the SIRP α or SIRP α variant is connected to the C-terminus of an antibody heavy chain or a portion thereof. A linker between SIRP α or a SIRP α variant and an immunoglobulin molecule or portion thereof is contemplated in some examples.

[0024] In certain examples, the tumor antigen to which the immunoglobulin molecule or portion thereof binds is selected from HER2, HER3, EGFR, CD20, GD2, PD-L1, and CD19.

[0024a] In another aspect, the present invention provides a SIRP α immunoglobulin fusion protein comprising: an IgV extracellular domain of SIRP α or of a SIRP α variant comprising an amino acid sequence at least 80% identical to residues 1-115 of SEQ ID NO:190; and an immunoglobulin molecule or portion thereof that binds to a surface antigen on a disease promoting cell.

[0025] In another example, the disclosure is directed to a SIRP α immunoglobulin fusion protein that includes an IgV extracellular domain of SIRP α or of a SIRP α variant having an amino acid sequence at least 80% identical to residues 1-115 of SEQ ID NO:190; and an immunoglobulin molecule or portion thereof that binds to a surface antigen on a disease promoting cell. The disease promoting cell may be a tumor cell and the surface antigen may be a tumor antigen.

[0026] In one example, the SIRP α variant has an amino acid sequence at least 85%, at least 90%, or at least 95% identical to residues 1-115 of SEQ ID NO:190.

[0027] In another example, the SIRP α variant has a modification to an amino acid at one or more positions corresponding to positions 6, 27, 31, 37, 54, 56, 66, or 72 of SEQ ID NO:190. In a further example, the modification is selected from the group consisting of: V6I; V27I; A27I; I31R; I31T; Q37W; Q37H; E54P; H56P; S66Q; L66Q; and M72R.

[0028] In another example, the disclosure is directed to a SIRP α immunoglobulin fusion protein that includes an anti-EGFR antibody or an antigen binding portion thereof and an IgV extracellular domain of SIRP α or of a SIRP α variant having an amino acid sequence at least 80% identical to residues 3-115 of SEQ ID NO:6 or to 3-114 of SEQ ID NO:8.

[0029] In a further example, the SIRP α or of a SIRP α variant has an amino acid sequence at least 85% identical, at least 90% identical, or at least 95% identical to residues 3-115 of SEQ ID NO:6 or to 3-114 of SEQ ID NO:8.

[0030] In yet another example, the SIRP α or of a SIRP α variant has an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical to residues 1-115 of SEQ ID NO:6 or to 1-114 of SEQ ID NO:8.

[0031] In a further example, the anti-EGFR antibody or antigen binding portion thereof contains the heavy chain variable region and light chain variable region from an antibody selected from cetuximab, panitumumab, nimotuzumumab, matuzumab, futuximab, imgatuzumab, or necitumumab. In yet another example, the anti-EGFR antibody or antigen binding portion thereof contains the complementarity determining regions from an antibody selected from cetuximab, panitumumab, nimotuzumumab, matuzumab, futuximab, imgatuzumab, or necitumumab. In yet another example, the anti-EGFR antibody or antigen binding portion thereof contains the heavy chain variable region and the light chain

variable region from an antibody selected from cetuximab, panitumumab, nimotuzumab, matuzumab, futuximab, imgatuzumab, or necitumumab. In yet a further example, the anti-EGFR antibody is selected from cetuximab, panitumumab, nimotuzumab, matuzumab, futuximab, imgatuzumab, or necitumumab. In another example, the anti-EGFR antibody is cetuximab.

[0032] In another example, the SIRP α or SIRP α variant is connected to the N-terminus of the heavy or light chain of the anti-EGFR antibody or antigen binding portion thereof, optionally via a linker. In another example, the SIRP α or SIRP α variant is connected to the C-terminus of the heavy or light chain of the anti-EGFR antibody or antigen binding portion thereof, optionally via a linker.

[0033] In a further example, the SIRP α -anti-EGFR immunoglobulin fusion protein includes an IgV extracellular domain of SIRP α or of a SIRP α variant having a modification at one or more of positions corresponding to positions 6, 27, 31, 37, 54, 56, 66 or 72 of SEQ ID NO:6 or SEQ ID NO:8. In one example, the modification is a substitution corresponding to Q37W. In another example, the modification is one or more substitutions corresponding to substitutions selected from V6I, C27I, A27I, I31R, Q37W, Q37H, E54P, H56P, S66Q, L66Q, and M72R.

[0033a] In yet another aspect, the present invention provides an immunoglobulin fusion protein comprising: an immunoglobulin molecule or portion thereof that binds a tumor cell antigen; and a CD47 binding moiety comprising an IgV extracellular domain of SIRP α or a SIRP α variant comprising an amino acid sequence at least 80% identical to residues 3-115 of SEQ ID NO:6 or 3-114 of SEQ ID NO:8; wherein the fusion protein has a % red blood cell (RBC) binding mean fluorescence intensity (MFI) of 35% or less when % RBC binding MFI to an anti-CD47 antibody is calibrated at 100%, wherein the anti-CD47 antibody is B6H12/huIgG1, wherein the fusion protein also binds to a CD47 antigen on a non-red blood cell.

[0034] In a further example, the disclosure is directed to an immunoglobulin fusion protein having an immunoglobulin molecule or portion thereof that binds a tumor cell antigen and a CD47 binding moiety comprising an IgV extracellular domain of SIRP α or a SIRP α variant having an amino acid sequence at least 80% identical to residues 3-115 of SEQ ID NO:6 or 3-114 of SEQ ID NO:8. The fusion protein has a % red blood cell (RBC) binding

mean fluorescence intensity (MFI) of 35% or less when % RBC binding MFI to an anti-CD47 antibody is calibrated at 100%. The anti-CD47 antibody is B6H12/huIgG1. The fusion protein also binds to CD47 on a non-red blood cell. The non-red blood cell, in one example, is a tumor cell.

[0035] In some examples, the immunoglobulin fusion protein has an IgV extracellular domain of SIRP α or a SIRP α variant having an amino acid sequence at least 85%, at least 90%, at least 95% identical to residues 3-115 of SEQ ID NO:6 or 3-114 of SEQ ID NO:8.

[0036] In some examples, the immunoglobulin fusion protein has an IgV extracellular domain of SIRP α or a SIRP α variant having an amino acid sequence at least 80%, at least

85%, at least 90%, at least 95% identical to residues 1-115 of SEQ ID NO:6 or 1-114 of SEQ ID NO:8.

[0037] In some examples, the tumor cell antigen is EGFR. In some examples, the immunoglobulin molecule is an intact antibody. For example, the intact antibody is an anti-EGFR antibody in some examples, while in certain examples the anti-EGFR-antibody is cetuximab.

[0038] In one example, the fusion protein has a % RBC binding MFI of less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1%. In one example, the %RBC binding MFI is less than 10%.

[0039] In yet another example, the fusion protein has a % RBC binding MFI of between 0-1%, 0-2%, 0-3%, 0-4%, 1-2%, 1-3%, 1-4%, 2-3%, 2-4%, 3-4%, 3-7%, 3-10% or 5-10%.

[0040] In yet another example, the fusion protein has a % RBC binding MFI of 5% or less, 4% or less, 3% or less, 2% or less, or 1% or less.

[0041] In a further example, the antibody moiety is an anti-EGFR antibody. For example, the anti-EGFR antibody is cetuximab, whereas in another example, the anti-EGFR antibody is panitumumab, nimotuzumab, matuzumab, futuximab, imgatuzumab, or necitumumab.

[0041a] In yet another aspect, the present invention provides a nucleic acid or nucleic acids encoding the immunoglobulin fusion protein disclosed herein.

[0041b] In yet another aspect, the present invention provides a cell comprising the nucleic acid or nucleic acids disclosed herein.

[0041c] In yet another aspect, the present invention provides a method of producing an immunoglobulin fusion protein by maintaining the cell disclosed herein under conditions that permit expression of the nucleic acid or nucleic acids disclosed herein.

[0042] Also disclosed are nucleic acids encoding the SIRP α immunoglobulin fusion proteins described herein. Because immunoglobulin

fusion proteins described herein may require assembly of two or more peptide chains, the disclosure contemplates the nucleic acids required to encode the individual peptide chains that upon expression assemble to form the fusion protein. Also disclosed is a cell comprising a nucleic acid or the nucleic acids encoding an immunoglobulin fusion protein as described herein. Also disclosed is a method of producing an immunoglobulin fusion protein by maintaining such a cell under conditions that permit expression of the nucleic acid or nucleic acids encoding an immunoglobulin fusion protein of the disclosure.

[0042a] In yet another aspect, the present invention provides a pharmaceutical composition comprising a pharmaceutically effective amount of the immunoglobulin fusion protein disclosed herein and a pharmaceutically acceptable carrier.

[0043] Also disclosed are pharmaceutical compositions that include pharmaceutically effective amounts of an immunoglobulin fusion protein described herein including a pharmaceutically acceptable carrier.

[0043a] In yet another aspect, the present invention provides the use of an effective amount of the immunoglobulin fusion protein disclosed herein in the manufacture of a medicament for treating cancer in a mammal in need thereof.

[0044] Also disclosed are methods of treating cancer by administering an effective amount of an immunoglobulin fusion protein described herein. The cancers that can be treated include breast, colorectal, lung, pancreatic, endometrial, ovarian, gastric, prostate, renal, cervical, myeloma, lymphoma, leukemia, thyroid, uterine, bladder, neuroendocrine, head and neck, liver, nasopharyngeal, testicular, small cell lung cancer, non-small cell lung cancer, melanoma, basal cell skin cancer, squamous cell skin cancer, dermatofibrosarcoma protuberans, Merkel cell carcinoma, glioblastoma, glioma, sarcoma, mesothelioma, or myelodysplastic syndromes.

BRIEF DESCRIPTION OF THE DRAWINGS

[0045] FIGS. 1A-O schematically illustrate the different DNA and protein constructs of the fusion proteins of the invention.

[0046] FIG. 1A shows two schematic diagrams of DNA constructs for the expression of an antibody-SIRP α fusion protein. DNA construct 1 (top) encodes the heavy chain variable domain of the antibody (VH) followed by heavy chain constant domains (CH1, hinge (H)-CH2-CH3) genetically fused via an optional linker (L) to SIRP α . DNA construct 2 (bottom) encodes the light chain variable domain of the antibody (VL) followed by light chain constant domain (CL).

[0047] FIG. 1B is a schematic drawing of an antibody-SIRP α fusion protein having a tetrameric structure where the two polypeptide components (i.e., light chain and heavy chain) are each encoded by a DNA construct shown in FIG. 1A.

[0048] FIG. 1C shows two schematic drawings of Fc fusion proteins. They are from left to right (1) SIRP α -Fc and (2) Fc-SIRP α .

[0049] FIG. 1D shows three DNA constructs for the expression of tetravalent bispecific antibodies. DNA construct 1 (top) encodes the heavy chain variable domain of a first antibody (VH(1)) followed by the heavy chain constant domains (CH1, hinge (H)-CH2-CH3) genetically fused via an optional linker (L) to the light chain variable domain of second

CLAIMS

1. A SIRP α immunoglobulin fusion protein comprising:
 - an IgV extracellular domain of SIRP α or a SIRP α variant comprising an amino acid sequence at least 80% identical to residues 3-115 of SEQ ID NO:6 or to residues 3-114 of SEQ ID NO:8; and
 - an immunoglobulin molecule or portion thereof that binds to a surface antigen on a disease promoting cell.
2. The SIRP α immunoglobulin fusion protein of claim 1, wherein the disease promoting cell is a tumor cell and the surface antigen is a tumor antigen.
3. The immunoglobulin fusion protein of claim 1, wherein the SIRP α variant comprises an amino acid sequence at least 85%, at least 90%, or at least 95% identical to residues 3-115 of SEQ ID NO:6 or to residues 3-114 of SEQ ID NO:8.
4. The immunoglobulin fusion protein of claim 1, wherein the SIRP α variant comprises an amino acid sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to residues 1-115 of SEQ ID NO:6 or to residues 1-114 of SEQ ID NO:8.
5. The immunoglobulin fusion protein of claim 1, wherein the SIRP α variant comprises an amino acid sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to a sequence selected from the group consisting of: residues 1-114 of SEQ ID NO:193, residues 1-115 of SEQ ID NO:194, residues 1-115 of SEQ ID NO:195, residues 1-115 of SEQ ID NO:196, residues 1-114 of SEQ ID NO:197, residues 1-114 of SEQ ID NO:198, residues 1-115 of SEQ ID NO:199, residues 1-114 of SEQ ID NO:200, and residues 1-115 of SEQ ID NO: 190.
6. The immunoglobulin fusion protein of claim 1, wherein the IgV extracellular domain comprises a sequence selected from the group consisting of residues 1-115 of SEQ ID NO: 6, residues 1-114 of SEQ ID NO:8, 1-114 of SEQ ID NO:193, residues 1-115 of SEQ ID NO:194, residues 1-115 of SEQ ID NO:195, residues 1-115 of SEQ ID NO:196, residues 1-114 of SEQ ID NO:197, residues 1-114 of SEQ ID NO:198, residues 1-115 of SEQ ID NO:199, residues 1-114 of SEQ ID NO:200, and residues 1-115 of SEQ ID NO:190.

7. The immunoglobulin fusion protein of claim 1, wherein the SIRP α variant comprises an amino acid sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to residues 1-343 of SEQ ID NO:6.
8. The immunoglobulin fusion protein of claim 1, wherein the SIRP α variant comprises a modification to an amino acid at one or more positions corresponding to positions 6, 27, 31, 37, 54, 56, 66, or 72 of SEQ ID NO:6 or SEQ ID NO: 8.
9. The immunoglobulin fusion protein of claim 8, wherein the modification is a substitution selected from the group consisting of: V6I; V27I; A27I; I31R; I31T; Q37W; Q37H; E54P; H56P; S66Q; L66Q; and M72R.
10. The immunoglobulin fusion protein of claim 1, wherein the SIRP α variant comprises a modification to an amino acid at one or more positions corresponding to positions 4, 6, 27, 31, 35, 37, 47, 52, 53, 54, 56, 66, 67, 68, 72, 92, or 94 of SEQ ID NO:6 or SEQ ID NO:8.
11. The immunoglobulin fusion protein of claim 10, wherein the modification is a substitution, deletion, or insertion of an amino acid.
12. The immunoglobulin fusion protein of claim 11, wherein the substitution is one or more selected from:
 - a substitution at a position corresponding to position 4 wherein the substitution is L4V;
 - a substitution at a position corresponding to position 6 of SEQ ID NO:6 or SEQ ID NO:8 selected from V6A, V6C, V6D, V6E, V6G, V6I, V6L, V6M, V6N, V6Q, V6S, or V6T;
 - a substitution at a position corresponding to position 27 of SEQ ID NO: 6 selected from A27C, A27D, A27G, A27H, A27I, A27L, A27N, A27K, A27Q, A27R, A27S, A27T, A27V, or corresponding to position 27 of SEQ ID NO:8 selected from V27A, V27C, V27D, V27G, V27H, V27I, V27K, V27L, V27N, V27Q, V27R, V27S, V27T;
 - a substitution at a position corresponding to position 31 of SEQ ID NO:6 or SEQ ID NO:8 selected from I31A, I31C, I31E, I31K, I31Q, I31R, I31T, or I31V;
 - a substitution at a position corresponding to position 35 of SEQ ID NO:6 or SEQ ID NO:8 selected from P35A, P35C, P35E, P35G, P35N, P35Q, or P35S;

a substitution at a position corresponding to position 37 of SEQ ID NO:6 or SEQ ID NO:8 selected from Q37A, Q37C, Q37E, Q37G, Q37H, Q37K, Q37L, Q37M, Q37N, Q37R, Q37S, Q37T, or Q37W;

a substitution at a position corresponding to position 47 of SEQ ID NO:6 or SEQ ID NO: 8 selected from E47A, E47C, E47D, E47F, E47G, E47H, E47I, E47K, E47L, E47M, E47N, E47Q, E47R, E47S, E47T, E47V, E47W, or E47Y;

a substitution at a position corresponding to position 52 of SEQ ID NO:6 or SEQ ID NO: 8 selected from Q52A, Q52C, Q52E, Q52H, or Q52M;

a substitution at a position corresponding to position 53 wherein the substitution is K53R;

a substitution at a position corresponding to position 54 of SEQ ID NO:6 or SEQ ID NO:8 selected from E54D or E54P;

a substitution at a position corresponding to position 56 of SEQ ID NO:6 or SEQ ID NO:8 selected from H56A, H56C, H56D, H56E, H56F, H56G, H56I, H56K, H56L, H56M, H56N, H56P, H56Q, H56R, H56S, H56T, H56V, H56W, or H56Y;

a substitution at a position corresponding to position 66 of SEQ ID NO:6 selected from L66A, L66C, L66D, L66E, L66F, L66G, L66H, L66I, L66K, L66M, L66N, L66P, L66Q, L66S, L66T, L66V, L66W, L66Y; or corresponding to position 66 of SEQ ID NO:8 selected from S66A, S66C, S66D, S66E, S66F, S66G, S66H, S66I, S66I, S66K, S66L, S66M, S66N, S66P, S66Q, S66R, S66V, S66W, S66Y;

a substitution at a position corresponding to position 67 of SEQ ID NO:6 or SEQ ID NO:8 selected from T67A, T67C, T67D, T67E, T67F, T67G, T67H, T67I, T67L, T67M, T67N, T67Q, T67R, T67S, T67V, T67W, or T67Y;

a substitution at a position corresponding to position 68 wherein the substitution is K68R;

a substitution at a position corresponding to position 72 of SEQ ID NO:6 or SEQ ID NO:8 selected from M72A, M72C, M72D, M72E, M72F, M72G, M72H, M72I, M72K, M72L, M72N, M72Q, M72R, M72S, M72T, M72V, M72W, or M72Y;

a substitution at a position corresponding to position 92 of SEQ ID NO:6 or SEQ ID NO:8 selected from V92A, V92C, V92D, V92E, V92G, V92I, V92M, V92N, V92Q, V92R, V92S, or V92T; and/or

a substitution at a position corresponding to position 94 wherein the substitution is F94L.

13. The SIRP α immunoglobulin fusion protein of claim 1, wherein the SIRP α or SIRP α variant is connected to the antibody light chain.
14. A SIRP α immunoglobulin fusion protein comprising:
 - an IgV extracellular domain of SIRP α or of a SIRP α variant comprising an amino acid sequence at least 80% identical to residues 1-115 of SEQ ID NO:190; and
 - an immunoglobulin molecule or portion thereof that binds to a surface antigen on a disease promoting cell.
15. An immunoglobulin fusion protein comprising:
 - an immunoglobulin molecule or portion thereof that binds a tumor cell antigen; and
 - a CD47 binding moiety comprising an IgV extracellular domain of SIRP α or a SIRP α variant comprising an amino acid sequence at least 80% identical to residues 3-115 of SEQ ID NO:6 or 3-114 of SEQ ID NO:8;
 - wherein the fusion protein has a % red blood cell (RBC) binding mean fluorescence intensity (MFI) of 35% or less when % RBC binding MFI to an anti-CD47 antibody is calibrated at 100%, wherein the anti-CD47 antibody is B6H12/huIgG1,
 - wherein the fusion protein also binds to a CD47 antigen on a non-red blood cell.
16. A nucleic acid or nucleic acids encoding the immunoglobulin fusion protein of claim 1.
17. A cell comprising the nucleic acid or nucleic acids of claim 16.
18. A method of producing an immunoglobulin fusion protein by maintaining the cell of claim 16 under conditions that permit expression of the nucleic acid or nucleic acids of claim 15.
19. A pharmaceutical composition comprising a pharmaceutically effective amount of the immunoglobulin fusion protein of claim 1 and a pharmaceutically acceptable carrier.
20. The use of an effective amount of the immunoglobulin fusion protein of claim 1 in the manufacture of a medicament for treating cancer in a mammal in need thereof.