[5] Several therapeutics have been developed to trap or sequester TGFβ, and, therefore, reduce or modulate TGFβ activity. Examples include monoclonal antibodies directed against TGFβ, for example, fresolimumab, which has been administered in several clinical trials for the treatment of cancer and systemic sclerosis (Connolly *et al.* (2012) INT. J. BIOL. SCI. 8(7): 964-78).

[6] An alternative approach to monoclonal antibodies includes the use of recombinant Fc-fusion proteins containing a soluble portion of the extracellular domain of the TGFβ type II receptor (TβRII) or the TGFβ type III receptor (TβRIII, or betaglycan) (Connolly *et al.* (2012) *supra*). Such molecules, known as TGFβ traps, typically contain extracellular domains of the two chains of the dimeric TGFβ receptor complex. Expression of a soluble TβRII-Fc fusion has been coupled to an oncolytic adenovirus and shown to result in a significant reduction of primary tumor growth and osteolytic bone destruction (Hu *et al.* (2010) HUM. GENE THER. 21(11): 1623-9).

[7] Despite the efforts to date, there is a need for improved fusion proteins, for example, cytokine receptor fusion proteins, in particular, improved TGFβ receptor fusion proteins that neutralize the biological activity of human TGFβ for treating disorders in human patients mediated by TGFβ.

SUMMARY

[8] The present disclosure is based, in part, upon the discovery of linker sequences that improve the function of fusion proteins, *e.g.*, cytokine receptor fusion proteins, *e.g.*, TGFβ type II (TβRII) receptor fusion proteins, *e.g.*, TGFβ traps. The linker sequences may permit a ligand binding portion of a fusion protein (*e.g.*, a cytokine receptor) to bind optimally to a ligand (*e.g.*, a cytokine), provide temporal and spatial colocalization of two or more components of a fusion protein (*e.g.*, two subunits of a dimeric cytokine), optimize expression from an expression vector (*e.g.*, a viral vector), reduce immunogenicity, or provide a cleavage site to allow for release of a component of the fusion protein. For example, the linker sequences may provide sufficient flexibility to allow a ligand binding domain of a cytokine receptor to adopt a native conformation in the context of a fusion protein, and minimize the potential immunogenicity of the fusion protein for use as a therapeutic agent.

[8a] In one aspect of the present disclosure, there is provided an isolated fusion protein comprising, in an N- to C- terminal orientation:

(i) a soluble portion of an extracellular domain of a cytokine receptor;
(ii) an amino acid linker;
(iii) an immunoglobulin (Ig) hinge region; and
(iv) an immunoglobulin (Ig) Fc domain;

wherein the linker comprises from about 5 to about 40 amino acid residues.

[8b] In another aspect of the present disclosure, there is provided a cytokine binding protein comprising two fusion proteins disclosed herein, wherein each fusion protein comprises an extracellular domain of a cytokine receptor, wherein the two fusion proteins are covalently linked together, and wherein the two extracellular domains together define a binding site for binding a cytokine.

[8c] In a further aspect of the present disclosure, there is provided an isolated nucleic acid comprising a nucleotide sequence encoding the fusion protein disclosed herein.

[8d] In another aspect of the present disclosure, there is provided an expression vector comprising the nucleic acid disclosed herein.

[8e] In a further aspect of the present disclosure, there is provided a host cell comprising the expression vector disclosed herein.

[8f] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising: (i) the expression vector disclosed herein; and (ii) at least one pharmaceutically acceptable carrier or diluent.

[8g] In a further aspect of the present disclosure, there is provided a use of a fusion protein disclosed herein in the manufacture of a medicament for treating cancer in a subject in need thereof.

[8h] In another aspect of the present disclosure, there is provided a use of an expression vector disclosed herein in the manufacture of a medicament for treating cancer in a subject in need thereof.

[8i] In a further aspect of the present disclosure, there is provided he fusion protein disclosed herein or the expression vector disclosed herein, for use in treating cancer.

[9] The present disclosure provides an isolated fusion protein that comprises, for

example, in an N- to C- terminal orientation: a first portion of an extracellular domain, transmembrane domain, or intracellular domain of a cytokine, cytokine receptor, or immunomodulatory protein; an amino acid linker; and at least one of, a second portion of an extracellular domain, transmembrane domain, or intracellular domain of a cytokine, cytokine receptor, or immunomodulatory protein; an immunoglobulin (Ig) hinge region; and an immunoglobulin (Ig) Fc domain. In certain embodiments, the linker comprises from about 5 to about 40 amino acid residues.

[10] The present disclosure also provides an isolated fusion protein that comprises, in an N- to C-terminal orientation: a soluble portion of an extracellular domain of a cytokine receptor; an amino acid linker; an immunoglobulin (Ig) hinge region; and an immunoglobulin (Ig) Fc domain; wherein the linker comprises from about 5 to about 40 amino acid residues.

[11] In certain embodiments of any of the foregoing fusion proteins, the amino acid linker may comprise, *e.g.*, from about 5 to about 15, from about 5 to about 20, from about 5 to about 30, from about 10 to about 15, from about 10 to about 20, from about 10 to about 30, from about 10 to about 40, from about 15 to about 20, from about 15 to about 30, or from about 15 to about 40 amino acid residues.

[12] In certain embodiments of any of the foregoing fusion proteins, the amino acid linker sequence is derived from an endogenous human protein, *e.g.,* IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, IgM, albumin, or casein. In certain embodiments, the amino acid linker comprises a C-terminal portion of an immunoglobulin (Ig) CH1 domain, *e.g.,* an IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM CH1 domain. In certain embodiments, the amino acid linker comprises an amino acid sequence selected from SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 60, and SEQ ID NO: 61. In certain embodiments, the amino acid linker comprises a C-terminal portion of an IgG1 CH1 domain, *e.g.,* the amino acid linker comprises an amino acid sequence selected from SEQ ID NO: 1, SEQ ID NO: 60, and SEQ ID NO: 61, *e.g.,* the amino acid sequence of SEQ ID NO: 1.

[13] In certain embodiments of any of the foregoing fusion proteins, the amino acid linker comprises a sequence derived from a cytokine, signaling molecule, immunomodulatory protein or peptide, or a biologically active peptide.

[14] In certain embodiments of any of the foregoing fusion proteins, the amino acid linker comprises a cleavage site, *e.g.,* a proteolytic cleavage site, *e.g.,* a proteolytic cleavage site that is cleaved by a protease present in the endoplasmic reticulum or golgi of a eukaryotic cell. In certain embodiments, the proteolytic cleavage site is a furin cleavage site, *e.g.,* a furin cleavage site comprising the sequence RX_1X_2R (SEQ ID NO: 50), wherein X_1 is any amino acid, and X_2 is Lys or Arg, *e.g.,* a furin cleavage site comprising the sequence RAKR (SEQ ID NO: 51). In certain embodiments of any of the foregoing fusion proteins, the amino acid linker is proteolytically stable in a mammal or plant.

[15] In certain embodiments of any of the foregoing fusion proteins, the soluble portion of an extracellular domain of a cytokine receptor is a soluble portion of an extracellular domain of the human TβRII receptor. For example, in certain embodiments, the soluble portion of an extracellular domain of a cytokine receptor comprises the amino acid sequence of SEQ ID NO: 12 or amino acid residues 23-159 of SEQ ID NO: 12.

[16] In certain embodiments of any of the foregoing fusion proteins, the fusion protein comprises one or more of TGF-β, CD80, CD19, CD20, IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-12B/p40, IL-23A/p19, IL27A/p28, IL-27B/EBI3, CD154, CD86, CD137, CD137L, IFN-α, IFN-β, BORIS/CTCFL, FGF, ICAM, IL-24, MAGE, NY-ESO-1, angiostatin, endostatin, acetylcholine, interferon-gamma, DKK1/Wnt, p53, thymidine kinase, an anti-PD-1 antibody heavy chain or light chain, and an anti-PD-L1 antibody heavy chain or light chain, or a functional fragment thereof. For example, in certain embodiments, a fusion protein may comprise: CD80 and CD137L; IL-23A/p19 and IL-12B/p40; or IL-27A/p28 and IL-27B/EBI3.

[17] In certain embodiments of any of the foregoing fusion proteins, the Ig hinge region is selected from an IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, and IgM hinge region, and the Ig Fc domain, is selected from IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, and IgM Fc domain. In certain embodiments, the Ig hinge region and Fc domain together comprise an amino acid sequence selected from SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20 and SEQ ID NO: 21. In certain embodiments, the Ig Fc, Ig hinge region, and Ig CH1 domain are derived from a single immunoglobulin.

[18] In certain embodiments of any of the foregoing fusion proteins, the fusion protein comprises an amino acid sequence selected from SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID

NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 62, and SEQ ID NO: 63. In certain embodiments, the fusion protein comprises an amino acid sequence selected from SEQ ID NO: 22, SEQ ID NO: 62, and SEQ ID NO: 63. In certain embodiments, the fusion protein comprises the amino acid sequence of SEQ ID NO: 22.

[19] In certain embodiments of any of the foregoing fusion proteins, the fusion protein comprises an amino acid sequence having greater than 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity to a sequence selected from SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 62, and SEQ ID NO: 63.

[20] The present disclosure further provides a dimeric cytokine binding protein comprising two of any of the foregoing fusion proteins covalently linked together, wherein each fusion protein comprises an extracellular domain of a cytokine receptor, and wherein the two extracellular domains together define a binding site for a cytokine.

[21] The present disclosure alsoprovides a nucleic acid comprising a nucleotide sequence that encodes for any of the foregoing fusion proteins.

[22] The present disclosure further provides an expression vector comprising any of the foregoing nucleic acids. The expression vector may be an oncolytic virus, *e.g.*, the virus may selectively replicate in a hyperproliferative cell and/or selectively express the fusion protein in a hyperproliferative cell. In certain embodiments, the oncolytic virus is an oncolytic adenovirus, *e.g.,* an oncolytic type 2 or type 5 adenovirus.

[23] In certain embodiments of any of the foregoing expression vectors, the nucleotide sequence encoding the fusion protein is inserted into an E1b-19K insertion site located between the start site of E1b-19K and the start site of E1b-55K. In certain embodiments, the E1b-19K insertion site is located between the start site of E1b-19K and the stop site of E1b-19K. In certain embodiments, the E1b-19K insertion site comprises a deletion of about 200 nucleotides, *e.g.,* 203 nucleotides adjacent the start site of E1b-19K. In certain embodiments, the E1b-19K insertion site comprises a deletion corresponding to nucleotides 1714-1916 of the Ad5 genome (SEQ ID NO: 52), or, the nucleotide sequence encoding the fusion protein is inserted between nucleotides corresponding to 1714 and 1916 of the Ad5 genome (SEQ ID NO: 5). In certain

embodiments, the nucleotide sequence encoding the fusion protein is inserted between CTGACCTC (SEQ ID NO: 53) and TCACCAGG (SEQ ID NO: 54), *e.g.,* the adenovirus comprises, in a 5' to 3' orientation, CTGACCTC (SEQ ID NO: 53), the nucleotide sequence encoding the fusion protein, and TCACCAGG (SEQ ID NO: 54).

[24] In certain embodiments of any of the foregoing expression vectors, the adenovirus may comprise a deletion of at least one Pea3 binding site, or a functional portion thereof, *e.g.,* the adenovirus may comprise a deletion of nucleotides corresponding to about -300 to about -250 upstream of the initiation site of E1a or a deletion of nucleotides corresponding to -305 to -255 upstream of the initiation site of E1a. In certain embodiments, the adenovirus may comprise a deletion of nucleotides corresponding to 195-244 of the Ad5 genome (SEQ ID NO: 52), and/or the recombinant adenovirus may comprise the sequence GGTGTTTTGG (SEQ ID NO: 55). In certain embodiments, the recombinant oncolytic adenovirus may comprise a deletion of at least one Pea3 binding site, or a functional portion thereof, and not comprise a deletion of an E2F binding site. In certain embodiments, the adenovirus may comprise a deletion of at least one E2F binding site, or a functional portion thereof. In certain embodiments, the adenovirus may comprise a deletion of at least one E2F binding site, or a functional portion thereof, and not comprise a deletion of a Pea3 binding site.

[25] In certain embodiments of any of the foregoing expression vectors, the adenovirus may comprise an E3 deletion. In certain embodiments, the E3 deletion comprises a deletion of from about 500 to about 3185, from about 500 to about 3000, from about 500 to about 2500, from about 500 to about 2000, from about 500 to about 1500, from about 500 to about 1000, from about 1000 to about 3185, from about 1000 to about 3000, from about 1000 to about 2500, from about 1000 to about 2000, from about 1000 to about 1500, from about 1500 to about 3185, from about 1500 to about 3000, from about 1500 to about 2000, from about 2000 to about 3185, from about 2000 to about 3000, from about 2000 to about 2500, from about 2500 to about 3185, from about 2500 to about 3000, or from about 3000 to about 3185 nucleotides. In certain embodiments, the E3 deletion site is located between the stop site of pVIII and the start site of Fiber. In certain embodiments, the E3 deletion site is located between the stop site of E3-10.5K and the stop site of E3-14.7K. In certain embodiments, the E3 deletion comprises a deletion of from about 500 to about 1551, from about 500 to about 1500, from about 500 to about 1000, from about 1000 to about 1551, from about 1000 to about 1500, or from about 1500 to about 1551 nucleotides adjacent to the stop site of E3-10.5K. In certain embodiments,

the E3 deletion comprises a deletion of about 1050 nucleotides adjacent to the stop site of E3-10.5K, *e.g.,* the E3 deletion comprises a deletion of 1064 nucleotides adjacent to the stop site of E3-10.5K. In certain embodiments, the E3 deletion comprises a deletion corresponding to the Ad5 dl309 E3 deletion. In certain embodiments, the E3 deletion comprises a deletion corresponding to nucleotides 29773-30836 of the Ad5 genome (SEQ ID NO: 52).

[26] In certain embodiments, the nucleotide sequence encoding the fusion protein is inserted into the E3 deletion, for example, the nucleotide sequence is inserted between CAGTATGA (SEQ ID NO: 56) and TAATAAAAAA (SEQ ID NO: 57), *e.g.,* the adenovirus comprises, in a 5' to 3' orientation, CAGTATGA (SEQ ID NO:56), the nucleotide sequence encoding the fusion protein, and TAATAAAAAA (SEQ ID NO: 57).

[27] In certain embodiments, the oncolytic adenovirus comprises a nucleotide sequence encoding a fusion protein inserted into an E1b-19K insertion site, wherein the insertion site is located between the start site of E1b-19K and the start site of E1b-55K, and/or a modified E1a regulatory sequence, wherein at least one Pea3 binding site, or a functional portion thereof, is deleted.

[28] The present disclosure alsoprovides a host cell comprising any of the foregoing the expression vectors.The present disclosure further provides a method of producing a fusion protein comprising growing a host cell under conditions to express the fusion protein and purifying the fusion protein. The present disclosure alsoprovides a method of expressing a fusion protein in a target cell comprising exposing the cell to an effective amount of any of the foregoing expression vectors. In certain embodiments, the fusion protein is cleaved posttranslationally into two polypeptide chains.

[29] In another embodiment, any of foregoing fusion proteins or expression vectors can be used, *e.g.,* to reduce cytokine activity in a subject, thereby treating various medical indications that are mediated by a cytokine, for example, TGFβ. In another embodiment, any of the foregoing fusion proteins or expression vectors can be used to inhibit proliferation of tumor cells *in vitro* and/or *in vivo*, inhibit tumor growth in a subject in need thereof, or treat cancer in a subject in need thereof. The subject may be*, e.g.,* an animal, *e.g.,* a mammal, *e.g.,* a human, *e.g.,* a pediatric human. For example, when administered to a human subject with cancer, the fusion proteins or expression vectors inhibit or reduce tumor growth, or, reduce the tumor load, in the subject.

[30] In certain embodiments, the cancer may be selected from melanoma, squamous cell

carcinoma of the skin, basal cell carcinoma, head and neck cancer, breast cancer, anal cancer, cervical cancer, non-small cell lung cancer, mesothelioma, small cell lung cancer, renal cell carcinoma, prostate cancer, gastroesophageal cancer, colorectal cancer, testicular cancer, bladder cancer, ovarian cancer, liver cancer, hepatocellular carcinoma, cholangiocarcinoma, brain and central nervous system cancer, thyroid cancer, parathyroid cancer (*e.g.,* parathyroid carcinoma), endometrial cancer, neuroendocrine cancer, lymphoma (*e.g.*, Hodgkin and non-Hodgkin), leukemia, merkel cell carcinoma, gastrointestinal stromal tumors, multiple myeloma, uterine cancer, a sarcoma, kidney cancer, ocular cancer, pancreatic cancer, and a germ cell cancer (*e.g.,* ovarian germ cell cancer). In certain embodiments, the cancer may be selected from leukemia, breast cancer, lung cancer, pancreatic cancer, endometrial cancer, ovarian cancer, prostate cancer, cervical cancer, brain cancer, skin cancer, colorectal cancer, gastric cancer, head and neck cancer, and leukemia.

[31] In certain embodiments, the fusion protein or expression vector is administered in combination with one or more therapies selected from surgery, radiation, chemotherapy, immunotherapy, hormone therapy, and virotherapy. In certain embodiments, the fusion protein or expression vector is administered in combination with a lymphocyte, *e.g.,* a T-cell, *e.g.,* a CAR T-cell.

[32] Any of the foregoing fusion proteins or expression vectors can also be used to treat an inflammatory condition or infection in a subject in need thereof.

[33] These and other embodiments and advantages of the present disclosure are illustrated by the following figures, detailed description and claims.

DESCRIPTION OF THE DRAWINGS

[34] The invention can be more completely understood with reference to the following drawings.

[35] **FIGURE 1A** depicts a schematic of a dimeric cytokine receptor on the cell surface (left), an antibody (middle), and a receptor-Fc fusion that optimally binds a target cytokine (right). **FIGURE 1B** depicts a receptor-Fc fusion, *e.g.*, a cytokine trap, that is sterically constrained from optimal binding to a target cytokine (left), or that adopts an optimal binding configuration (right).

WHAT IS CLAIMED IS:

1. An isolated fusion protein comprising, in an N- to C- terminal orientation:

(i) a soluble portion of an extracellular domain of a cytokine receptor;

(ii) an amino acid linker;

(iii) an immunoglobulin (Ig) hinge region; and

(iv) an immunoglobulin (Ig) Fc domain;

wherein the linker comprises from about 5 to about 40 amino acid residues.

2. The isolated fusion protein of claim 1, wherein the linker comprises from about 10 to about 40 amino acid residues.

3. The isolated fusion protein of claim 1, wherein the linker comprises from about 10 to about 30 amino acid residues.

4. The isolated fusion protein of claim 1, wherein the linker comprises from about 10 to about 20 amino acid residues.

5. The isolated fusion protein of claim 1, wherein the linker comprises from about 10 to about 15 amino acid residues.

6. The isolated fusion protein of any one of claims 1-5, wherein the linker comprises a C-terminal portion of an immunoglobulin (Ig) CH1 domain.

7. The isolated fusion protein of claim 6, wherein the Ig CH1domain is selected from an IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, and IgM CH1domain.

8. The isolated fusion protein of claim 7, wherein the Ig CH1domain is an IgG1 CH1 domain.

9. The isolated fusion protein of claim 8, wherein the linker comprises an amino acid sequence selected from SEQ ID NO: 1, SEQ ID NO: 60, and SEQ ID NO: 61.

10. The isolated fusion protein of any one of claims 1-9, wherein the cytokine receptor is a human TGFβ type II receptor.

11. The isolated fusion protein of claim 10, wherein the soluble portion of an extracellular domain of a cytokine receptor comprises amino acid residues 23-159 of SEQ ID NO: 12.

12. The isolated fusion protein of any one of claims 1-11, wherein the Ig Fc domain and hinge region are selected from a human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, and IgM Fc domain and hinge region.

13. The isolated fusion protein of claim 12, wherein the Ig Fc domain and hinge region are a human IgG1 Fc domain and hinge region.

14. The isolated fusion protein of claim 13, wherein the Ig Fc domain and hinge region comprise the amino acid sequence of SEQ ID NO: 13.

15. The isolated fusion protein of any one of claims 1-14, wherein the Ig Fc, Ig hinge region, and Ig CH1 domain are derived from a single immunoglobulin.

16. The isolated fusion protein of any one of claims 1-15, wherein the fusion protein comprises an amino acid sequence selected from SEQ ID NO: 22, SEQ ID NO: 62, and SEQ ID NO: 63.

17. A cytokine binding protein comprising two fusion proteins of any one of claims 1-16, wherein each fusion protein comprises an extracellular domain of a cytokine receptor, wherein the two fusion proteins are covalently linked together, and wherein the two extracellular domains together define a binding site for binding a cytokine.

18. An isolated nucleic acid comprising a nucleotide sequence encoding the fusion protein of any one of claims 1-17.

19. An expression vector comprising the nucleic acid of claim 18.

20. The expression vector of claim 19, wherein the expression vector is an oncolytic virus.

21. The expression vector of claim 20, wherein the oncolytic virus is an adenovirus.

22. The expression vector of claim 21, wherein the adenovirus is a type 5 adenovirus .

23. The expression vector of claim 22, wherein the nucleotide sequence encoding the fusion protein is inserted into an E1b-19K insertion site located between the start site of E1b-19K and the start site of E1b-55K.

24. The expression vector of claims 22 or 23, wherein the adenovirus comprises a deletion of a Pea3 binding site, or a functional fragment thereof.

25. A host cell comprising the expression vector of any one of claims 19-24.

26. A pharmaceutical composition comprising: (i) the expression vector of any one of claims 19-24; and (ii) at least one pharmaceutically acceptable carrier or diluent.

27. Use of a fusion protein of any one of claims 1-16 in the manufacture of a medicament for treating cancer in a subject in need thereof.

28. Use of an expression vector of any one of claims 19-24 in the manufacture of a medicament for treating cancer in a subject in need thereof.

29. The use of claim 27 or 28, wherein the cancer is selected from melanoma, squamous cell carcinoma of the skin, basal cell carcinoma, head and neck cancer, breast cancer, anal cancer, cervical cancer, non-small cell lung cancer, mesothelioma, small cell lung cancer, renal cell carcinoma, prostate cancer, gastroesophageal cancer, colorectal cancer, testicular cancer, bladder cancer, ovarian cancer, liver cancer, hepatocellular carcinoma, cholangiocarcinoma, brain and central nervous system cancer, thyroid cancer, parathyroid cancer (*e.g.,* parathyroid carcinoma), endometrial cancer, neuroendocrine cancer, lymphoma (*e.g.*, Hodgkin and non-Hodgkin), leukemia, merkel cell carcinoma, gastrointestinal stromal tumors, multiple myeloma, uterine cancer, a sarcoma, kidney cancer, ocular cancer, pancreatic cancer, and a germ cell cancer (*e.g.,* ovarian germ cell cancer).

30. The fusion protein of any one of claims 1-16 or the expression vector of any one of claims 19-24, for use in treating cancer.