BI-SPECIFIC ANTIBODIES FOR USE IN PRODUCING ARMED IMMUNE CELLS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of the filing date of U.S. Provisional Application No. 62/993,080, filed March 23, 2020, the entire contents of which is incorporated by reference herein.

BACKGROUND OF THE INVENTION

Cancer is a disease characterized by abnormal cells that divide uncontrollably and have the ability to infiltrate and destroy normal tissue and/or organ of a subject. Cancer is the second leading cause of death globally, and is responsible for an estimated 9.6 million deaths in 2018, in which the most common cancers include, lung cancer (about 2.09 million cases), breast cancer (about 2.09 million cases), colorectal cancer (about 1.80 million cases), prostate cancer (about 1.28 million cases), skin cancer (about 1.04 million cases), and gastric cancer (about 1.03 million cases).

Treatments for cancers may vary with the type of cancer and how advanced it is. Conventional treatments for cancers include surgery, radiation therapy, and chemotherapy. Such treatments usually cause a variety of complications or side effects, such as infection, blood clot, bleeding, nausea and vomiting, diarrhea, nerve or muscle damage, incontinence, and sex and fertility issues. Immunotherapy provides an alternative strategy for cancer treatment that aims at specifically stimulating immune responses of a subject against cancer cells via, for example, blocking immune checkpoints, or enhancing the ability of immune cells (e.g., T cells or B cells) to target and destroy cancer cells. Serious adverse effects associated with immunotherapy-medicated overstimulation or non-specific toxicity have been reported in cancer patients, including neurotoxicity, cytokine release syndrome (CRS), allergy, organ inflammation, and autoimmune disorders.

It is therefore of great importance to develop efficient cancer treatment specifically targeting cancer cells without affecting normal cells and/or tissues.

SUMMARY ~~OF THE INVENTION~~

The present disclosure is based on the development of bispecific antibodies (BsAbs) capable of binding to CD3 (*e.g.*, human CD3) and a tumor associated antigen (TAA). Such BsAbs are capable of attaching to the surface of CD3-positive immune cells *via* binding of the anti-CD3 moiety in the BsAb to the cell surface CD3 to produce armed immune cells.

In one aspect, the present disclosure refers to an armed immune cell, comprising an

immune cell that expresses surface CD3, and a bi-specific antibody; wherein the bi-specific antibody comprises: (a) a first antigen binding fragment that binds human CD3, wherein the first antigen binding fragment comprises a first heavy chain comprising a first heavy chain variable region (V_H) and a first light chain comprising a first light chain variable region (V_L), wherein the first V_H comprises the same heavy chain complementary determining regions (CDRs) or no more than 5 amino acid variations relative to a first reference antibody and the first V_L comprises the same light chain CDRs or no more than 5 amino acid variations relative to the reference antibody, and wherein the first reference antibody is CTA.02, CTA.03, CTA.04, or CTA.05; and (b) a second antigen binding fragment that binds a tumor associated antigen (TAA), wherein the second antigen binding fragment comprises a second heavy chain comprising a second heavy chain variable region (V_H) and a second light chain comprising a second light chain variable region (V_L); and wherein the armed immune cell displays the bi-specific antibody on the surface via interaction between the first antigen binding fragment in the bi-specific antibody and the CD3 expressed by the immune cell.

In another aspect, the present disclosure refers to a use of a population of armed immune cells as described herein in the manufacture of a medicament for treating cancer in a human cancer patient, wherein the human cancer patient has or suspected of having a cancer that is positive with the TAA, to which the second antigen binding fragment of the bi-specific antibody binds.

Accordingly, the present disclosure features, in some ~~aspect~~examples, a bi-specific antibody,

comprising: (a) a first antigen binding fragment that binds human CD3, and (b) a second antigen binding fragment that binds a tumor associated antigen (TAA). The first antigen binding fragment comprises (i) a first heavy chain comprising a first heavy chain variable region (V_H) and (ii) a first light chain comprising a first light chain variable region (V_L). In some ~~embodiment~~examples, the first V_H comprises the same heavy chain complementary determining regions (CDRs) as a first reference antibody. In other ~~embodiment~~examples, the first V_H comprises or no more than 5 amino acid variations in CDRs relative to the first reference antibody. Alternatively or in addition, the first V_L may comprise the same light chain CDRs as the first reference antibody. In other ~~embodiment~~examples, the first V_L may comprise no more than 5 amino acid variations in the CDRs relative to the first reference antibody. In some examples, the first reference antibody is CTA.02. In some examples, the first reference antibody is CTA.03. In other examples, the first reference antibody is CTA.04. In yet other examples, the first reference antibody is CTA.05. Structural information of these exemplary reference antibodies are provided in **Table 1** below. In some examples, the first heavy chain and the first light chain comprise the same V_H and V_L as the first reference antibody.

The second antigen binding fragment comprises a second heavy chain comprising (i) a second heavy chain variable region (V_H), and (ii) a second light chain comprising a second light chain variable region (V_L). The second antigen binding fragment binds a TAA. Examples include CD20, CD19, EGFR, HER2, PSMA, CEA, EpCAM, FAP, PD-L1, CD38, CD33, cMET, CD47, TRAIL-R2, mesothelin, or GD2. In some instances, the second V_H comprises the same heavy chain complementary determining regions (CDRs) as a second reference antibody. Alternatively, the second V_H may comprise no more than five amino acid variations in the CDRs relative to the second reference antibody. Alternatively or in addition, the second V_L may comprise the same light chain CDRs. In other examples, the second V_L may comprise no more than 5 amino acid variations in the CDRs relative to the second reference antibody. In some instances, the second reference antibody is CTAT.01, CTAT.02, CTAT.03, CTAT.04, CTAT.05, CTAT.06, CTAT.07, CTAT.08, CTAT.09, CTAT.10, CTAT.11, CTAT.12, CTAT.13, CTAT.14, CTAT.15, or CTAT.16. See **Table 2** below. In some examples, the second antigen binding fragment comprises the same V_H and same V_L as the second reference antibody.

In some ~~embodiment~~examples, the first antigen binding fragment is a Fab fragment and the second antigen binding fragment is a single chain variable fragment (scFv). In some examples, the Fab fragment comprises the first heavy chain, which comprises the first V_H and a CH1 fragment, and the first light chain, which comprises the first V_L and a light chain constant

region. In specific examples, the Fab fragment may comprise the first heavy chain and the first light chain, which respectively comprise the amino acid sequences of (a) SEQ ID NO:10 and SEQ ID NO: 11, (b) SEQ ID NO: 23 and SEQ ID NO: 24, 25, or 228, (c) SEQ ID NO: 35 and SEQ ID NO: 36, or (d) SEQ ID NO: 46 and SEQ ID NO: 47. In some examples, the scFv of the second antigen binding fragment comprises the amino acid sequence of any one of SEQ ID NOs: 254-271.

In some instances, the scFv is linked to the CH1 fragment, w optionally is via a peptide linker. Alternatively, the scFv is linked to the light chain constant region, optionally via a peptide linker. For example, the bi-specific antibody may comprise a first polypeptide comprising the first light chain and a second polypeptide comprising, from N-terminus to C-terminus, the first heavy chain, the peptide linker, and the scFv. Examples include any one of SEQ ID NOs: 229-248. Such a bi-specific antibody may comprise a second polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 24, 25, and 228. See **Table 3** below.

In other instances, the first antigen binding fragment is a single chain variable fragment (scFv) and the second antigen binding fragment is a Fab fragment. The scFv may comprise the amino acid sequence of any one of SEQ ID NOs: 250-253. In some examples, the Fab fragment comprises the second heavy chain, which comprises the second V_H and a CH1 fragment, and the second light chain, which comprises the second V_L and a light chain constant region. In specific examples, the Fab fragment comprises the first heavy chain and the first light chain, which respectively comprise the amino acid sequences of (1) SEQ ID NO:57 and SEQ ID NO: 58, (2) SEQ ID NO: 72 and SEQ ID NO: 73, (3) SEQ ID NO: 83 and SEQ ID NO: 84, (4) SEQ ID NO: 94 and SEQ ID NO: 95, (5) SEQ ID NO:105 and SEQ ID NO:106, (6) SEQ ID NO: 116 and SEQ ID NO:117, (7) SEQ ID NO: 127 and SEQ ID NO:128, (8) SEQ ID NO:138 and SEQ ID NO:139, (9) SEQ ID NO:149 and SEQ ID NO:150, (10) SEQ ID NO:160 and SEQ ID NO:161, (11) SEQ ID NO: 171 and SEQ ID NO:172, (12) SEQ ID NO:182 and SEQ ID NO:183, (13) SEQ ID NO:193 and SEQ ID NO:194, (14) SEQ ID NO:204 and SEQ ID NO:205, (15) SEQ ID NO:215 and SEQ ID NO:216, or (16) SEQ ID NO:226 and SEQ ID NO:227.

In some examples, the scFv is linked to the CH1 fragment, optionally via a peptide linker. Alternatively, the scFv is linked to the light chain constant region, optionally via a peptide linker. Any of the peptide linker may be at least 5 amino acids in length.

In yet other instances, both the first antigen binding fragment and the second antigen binding fragment are scFv antibodies. In some examples, the bi-specific antibody comprises a

polypeptide comprising the two scFv antibodies.

In other ~~aspect~~examples, the present disclosure provides an armed immune cell, comprising an immune cell that expresses surface CD3, and any of the bi-specific antibodies disclosed herein (e.g., those exemplified in **Tables 1-3**). The armed immune cell displays the bi-specific antibody on the surface via interaction between the first antigen binding fragment in the bi-specific antibody and the CD3 expressed by the immune cell. In some ~~embodiment~~examples, the immune cell is a T cell, a B cell, a monocyte, a macrophage, or a combination thereof. In some instances, the T cell can be a CD4+ T cell, a CD8+ T cell, a regulatory T cell, or a natural killer T cell. In some examples, the immune cell is a human immune cell, for example, immune cells derived from a human donor.

In ~~addition~~another aspect, provided herein is a method of producing the armed immune cell as disclosed herein. The method may comprise cultivating a cell population comprising the immune cells in the presence of the bi-specific antibody as disclosed herein to allow for binding of the bi-specific antibody to the immune cells, thereby producing the armed immune cell. The armed immune cells produced by any of the methods disclosed herein are also within the scope of the present disclosure.

In some ~~embodiment~~examples, the cell population comprises T cells, B cells, monocytes, macrophages, or a combination thereof. In some examples, the cell population comprises peripheral blood mononuclear cells (PBMCs) or immune cells derived from stem cells *in vitro*. The stem cells may be hematopoietic stem cells, umbilical cord blood stem cells, or induced pluripotent stem (iPS) cells.

In some ~~embodiment~~examples, the cultivating step is performed in a culture medium comprising a cytokine, which optionally comprises interleukin 2 (IL-2), interleukin 7 (IL-7), transforming growth factor-beta (TGF-β), or a combination thereof.

Further, provided herein is a method for treating cancer, comprising administering to a subject in need thereof an effective amount of a population of any of the armed immune cells disclosed herein. The subject has or suspected of having a cancer that is positive with the TAA, to which the second antigen binding fragment of the bi-specific antibody binds. In some ~~embodiment~~examples, the subject is a human cancer patient. In some ~~embodiment~~examples, the armed immune cells are autologous to the subject. Alternatively, the armed immune cells are allogenic to the subject. Exemplary cancers include, but are not limited to, melanoma, esophageal carcinoma, gastric carcinoma, brain tumor, small cell lung cancer, non-small cell lung cancer, bladder cancer, breast cancer, pancreatic cancer, colon cancer, rectal cancer, colorectal cancer, renal cancer, hepatocellular carcinoma, ovary cancer, prostate cancer, thyroid cancer, testis cancer,

head and neck squamous cell carcinoma, leukemia, lymphoma, and myeloma.

In other ~~aspect~~examples, the present disclosure features a nucleic acid or a set of nucleic acids (two nucleic acid molecules), which encodes or collectively encodes any of the bi-specific antibodies disclosed herein. In some examples, the nucleic acid or set of nucleic acids is a vector or a set of vectors, for examples, expression vector(s). Host cells (e.g., a bacterial cell, a yeast cell, or a mammalian cell) comprising any of the nucleic acid or set of nucleic acids disclosed herein are also within the scope of the present disclosure.

In addition, the present disclosure features a method for producing a bi-specific antibody, comprising: (i) culturing a host cell as disclosed herein under conditions allowing for expressing of the bi-specific antibody; and (ii) harvesting the bi-specific antibody.

Also within the scope of the present disclosure are armed immune cells as disclosed herein for use in cancer treatment or use of any of the armed immune cells for manufacturing a medicament for use in treating a target cancer.

The details of one or more ~~embodiment~~examples of the ~~invention~~disclosure are set forth in the description below. Other features or advantages of the present ~~invention~~disclosure will be apparent from the following drawings and detailed description of several ~~embodiment~~examples, and also from the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure, which can be better understood by reference to the drawing in combination with the detailed description of specific embodiments presented herein.

FIGs 1A-1N are schematic diagrams of exemplary bi-specific antibody formats. FIGs. 1A-1D: structures of anti-CD3 Fab/anti-TAA scFv bi-specific formats. FIGs. 1E-1H: structures of anti-CD3 scFv/anti-TAA Fab bi-specific formats. FIGs. 1I-1L: structures of anti-CD3 scFv/anti-TAA scFv bi-specific formats. FIGs. 1M: structure of anti-CD3 knob/anti-TAA hole bi-specific antibody formats, which comprises a monovalent anti-CD3 antibody and a monovalent anti-TAA antibody. FIG. 1N: anti-CD3 knob/anti-TAA scFv hole antibody, which comprises a monovalent anti-CD3 antibody and a monovalent anti-TAA scFv-Fc fusion protein.

FIGs. 2A-2E include schematic diagrams of DNA constructs for expressing the illustrated recombinant bi-specific antibodies. FIG. 2A: exemplary constructs for expressing anti-CD3Fab/anti-TAA scFv bi-specific antibodies. FIG. 2B: exemplary constructions for expressing anti-CD3scFv/anti-TAA Fab bi-specific antibodies. FIG. 2C: exemplary constructs

What Is Claimed Is:

1. An armed immune cell, comprising an immune cell that expresses surface CD3, and ~~A~~ a bi-specific antibody;~~,~~ wherein the bi-specific antibody comprises~~comprising~~:

(a) a first antigen binding fragment that binds human CD3, wherein the first antigen binding fragment comprises a first heavy chain comprising a first heavy chain variable region (V_H) and a first light chain comprising a first light chain variable region (V_L), wherein the first V_H comprises the same heavy chain complementary determining regions (CDRs) or no more than 5 amino acid variations relative to a first reference antibody and the first V_L comprises the same light chain CDRs or no more than 5 amino acid variations relative to the reference antibody, and wherein the first reference antibody is CTA.02, CTA.03, CTA.04, or CTA.05; and

(b) a second antigen binding fragment that binds a tumor associated antigen (TAA), wherein the second antigen binding fragment comprises a second heavy chain comprising a second heavy chain variable region (V_H) and a second light chain comprising a second light chain variable region (V_L); and

wherein the armed immune cell displays the bi-specific antibody on the surface via interaction between the first antigen binding fragment in the bi-specific antibody and the CD3 expressed by the immune cell.

2. The armed immune cell ~~bi-specific antibody~~ of claim 1, wherein the first heavy chain and the first light chain comprise the same V_H and V_L as the first reference antibody; and/or~~.~~

~~3. The bi-specific antibody of claim 1 or claim 2,~~ wherein the second antigen binding fragment binds a TAA, which is CD20, CD19, EGFR, HER2, PSMA, CEA, EpCAM, FAP, PD-L1, CD38, CD33, cMET, CD47, TRAIL-R2, mesothelin, or GD2.

~~4~~3. The armed immune cell ~~bi-specific antibody~~ of claim ~~3~~2, wherein the second V_H comprises the same heavy chain complementary determining regions (CDRs) or no more than five amino acid variations relative to a second reference antibody and the second V_L comprises the same light chain CDRs or no more than 5 amino acid variations relative to the second reference antibody, and wherein the second reference antibody is CTAT.01,

CTAT.02, CTAT.03, CTAT.04, CTAT.05, CTAT.06, CTAT.07, CTAT.08, CTAT.09, CTAT.10, CTAT.11, CTAT.12, CTAT.13, CTAT.14, CTAT.15, or CTAT.16.

~~5~~4. The armed immune cell ~~bi-specific antibody~~ of claim ~~4~~3, wherein the second antigen binding fragment comprises the same V_H and same V_L as the second reference antibody.

~~6~~5. The armed immune cell ~~bi-specific antibody~~ of any one of claims 1-~~5~~4, wherein the first antigen binding fragment is a Fab fragment and the second antigen binding fragment is a single chain variable fragment (scFv), and wherein the Fab fragment comprises the first heavy chain, which comprises the first V_H and a CH1 fragment, and the first light chain, which comprises the first V_L and a light chain constant region.

~~7~~6. The armed immune cell ~~bi-specific antibody~~ of claim ~~6~~5, wherein the Fab fragment comprises the first heavy chain and the first light chain, which respectively comprise the amino acid sequences of (a) SEQ ID NO:10 and SEQ ID NO: 11, (b) SEQ ID NO: 23 and SEQ ID NO: 24, 25, or 228, (c) SEQ ID NO: 35 and SEQ ID NO: 36, or (d) SEQ ID NO: 46 and SEQ ID NO: 47; and/or~~.~~

~~8. The bi-specific antibody of claim 6 or claim 7,~~ wherein the scFv of the second antigen binding fragment comprises the amino acid sequence of any one of SEQ ID NOs: 254-271.

~~9~~7. The armed immune cell ~~bi-specific antibod~~y of ~~any one of~~ claim~~s 6-8~~ 5 or claim 6, wherein the scFv is linked to the CH1 fragment or the light chain constant region via a peptide linker.

~~10~~8. The armed immune cell ~~bi-specific antibody~~ of claim ~~6~~7, wherein the bi-specific antibody comprises a first polypeptide comprising the first light chain and a second polypeptide comprising, from N-terminus to C-terminus, the first heavy chain, the peptide linker, and the scFv.

~~11~~9. The armed immune cell ~~bi-specific antibody~~ of claim 8, wherein the first polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 229-248; and/or~~.~~

~~12. The bi-specific antibody of claim 10 or claim 11,~~ wherein the second polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 24, 25, and 228.

~~13~~10. The armed immune cell ~~bi-specific antibody~~ of any one of claims 1-~~5~~4, wherein the first antigen binding fragment is a single chain variable fragment (scFv) and the second antigen binding fragment is a Fab fragment, wherein the Fab fragment comprises the second heavy chain, which comprises the second V_H and a CH1 fragment, and the second light chain, which comprises the second V_L and a light chain constant region.

~~14~~11. The armed immune cell ~~bi-specific antibody~~ of claim ~~13~~10, wherein the scFv comprises the amino acid sequence of any one of SEQ ID NOs:250-253~~.~~; and/or

~~15. The bi-specific antibody of claim 13 or claim 14,~~ wherein the Fab fragment comprises the first heavy chain and the first light chain, which respectively comprise the amino acid sequences of (1) SEQ ID NO:57 and SEQ ID NO: 58, (2) SEQ ID NO: 72 and SEQ ID NO: 73, (3) SEQ ID NO: 83 and SEQ ID NO: 84, (4) SEQ ID NO: 94 and SEQ ID NO: 95, (5) SEQ ID NO:105 and SEQ ID NO:106, (6) SEQ ID NO: 116 and SEQ ID NO:117, (7) SEQ ID NO: 127 and SEQ ID NO:128, (8) SEQ ID NO:138 and SEQ ID NO:139, (9) SEQ ID NO:149 and SEQ ID NO:150, (10) SEQ ID NO:160 and SEQ ID NO:161, (11) SEQ ID NO: 171 and SEQ ID NO:172, (12) SEQ ID NO:182 and SEQ ID NO:183, (13) SEQ ID NO:193 and SEQ ID NO:194, (14) SEQ ID NO:204 and SEQ ID NO:205, (15) SEQ ID NO:215 and SEQ ID NO:216, or (16) SEQ ID NO:226 and SEQ ID NO:227.

~~16~~12. The armed immune cell ~~bi-specific antibody~~ of ~~any one of~~ claim~~s~~ 10 or claim 11~~13-15~~, wherein the scFv is linked to the CH1 fragment or the light chain constant region via a peptide linker, which optionally is at least 5 amino acids in length.

~~17~~13. The armed immune cell~~bi-specific antibody~~ of any one of claims 1-~~5~~4, wherein both the first antigen binding fragment and the second antigen binding fragment are scFv antibodies.

~~18~~14. The armed immune cell~~bi-specific antibody~~ of claim 13, wherein the bi-specific antibody comprises a polypeptide comprising the two scFv antibodies.

~~19. An armed immune cell, comprising an immune cell that expresses surface CD3, and a bi-specific antibody of any one of claims 1-18, wherein the armed immune cell displays the bi-specific antibody on the surface via interaction between the first antigen binding fragment in the bi-specific antibody and the CD3 expressed by the immune cell.~~

~~20~~15. The armed immune cell of any one of claims 1-14~~19~~, wherein the immune cell is a T cell, a B cell, a monocyte, a macrophage, or a combination thereof.

~~21~~16. The armed immune cell of claim ~~20~~15, wherein the T cell is a CD4+ T cell, a CD8+ T cell, a regulatory T cell, or a natural killer T cell.

~~22~~17. The armed immune cell of any one of claims 1~~9~~-~~21~~14, wherein the immune cell is a human immune cell.

~~23~~18. The armed immune cell of claim ~~22~~17, wherein the human immune cell is derived from a human donor.

~~24~~19. A method of producing the armed immune cell of any one of claims 1-14~~19~~, comprising cultivating a cell population comprising the immune cells in the presence of the bi-specific antibody to allow for binding of the bi-specific antibody to the immune cells, thereby producing the armed immune cell.

~~25~~20. The method of claim ~~24~~19, wherein the cell population comprises T cells, B cells, monocytes, macrophages, or a combination thereof; or.

~~26. The method of claim 25,~~ wherein the cell population comprises peripheral blood mononuclear cells (PBMCs) or immune cells derived from stem cells in vitro, and

optionally wherein the stem cells are hematopoietic stem cells, umbilical cord blood stem cells, or induced pluripotent stem (iPS) cells.

~~27~~21. The method of claim 19 or claim 20~~any one of claims 24-26~~, wherein the cultivating step is performed in a culture medium comprising a cytokine, which optionally comprises interleukin 2 (IL-2), interleukin 7 (IL-7), transforming growth factor-beta (TGF-β), or a combination thereof.

~~28. A population of armed immune cells, which is produced by a method of any one of claims 24-27.~~

~~29~~22. ~~A method for treating cancer, comprising administering to a subject in need thereof an effective amount~~ Use of a population of armed immune cells set forth in any one of claims 1-18~~19-23 and 28~~ in the manufacture of a medicament for treating cancer in a human cancer patient, wherein the subject has or suspected of having a cancer that is positive with the TAA, to which the second antigen binding fragment of the bi-specific antibody binds.

~~30. The method of claim 29, wherein the subject is a human cancer patient.~~

~~31~~23. The ~~method~~ use of claim ~~29~~ 22~~or claim 30~~, wherein the armed immune cells are autologous to the human patient~~subject.~~

~~32. The method of claim 29 or claim 30~~, wherein the armed immune cells are allogenic to the ~~subject~~human patient.

~~33~~24. The ~~method~~ use of ~~any one of~~ claim~~s~~ 22 or claim 23~~29-32~~, wherein the cancer is selected from the group consisting of melanoma, esophageal carcinoma, gastric carcinoma, brain tumor, small cell lung cancer, non-small cell lung cancer, bladder cancer, breast cancer, pancreatic cancer, colon cancer, rectal cancer, colorectal cancer, renal cancer, hepatocellular carcinoma, ovary cancer, prostate cancer, thyroid cancer, testis cancer, head and neck squamous cell carcinoma, leukemia, lymphoma, and myeloma.

~~34. A nucleic acid or a set of nucleic acids, which encodes or collectively encodes a bi-specific antibody set forth in any one of claims 1-18.~~

~~35. The nucleic acid or set of nucleic acids of claim 34, which is a vector or a set of vectors.~~

~~36. The nucleic acid or set of nucleic acids of claim 35, wherein the vector(s) is an expression vector(s).~~

~~37. A host cell, comprising the nucleic acid or set of nucleic acids set forth in any one of claims 34-36.~~

~~38. The host cell of claim 37, wherein the host cell is a bacterial cell, a yeast cell, or a mammalian cell.~~

~~39. A method for producing a bi-specific antibody, comprising:~~

~~(i) culturing a host cell of claim 37 or claim 38 under conditions allowing for expressing of the bi-specific antibody; and~~

~~(ii) harvesting the bi-specific antibody.~~