

Summary of the Invention

~~The invention~~In one aspect, the disclosure described herein provides an antibody that binds to human HLA-G comprising

5 A) (a) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:1, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:2, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:3; and (b) a VL domain comprising (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:23; (ii) CDR-L2 comprising the amino acid sequence of SEQ ID
10 NO:5 and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:6, or

B) (a) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:1, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:2, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:3; and (b) a VL domain comprising (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:25; (ii) CDR-L2 comprising the amino acid sequence of SEQ ID
15 NO:5 and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:6.

One ~~embodiment~~example of the ~~invention~~disclosure is an antibody that binds to human HLA-G wherein the antibody

A) comprises a VH domain comprising the amino acid sequence of SEQ ID
20 NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:24; or

B) comprises a VH domain comprising the amino acid sequence of SEQ ID NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:26.

One ~~embodiment~~example of the ~~invention~~disclosure is an antibody that binds to human HLA-G wherein the antibody comprises a VH domain comprising the amino
25 acid sequence of SEQ ID NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:24.

One ~~embodiment~~example of the ~~invention~~disclosure is an antibody that binds to human HLA-G wherein the antibody comprises a VH domain comprising the amino
30 acid sequence of SEQ ID NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:26.

Such antibodies have highly valuable properties like their binding properties, their high specificity towards HLA-G with no crossreactivity to HLA-A and HLA MHC I complexes from other species. They can bind to HLA-G on cells and inhibit ILT2

and/or ILT4 binding to HLA-G expressed on these cells. They have been generated from the HLA-G antibody HLA-G-0090.

As the HLA-G antibody HLA-G-0090 described in WO 2019/202040 comprises a glycosylation site in one of the CDRs (CDR-L1 which comprises a NSS motif at amino acids 31, 32 and 33 of the light chain (LC)), its binding properties are impacted by the N-glycosylation which constitutes a potential developability liability.

A homology model of the variable region of HLA-G-0090 indicated that light chain (LC) positions 31 to 33 are highly solvent accessible. Furthermore, the side chains of N31 and S32 are predicted to point inwards, in the direction of CDR-H3, making them likely candidates for being part of the antibody paratope. In fact, a number of published antibody-antigen X-ray complex structures document these residues to be undergoing chemical interactions with the antigen. Therefore, the risk of worsening the binding affinity of the antibody by introducing mutations at LC positions 31-33 was high. Therefore various variants of antibody HLA-G-0090 with mutations on LC positions 31, 32, and 33 were designed from which however most variants worsened binding properties or expressability. Surprisingly it was found that among these various variants of HLA-G-0090 in which the glycosylation site was removed only the two variants HLA-G-0090-VL-S32P and HLA-G-0090-VL-S33A show even improved binding properties, good expressability and stability, while showing no more N-glycosylation at the CDR-L1 of the LC (so no Fab glycosylation could be detected). As all recently approved pharmaceutical antibody products are produced in mammalian cells, especially CHO cells (see e.g. Walsh G., Nature Biotech (2018) 1136-1145), providing an antibody without glycosylation sites in the binding region (VH and VL and especially the CDRs) represents a valuable advantage, as these antibodies can readily be used for production in mammalian expression systems without the risk of (at least partially) impairing the binding properties by glycosylation.

In a further embodimentexample the HLA-G antibody of the present inventiondisclosure comprises a Fc domain of human origin. In one embodimentexample the Fc domain is of the IgG isotype, in one preferred embodimentexample of the IgG1 isotype.

In a further embodimentexample the HLA-G antibody of the present inventiondisclosure is a bispecific antibody, in particular an a bispecific antibody that binds to human HLA-G and to human CD3, comprising a first antigen binding moiety that binds to human HLA-G and a second antigen binding moiety that binds to human CD3.

In one ~~embodiment~~example the HLA-G antibody of the present ~~invention~~disclosure is a bispecific antibody that binds to human HLA-G and to human CD3, comprising a first antigen binding moiety that binds to human HLA-G and a second antigen binding moiety that binds to human CD3,

wherein the first antigen binding moiety that binds to human HLA-G comprises

A) (a) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:1, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:2, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:3; and (b) a VL domain comprising (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:23; (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO:5 and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:6, or

B) (a) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:1, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:2, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:3; and (b) a VL domain comprising (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:25; (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO:5 and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:6;

and wherein the second antigen binding moiety that binds to a T cell activating antigen binds to human CD3 comprises

C) (a) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:52, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:53, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:54; and (b) a VL domain comprising (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:55; (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO:56 and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:57, or

D) (a) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:60, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:61, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:62; and (b) a VL domain comprising (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:63; (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO:64 and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:65, or

- 5 E) (a) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:68, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:69, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:70; and (b) a VL domain comprising (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:71; (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO:72 and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:73.

- One ~~embodiment~~example of the ~~invention~~disclosure is such bispecific antibody,
wherein the first antigen binding moiety
- 10 A) comprises a VH domain comprising the amino acid sequence of SEQ ID NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:24; or
- B) comprises a VH domain comprising the amino acid sequence of SEQ ID NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:26,
and wherein the second antigen binding moiety
- 15 C) comprises a VH domain comprising the amino acid sequence of SEQ ID NO:58 and a VL domain comprising the amino acid sequence of SEQ ID NO:59; or
- D) comprises a VH domain comprising the amino acid sequence of SEQ ID NO:66 and a VL domain comprising the amino acid sequence of SEQ ID NO:67; or
- 20 E) comprises a VH domain comprising the amino acid sequence of SEQ ID NO:74 and a VL domain comprising the amino acid sequence of SEQ ID NO:75.

- One ~~embodiment~~example of the ~~invention~~disclosure is such bispecific antibody,
wherein the first antigen binding moiety
- comprises a VH domain comprising the amino acid sequence of SEQ ID NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:24;
- 25 and wherein the second antigen binding moiety
- comprises a VH domain comprising the amino acid sequence of SEQ ID NO:58 and a VL domain comprising the amino acid sequence of SEQ ID NO:59.

One ~~embodiment~~example of the ~~invention~~disclosure is such bispecific antibody,

wherein the first antigen binding moiety

comprises a VH domain comprising the amino acid sequence of SEQ ID NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:24;

and wherein the second antigen binding moiety

5 comprises a VH domain comprising the amino acid sequence of SEQ ID NO:66 and a VL domain comprising the amino acid sequence of SEQ ID NO:67.

One ~~embodiment~~example of the ~~invention~~disclosure is such bispecific antibody,

wherein the first antigen binding moiety

10 comprises a VH domain comprising the amino acid sequence of SEQ ID NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:24;

and wherein the second antigen binding moiety

comprises a VH domain comprising the amino acid sequence of SEQ ID NO:74 and a VL domain comprising the amino acid sequence of SEQ ID NO:75.

15 Such bispecific antibodies binding to human HLA-G and human CD3 show in addition to the properties of the HLA-G-antibodies further valuable properties like the induction of antibody mediated IFN gamma secretion by T cells on HLA-G expressing cells, T cell activation in the presence of HLA-G expressing tumor cells, induction of T cell mediated tumor cell killing on HLA-G expressing cells and in vivo anti-tumor efficacy and even tumor regression in different cancer xenograft mouse models.

~~The invention~~In another aspect, the disclosure provides an isolated nucleic acid encoding the antibody as described herein or the bispecific antibody as described herein.

25 The ~~invention~~disclosure provides a host cell comprising such nucleic acid. In another aspect, the present disclosure provides a host cell, preferably an eukaryotic host cell, comprising the nucleic acid as described herein.

The ~~invention~~disclosure provides a method of producing an antibody comprising culturing the host cell so that the antibody is produced.

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The ~~invention~~disclosure provides such method of producing an antibody, further comprising recovering the antibody from the host cell. In another aspect, the present disclosure provides a method of producing the antibody as described herein or the bispecific antibody as described herein comprising culturing the host cell as described herein so that the antibody or bispecific antibody is produced.

The ~~invention~~disclosure provides an antibody produced by such an host cell where the host cell is eukaryotic.

The ~~invention~~disclosure provides a pharmaceutical formulation comprising the antibody described herein and a pharmaceutically acceptable carrier. In another aspect, the present disclosure provides a pharmaceutical formulation comprising the antibody as described herein or the bispecific antibody as described herein and a pharmaceutically acceptable carrier.

The ~~invention~~disclosure provides the antibody described herein for use as a medicament. In another aspect, the present disclosure provides the antibody as described herein or the bispecific antibody as described herein for use as a medicament.

The ~~invention~~disclosure provides the antibody described herein for use in treating cancer. In another aspect, the present disclosure provides the antibody as described herein or the bispecific antibody as described herein for use in treating cancer.

The ~~invention~~disclosure provides the use of the antibody described herein in the manufacture of a medicament. In another aspect, the present disclosure provides use of the antibody as described herein or the bispecific antibody as described herein in the manufacture of a medicament. In one ~~embodiment~~example the medicament is for treatment of cancer.

The ~~invention~~disclosure provides a method of treating an individual having cancer comprising administering to the individual an effective amount of the antibody described herein.

Description of the Figures

Figure 1: Different isoforms of HLA-G

Figure 2: Fig. 2A: Schematic representation of the HLA-G molecule in association with β 2M:

Schematic representation of the HLA-G wt molecule

Fig. 2B: Schematic representation of the HLA-G molecule in association with β 2M:

The KIR2DL4 and ILT2/4 interactions are extracted from crystal structures: the HLA-G:ILT4 complex structure (PDB code: 2DYP). The KIR2DL1 structure is taken from PDB code 1IM9 (KIR2DL1:HLA-Cw4 complex structure) and was positioned on HLA-G by superposition of the HLA-Cw4 and HLA-G structures.

Fig. 2C: Schematic representation of the HLA-G molecule in association with β 2M:

Schematic representation of the HLA-G chimeric molecule that was used as a counter antigen for the identification of specific HLA-G binders. White dots represent surface residues that were identified as unique for HLA-G. These residues were replaced by a HLA consensus sequence in the chimeric molecule.

Fig. 2D: Structure of HLA-G molecule in association with certain receptors : HLA-G structure in complex with given receptors such as ILT4 and KIR2DL1. ILT4 structure (PDB code: 2DYP). The KIR2DL1 structure is taken from PDB code 1IM9 (KIR2DL1: HLA-Cw4 complex structure) and was positioned on HLA-G by superposition of the HLA-Cw4 and HLA-G structures. Receptors are shown in a ribbon representation, HLA-G is shown in a molecular surface representation. HLA-G residues that are unique or conserved in other HLA paralogs are colored in white and gray, respectively. Unique surface residues were replaced by a HLA consensus sequence in the chimeric counter antigen.

Figure 3: Schematic antibody-antigen binding assay principle - relative active concentration (RAC) of HLA-G antibodies for binding to HLA-G

Figure 4A: Mass spectrum of N-glycosylation of HLA-G-0090 indicates Fab-glycosylation

Patent Claims

1. An antibody that binds to human HLA-G comprising
 - A) (a) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:1, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:2, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:3; and (b) a VL domain comprising (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:23; (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO:5 and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:6, or
 - 10 B) (a) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:1, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:2, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:3; and (b) a VL domain comprising (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:25; (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO:5 and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:6.
- 15 2. The antibody according to claim 1, wherein the antibody
 - A) comprises a VH domain comprising the amino acid sequence of SEQ ID NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:24; or
 - 20 B) comprises a VH domain comprising the amino acid sequence of SEQ ID NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:26.
3. The antibody of claims 1 or 2, wherein the antibody comprises a Fc domain of human origin, particularly of the IgG isotype, more particularly of the IgG1 isotype.
- 25 4. The antibody according to any one of claims 1 to 3, wherein the antibody comprises a constant region of human origin, particularly of the IgG isotype, more particularly of the IgG1 isotype, comprising a human CH1, CH2, CH3 and/or CL domain..
5. The antibody according to any one of claim 1 to 4, wherein the antibody

- a) does not crossreact with a modified human HLA-G β 2M MHC I complex, wherein the HLA-G specific amino acids have been replaced by HLA-A consensus amino acids, the complex comprising SEQ ID NO:40; and/ or
- 5 b) does not crossreact with a mouse H2Kd β 2M MHC I complex comprising SEQ ID NO:41; and/ or
- c) does not crossreact with rat RT1A β 2M MHC I complex comprising SEQ ID NO:43.
- 6. The antibody according to any one of claims 1 to 5, wherein the antibody
- 10 a) inhibits ILT2 binding to (HLA-G expressed on) JEG3 cells (ATCC No. HTB36); or
- b) binds to (HLA-G expressed on) JEG3 cells (ATCC No. HTB36), and inhibits ILT2 binding to (HLA-G expressed on) JEG-3 cells (ATCC No. HTB36).
- 7. The antibody according to any one of claims 1 to 4, wherein the antibody is a multispecific antibody .
- 15 8. The antibody according to any one of claims 1 to 4, wherein the antibody is a bispecific antibody that binds to human HLA-G and to human CD3.
- 9. The antibody according to claim 5, wherein the antibody is a bispecific antibody that binds to human HLA-G and to human CD3, comprising a first antigen binding moiety that binds to human HLA-G and a second antigen
- 20 binding moiety that binds to human CD3,
wherein the first antigen binding moiety that binds to human HLA-G comprises
- A) (a) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:1, (ii) CDR-H2 comprising the amino acid sequence of SEQ
- 25 ID NO:2, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:3; and (b) a VL domain comprising (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:23; (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO:5 and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:6, or

- 5 B) (a) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:1, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:2, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:3; and (b) a VL domain comprising (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:25; (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO:5 and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:6;

and wherein the second antigen binding moiety that binds to a T cell activating antigen binds to human CD3 comprises

- 10 C) (a) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:52, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:53, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:54; and (b) a VL domain comprising (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:55; (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO:56 and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:57, or

- 20 D) (a) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:60, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:61, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:62; and (b) a VL domain comprising (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:63; (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO:64 and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:65, or

- 25 E) (a) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:68, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:69, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:70; and (b) a VL domain comprising (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:71; (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO:72 and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:73.

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10. The bispecific antibody according to claim 9,

wherein the first antigen binding moiety

- A) comprises a VH domain comprising the amino acid sequence of SEQ ID NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:24; or
- B) comprises a VH domain comprising the amino acid sequence of SEQ ID NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:26,
- 5 and wherein the second antigen binding moiety
- C) comprises a VH domain comprising the amino acid sequence of SEQ ID NO:58 and a VL domain comprising the amino acid sequence of SEQ ID NO:59; or
- D) comprises a VH domain comprising the amino acid sequence of SEQ ID NO:66 and a VL domain comprising the amino acid sequence of SEQ ID NO:67; or
- 10 E) comprises a VH domain comprising the amino acid sequence of SEQ ID NO:74 and a VL domain comprising the amino acid sequence of SEQ ID NO:75.
- 15 11. The bispecific antibody according to claim 10,
- wherein the first antigen binding moiety
- comprises a VH domain comprising the amino acid sequence of SEQ ID NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:24;
- and wherein the second antigen binding moiety
- 20 comprises a VH domain comprising the amino acid sequence of SEQ ID NO:58 and a VL domain comprising the amino acid sequence of SEQ ID NO:59.
12. The bispecific antibody according to claim 10,
- wherein the first antigen binding moiety
- 25 comprises a VH domain comprising the amino acid sequence of SEQ ID NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:24;
- and wherein the second antigen binding moiety

comprises a VH domain comprising the amino acid sequence of SEQ ID NO:66 and a VL domain comprising the amino acid sequence of SEQ ID NO:67.

13. The bispecific antibody according to claim 10,

5 wherein the first antigen binding moiety

comprises a VH domain comprising the amino acid sequence of SEQ ID NO:7 and a VL domain comprising the amino acid sequence of SEQ ID NO:24;

and wherein the second antigen binding moiety

10 comprises a VH domain comprising the amino acid sequence of SEQ ID NO:74 and a VL domain comprising the amino acid sequence of SEQ ID NO:75.

14. The bispecific antibody according to any one of claims 7 to 13, wherein the bispecific antibody shows

a) inhibition of ILT2 and/or ILT4 binding to HLA-G; and/or

15 b) antibody mediated IFN gamma secretion by T cells on SKOV3 cells transfected with recombinant HLA-G (SKOV3 HLA-G) and/or on JEG3 cells expressing endogenous HLA-G wherein the IFN gamma secretion was detected; and or

20 c) T cell mediated cytotoxicity/tumor cell killing on SKOV3 cells transfected with recombinant HLA-G (SKOV 3HLA-G) and/or JEG3 cells expressing endogenous HLA-G wherein the cytotoxicity was detected by measuring Caspase 8 activation in cells after treatment with bispecific antibody; and/or

25 d) in vivo anti-tumor efficacy/ tumor regression in humanized NSG mice bearing SKOV3 human ovarian carcinoma transfected with recombinant HLA-G (SKOV3 HLA-G) humanized NSG mice; and/or

e) in vivo anti-tumor efficacy /tumor of HLA-G CD3 T cell bi-specific in humanized NSG mice bearing human breast cancer PDX tumors (BC004).

15. Isolated nucleic acid encoding the antibody according to any one of claims 1-4 or the bispecific antibody according to any one of claims 7-13.

16. A host cell, preferably an eukaryotic host cell, comprising the nucleic acid of ~~embodiment-claim~~ 15.

17. A method of producing the antibody according to any one of claims 1-4 or the bispecific antibody according to any one of claims 7-13 comprising culturing the host cell of claim 16 so that the antibody or bispecific antibody is produced.

18. The method of claim ~~30~~17, further comprising recovering the antibody or bispecific antibody from the host cell.

19. The antibody according to any one of claims 1-4 or the bispecific antibody according to any one of claims 7-13, wherein the antibody is produced in an eukaryotic host cell.

20. A pharmaceutical formulation comprising the antibody according to any one of claims 1-4 or the bispecific antibody according to any one of claims 7-13 and a pharmaceutically acceptable carrier.

21. The antibody according to any one of claims 1-4 or the bispecific antibody according to any one of claims 7-13 for use as a medicament.

22. The antibody according to any one of claims 1-4 or the bispecific antibody according to any one of claims 7-13 for use in treating cancer.

23. Use of the antibody according to any one of claims 1-4 or the bispecific antibody according to any one of claims 7-13 in the manufacture of a medicament.

24. The use of claim 23, wherein the medicament is for treatment of cancer.

~~25.—A method of treating an individual having cancer comprising administering to the individual an effective amount of the antibody according to any one of claims 1-4 or the bispecific antibody according to any one of claims 7-13.~~