

SUMMARY

[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: (i) an IgV extracellular domain of SIRP α or a SIRP α variant comprising an amino acid sequence at least 80% identical to (a) residues 3-115 of SEQ ID NO:6, or (b) residues 3-114 of SEQ ID NO:8, or (c) residues 1-115 of SEQ ID NO:190, 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, or 72 of SEQ ID NO:6, SEQ ID NO: 8 or SEQ ID NO:190, wherein the modification is a substitution selected from the group consisting of: V6I; V27I; A27I; I31R; I31T; Q37W; Q37H; E54P; H56P; and M72R; and (ii) an immunoglobulin molecule or portion thereof that binds to a surface antigen on a disease promoting cell, wherein the disease promoting cell is a tumor cell and the surface antigen is a tumor antigen.

[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

CLAIMS

1. A SIRP α immunoglobulin fusion protein comprising:
 - (i) an IgV extracellular domain of SIRP α or a SIRP α variant comprising an amino acid sequence at least 80% identical to (a) residues 3-115 of SEQ ID NO:6, or (b) residues 3-114 of SEQ ID NO:8, or (c) residues 1-115 of SEQ ID NO:190, 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, or 72 of SEQ ID NO:6, SEQ ID NO: 8 or SEQ ID NO:190, wherein the modification is a substitution selected from the group consisting of: V6I; V27I; A27I; I31R; I31T; Q37W; Q37H; E54P; H56P; and M72R; and
 - (ii) an immunoglobulin molecule or portion thereof that binds to a surface antigen on a disease promoting cell, wherein the disease promoting cell is a tumor cell and the surface antigen is a tumor antigen.
2. The SIRP α 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, or to residues 1-115 of SEQ ID NO:190.
3. The SIRP α 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.
4. The SIRP α 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.
5. The SIRP α 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.

6. The SIRP α immunoglobulin fusion protein of any one of claims 1 to 5, wherein the SIRP α or SIRP α variant is connected to an antibody light chain.
7. The SIRP α immunoglobulin fusion protein of claim 1,
wherein the fusion protein has a % red blood cell (RBC) binding mean fluorescence intensity (MFI) of 10% or less when % RBC binding MFI to an anti-CD47 antibody is calibrated at 100%, wherein the anti-CD47 antibody is B6H12/huIgG1; and
wherein the fusion protein also binds to a CD47 antigen on a non-red blood cell.
8. A nucleic acid or nucleic acids encoding the SIRP α immunoglobulin fusion protein of any one of claims 1-7.
9. A cell comprising the nucleic acid or nucleic acids of claim 8.
10. A method of producing an SIRP α immunoglobulin fusion protein by maintaining the cell of claim 9 under conditions that permit expression of the nucleic acid or nucleic acids of claim 8.
11. A pharmaceutical composition comprising a pharmaceutically effective amount of the SIRP α immunoglobulin fusion protein of any one of claims 1-7 and a pharmaceutically acceptable carrier.
12. The use of an effective amount of the SIRP α immunoglobulin fusion protein of any one of claims 1-7 in the manufacture of a medicament for treating cancer in a mammal in need thereof.