bispecific derivative thereof (additionally targeting CD3), has also been generated (WO 2016/199141).

Bispecific antibodies that bind to a surface antigen on target cells and an activating T cell antigen such as CD3 on T-cells (also called herein T cell bispecific antibodies or "TCBs") hold great promise for the treatment of various cancers. The simultaneous binding of such an antibody to both of its targets will force a temporary interaction between target cell and T cell, causing crosslinking of the T cell receptor and subsequent activation of any cytotoxic T cell and subsequent lysis of the target cell. Given their potency in target cell killing, the choice of target and the specificity of the targeting antibody is of utmost importance for T cell bispecific antibodies to avoid on- and off-target toxicities. Intracellular proteins such as MAGE-A4 represent attractive targets, but are only accessible to T cell receptor (TCR)-like antibodies that bind major histocompatibility complex (MHC) presenting peptide antigens derived from the intracellular protein on the cell surface. An inherent issue of TCR-like antibodies is potential cross-reactivity with MHC molecules per se, or MHC molecules presenting peptides other than the desired one, which could compromise organ or tissue selectivity.

SUMMARY

The present disclosure provides novel antibodies, including multispecific (e.g. bispecific) antibodies, that bind HLA-A2/MAGE-A4 and have particularly favorable properties for therapeutic purposes. In particular, the (multispecific) antibodies bind HLA-A2/MAGE-A4 with good affinity and remarkable specificity, and combine good efficacy and produceability with low toxicity and favorable pharmacokinetic properties.

In one aspect, the disclosure provides an antibody that binds to HLA-A2/MAGE-A4, wherein the antibody comprises a first antigen binding domain, comprising

(i) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 25, a HCDR 2 of SEQ ID NO: 26, and a HCDR 3 of SEQ ID NO: 27, and a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 28, a LCDR 2 of SEQ ID NO: 29 and a LCDR 3 of SEQ ID NO: 30;

(ii) a VH comprising a HCDR 1 of SEQ ID NO: 1, a HCDR 2 of SEQ ID NO: 2, and a HCDR 3 of SEQ ID NO: 3, and a VL comprising a LCDR 1 of SEQ ID NO: 4, a LCDR 2 of SEQ ID NO: 5 and a LCDR 3 of SEQ ID NO: 6;

(iii) a VH comprising a HCDR 1 of SEQ ID NO: 41, a HCDR 2 of SEQ ID NO: 42, and a HCDR 3 of SEQ ID NO: 43, and a VL comprising a LCDR 1 of SEQ ID NO: 44, a LCDR 2 of SEQ ID NO: 45 and a LCDR 3 of SEQ ID NO: 46;

(iv) a VH comprising a HCDR 1 of SEQ ID NO: 9, a HCDR 2 of SEQ ID NO: 10, and a HCDR 3 of SEQ ID NO: 11, and a VL comprising a LCDR 1 of SEQ ID NO: 12, a LCDR 2 of SEQ ID NO: 13 and a LCDR 3 of SEQ ID NO: 14;

(v) a VH comprising a HCDR 1 of SEQ ID NO: 17, a HCDR 2 of SEQ ID NO: 18, and a HCDR 3 of SEQ ID NO: 19, and a VL comprising a LCDR 1 of SEQ ID NO: 20, a LCDR 2 of SEQ ID NO: 21 and a LCDR 3 of SEQ ID NO: 22; or

(vi) a VH comprising a HCDR 1 of SEQ ID NO: 33, a HCDR 2 of SEQ ID NO: 34, and a HCDR 3 of SEQ ID NO: 35, and a VL comprising a LCDR 1 of SEQ ID NO: 36, a LCDR 2 of SEQ ID NO: 37 and a LCDR 3 of SEQ ID NO: 38.

In one example, the first antigen binding domain comprises

(i) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 31, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 32;

(ii) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 7, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 8;

(iii) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 47, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 48;

(iv) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 15, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 16;

(v) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 23, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 24; or

(vi) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 39, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 40.

In a further example, the disclosure provides an antibody that binds to HLA-A2/MAGE-A4, wherein the antibody comprises a first antigen binding domain comprising

(i) a VH comprising the amino acid sequence of SEQ ID NO: 31, and/or a VL comprising the amino acid sequence of SEQ ID NO: 32;

(ii) a VH comprising the amino acid sequence of SEQ ID NO: 7, and/or a VL comprising the amino acid sequence of SEQ ID NO: 8;

(iii) a VH comprising the amino acid sequence of SEQ ID NO: 47, and/or a VL comprising the amino acid sequence of SEQ ID NO: 48;

(iv) a VH comprising the amino acid sequence of SEQ ID NO: 15, and/or a VL comprising the amino acid sequence of SEQ ID NO: 16;

(v) a VH comprising the amino acid sequence of SEQ ID NO: 23, and/or a VL comprising the amino acid sequence of SEQ ID NO: 24; or

(vi) a VH comprising the amino acid sequence of SEQ ID NO: 39, and/or a VL comprising the amino acid sequence of SEQ ID NO: 40.

In one example, the antibody is a multispecific, particularly a bispecific, antibody.

In one example, the antibody comprises a second antigen binding domain which binds to a second antigen.

In one example, the second antigen is an activating T cell antigen, particularly CD3, most particularly CD3ε.

In one example, the second antigen binding domain comprises

(i) a VH comprising a HCDR 1 of SEQ ID NO: 59, a HCDR 2 of SEQ ID NO: 60, and a HCDR 3 of SEQ ID NO: 61, and a VL comprising a LCDR 1 of SEQ ID NO: 62, a LCDR 2 of SEQ ID NO: 63 and a LCDR 3 of SEQ ID NO: 64; or

(ii) a VH comprising a HCDR 1 of SEQ ID NO: 51, a HCDR 2 of SEQ ID NO: 52, and a HCDR 3 of SEQ ID NO: 53, and a VL comprising a LCDR 1 of SEQ ID NO: 54, a LCDR 2 of SEQ ID NO: 55 and a LCDR 3 of SEQ ID NO: 56.

In one example, the second antigen binding domain comprises

(i) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 65, and/or a VL comprising an amino

acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 66; or

(ii) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 57, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 58.

In one example, the second antigen binding domain comprises

(i) a VH comprising the amino acid sequence of SEQ ID NO: 65, and/or a VL comprising the amino acid sequence of SEQ ID NO: 66;

(ii) a VH comprising the amino acid sequence of SEQ ID NO: 57, and/or a VL comprising the amino acid sequence of SEQ ID NO: 58.

In one example, the antibody comprises a third antigen binding domain. In one example, the third antigen domain binds to HLA-A2/MAGE-A4. The third antigen binding domain may incorporate, singly or in combination, any of the features described herein in relation to the first antigen binding domain. In one example, the third antigen domain is identical to the first antigen binding domain.

In one example, the first antigen binding domain, the second antigen binding domain (where present) and/or the third antigen binding domain (where present) is a Fab molecule.

In one example, the second antigen binding domain is a Fab molecule wherein the variable domains VL and VH or the constant domains CL and CH1, particularly the variable domains VL and VH, of the Fab light chain and the Fab heavy chain are replaced by each other.

In one example the first and, where present, the third antigen binding domain is a conventional Fab molecule.

In one example, the first and, where present, the third antigen binding domain is a Fab molecule wherein in the constant domain CL the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat) and the amino acid at position 123 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat), and in the constant domain CH1 the amino acid at position 147 is substituted independently by glutamic acid (E), or aspartic acid (D) (numbering according to Kabat EU index) and the amino acid at position 213 is substituted independently by glutamic acid (E), or aspartic acid (D) (numbering according to Kabat EU index).

In one example, the first and the second antigen binding domain are fused to each other, optionally via a peptide linker.

In one example, the first and the second antigen binding domain are each a Fab molecule and either (i) the first antigen binding domain is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the second antigen binding domain, or (ii) the second antigen binding domain is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the first antigen binding domain.

In one example, the antibody comprises an Fc domain composed of a first and a second subunit.

In one example, the first, the second and, where present, the third antigen binding domain are each a Fab molecule and the antibody comprises an Fc domain composed of a first and a second subunit; and either (i) the first antigen binding domain is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the second antigen binding domain and the second antigen binding domain is fused at the C-terminus of the Fab heavy chain to the N-terminus of the first subunit of the Fc domain, or (ii) the second antigen binding domain is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the first antigen binding domain and the first antigen binding domain is fused at the C-terminus of the Fab heavy chain to the N-terminus of the first subunit of the Fc domain; and the third antigen binding domain, where present, is fused at the C-terminus of the Fab heavy chain to the N-terminus of the second subunit of the Fc domain.

In one example, the Fc domain is an IgG, particularly an IgG_1, Fc domain. In one example the Fc domain is a human Fc domain. In one example, the Fc comprises a modification promoting the association of the first and the second subunit of the Fc domain. In one example, the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor and/or effector function.

According to a further aspect of the disclosure there is provided an isolated polynucleotide encoding an antibody of the disclosure. In another aspect there is provided a host cell comprising the isolated polynucleotide of the disclosure.

In another aspect there is provided a method of producing an antibody that binds to HLA-A2/MAGE-A4, comprising the steps of (a) culturing the host cell of the disclosure under conditions suitable for the expression of the antibody and optionally (b) recovering the antibody. In another aspect, the disclosure also encompasses an antibody that binds to HLA-A2/MAGE-A4 produced by the method of the disclosure.

In another aspect, the disclosure further provides a pharmaceutical composition comprising the antibody of the disclosure and a pharmaceutically acceptable carrier.

Also encompassed by the disclosure are methods of using the antibody and pharmaceutical composition of the disclosure. In one aspect, the disclosure provides the antibody according to the disclosure or the pharmaceutical composition according to the disclosure for use as a medicament. In one aspect there is provided the antibody according to the disclosure or the pharmaceutical composition according to the disclosure for use in the treatment of a disease. In a specific example, the disease is cancer.

In another aspect, also provided is use of the antibody according to the disclosure or the pharmaceutical composition according to the disclosure in the manufacture of a medicament. In another aspect, also provided is use of the antibody according to the disclosure or the pharmaceutical composition according to the disclosure in the manufacture of a medicament for the treatment of a disease, particularly cancer. The disclosure also provides a method of treating a disease in an individual, comprising administering to said individual an effective amount of the antibody or pharmaceutical composition according to the disclosure. In a specific example, the disease is cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Exemplary configurations of the bispecific antigen binding molecules of the invention. (A, D) Illustration of the "1+1 CrossMab" molecule. (B, E) Illustration of the "2+1 IgG Crossfab" molecule with alternative order of Crossfab and Fab components ("inverted"). (C, F) Illustration of the "2+1 IgG Crossfab" molecule. (G, K) Illustration of the "1+1 IgG Crossfab" molecule with alternative order of Crossfab and Fab components ("inverted"). (H, L) Illustration of the "1+1 IgG Crossfab" molecule. (I, M) Illustration of the "2+1 IgG Crossfab" molecule with two CrossFabs. (J, N) Illustration of the "2+1 IgG Crossfab" molecule with two CrossFabs and alternative order of Crossfab and Fab components ("inverted"). (O, S) Illustration of the "Fab-Crossfab" molecule. (P, T) Illustration of the "Crossfab-Fab" molecule. (Q, U) Illustration of the "$(Fab)_2$-Crossfab" molecule. (R, V) Illustration of the "Crossfab-$(Fab)_2$" molecule. (W, Y) Illustration of the "Fab-$(Crossfab)_2$" molecule. (X, Z) Illustration of the "$(Crossfab)_2$-Fab" molecule. Black dot: optional modification in the Fc domain promoting heterodimerization. ++, --: amino acids of opposite charges optionally introduced in the CH1 and CL domains. Crossfab molecules are depicted as comprising an exchange of VH and VL regions, but may – in aspects wherein no charge modifications are introduced in CH1 and CL domains – alternatively comprise an exchange of the CH1 and CL domains.

Figure 2. Illustration of the T-cell bispecific (TCB) antibody molecules prepared in the Examples. All tested TCB antibody molecules were produced as "2+1 IgG CrossFab, inverted" with charge modifications (VH/VL exchange in CD3 binder, charge modifications in MAGE-A4 binders, EE = 147E, 213E; RK = 123R, 124K).

CLAIMS

1. An antibody that binds to HLA-A2/MAGE-A4, wherein the antibody comprises a first antigen binding domain, comprising

(i) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 25, a HCDR 2 of SEQ ID NO: 26, and a HCDR 3 of SEQ ID NO: 27, and a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 28, a LCDR 2 of SEQ ID NO: 29 and a LCDR 3 of SEQ ID NO: 30;

(ii) a VH comprising a HCDR 1 of SEQ ID NO: 1, a HCDR 2 of SEQ ID NO: 2, and a HCDR 3 of SEQ ID NO: 3, and a VL comprising a LCDR 1 of SEQ ID NO: 4, a LCDR 2 of SEQ ID NO: 5 and a LCDR 3 of SEQ ID NO: 6;

(iii) a VH comprising a HCDR 1 of SEQ ID NO: 41, a HCDR 2 of SEQ ID NO: 42, and a HCDR 3 of SEQ ID NO: 43, and a VL comprising a LCDR 1 of SEQ ID NO: 44, a LCDR 2 of SEQ ID NO: 45 and a LCDR 3 of SEQ ID NO: 46;

(iv) a VH comprising a HCDR 1 of SEQ ID NO: 9, a HCDR 2 of SEQ ID NO: 10, and a HCDR 3 of SEQ ID NO: 11, and a VL comprising a LCDR 1 of SEQ ID NO: 12, a LCDR 2 of SEQ ID NO: 13 and a LCDR 3 of SEQ ID NO: 14;

(v) a VH comprising a HCDR 1 of SEQ ID NO: 17, a HCDR 2 of SEQ ID NO: 18, and a HCDR 3 of SEQ ID NO: 19, and a VL comprising a LCDR 1 of SEQ ID NO: 20, a LCDR 2 of SEQ ID NO: 21 and a LCDR 3 of SEQ ID NO: 22; or

(vi) a VH comprising a HCDR 1 of SEQ ID NO: 33, a HCDR 2 of SEQ ID NO: 34, and a HCDR 3 of SEQ ID NO: 35, and a VL comprising a LCDR 1 of SEQ ID NO: 36, a LCDR 2 of SEQ ID NO: 37 and a LCDR 3 of SEQ ID NO: 38.

2. The antibody of claim 1, wherein the first antigen binding domain comprises

(i) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 31, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 32;

(ii) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 7, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 8;

(iii) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 47, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 48;

(iv) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 15, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 16;

(v) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 23, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 24; or

(vi) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 39, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 40.

3. An antibody that binds to HLA-A2/MAGE-A4, wherein the antibody comprises a first antigen binding domain comprising

(i) a VH comprising the amino acid sequence of SEQ ID NO: 31, and/or a VL comprising the amino acid sequence of SEQ ID NO: 32;

(ii) a VH comprising the amino acid sequence of SEQ ID NO: 7, and/or a VL comprising the amino acid sequence of SEQ ID NO: 8;

(iii) a VH comprising the amino acid sequence of SEQ ID NO: 47, and/or a VL comprising the amino acid sequence of SEQ ID NO: 48;

(iv) a VH comprising the amino acid sequence of SEQ ID NO: 15, and/or a VL comprising the amino acid sequence of SEQ ID NO: 16;

(v) a VH comprising the amino acid sequence of SEQ ID NO: 23, and/or a VL comprising the amino acid sequence of SEQ ID NO: 24; or

(vi) a VH comprising the amino acid sequence of SEQ ID NO: 39, and/or a VL comprising the amino acid sequence of SEQ ID NO: 40.

4. The antibody of any one of the preceding claims, wherein the antibody is a multispecific, particularly a bispecific, antibody.

5. The antibody of any one of the preceding claims, wherein the antibody comprises a second antigen binding domain which binds to a second antigen.

6. The antibody of claim 5, wherein the second antigen is an activating T cell antigen, particularly CD3, most particularly CD3ε.

7. The antibody of claim 5 or 6, wherein the second antigen binding domain comprises

(i) a VH comprising a HCDR 1 of SEQ ID NO: 59, a HCDR 2 of SEQ ID NO: 60, and a HCDR 3 of SEQ ID NO: 61, and a VL comprising a LCDR 1 of SEQ ID NO: 62, a LCDR 2 of SEQ ID NO: 63 and a LCDR 3 of SEQ ID NO: 64; or

(ii) a VH comprising a HCDR 1 of SEQ ID NO: 51, a HCDR 2 of SEQ ID NO: 52, and a HCDR 3 of SEQ ID NO: 53, and a VL comprising a LCDR 1 of SEQ ID NO: 54, a LCDR 2 of SEQ ID NO: 55 and a LCDR 3 of SEQ ID NO: 56.

8. The antibody of any one of claims 5-7, wherein the second antigen binding domain comprises

(i) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 65, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 66; or

(ii) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 57, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 58.

9. The antibody of any one of claims 5-8, wherein the second antigen binding domain comprises

(i) a VH comprising the amino acid sequence of SEQ ID NO: 65, and/or a VL comprising the amino acid sequence of SEQ ID NO: 66;

(ii) a VH comprising the amino acid sequence of SEQ ID NO: 57, and/or a VL comprising the amino acid sequence of SEQ ID NO: 58.

10. The antibody of any one of the preceding claims, wherein the antibody comprises a third antigen binding domain.

11. The antibody of claim 10, wherein the third antigen domain binds to HLA-A2/MAGE-A4.

12. The antibody of claim 10, wherein the third antigen binding domain comprises

(i) a VH comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 25, a HCDR 2 of SEQ ID NO: 26, and a HCDR 3 of SEQ ID NO: 27, and a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 28, a LCDR 2 of SEQ ID NO: 29 and a LCDR 3 of SEQ ID NO: 30;

(ii) a VH comprising a HCDR 1 of SEQ ID NO: 1, a HCDR 2 of SEQ ID NO: 2, and a HCDR 3 of SEQ ID NO: 3, and a VL comprising a LCDR 1 of SEQ ID NO: 4, a LCDR 2 of SEQ ID NO: 5 and a LCDR 3 of SEQ ID NO: 6;

(iii) a VH comprising a HCDR 1 of SEQ ID NO: 41, a HCDR 2 of SEQ ID NO: 42, and a HCDR 3 of SEQ ID NO: 43, and a VL comprising a LCDR 1 of SEQ ID NO: 44, a LCDR 2 of SEQ ID NO: 45 and a LCDR 3 of SEQ ID NO: 46;

(iv) a VH comprising a HCDR 1 of SEQ ID NO: 9, a HCDR 2 of SEQ ID NO: 10, and a HCDR 3 of SEQ ID NO: 11, and a VL comprising a LCDR 1 of SEQ ID NO: 12, a LCDR 2 of SEQ ID NO: 13 and a LCDR 3 of SEQ ID NO: 14;

(v) a VH comprising a HCDR 1 of SEQ ID NO: 17, a HCDR 2 of SEQ ID NO: 18, and a HCDR 3 of SEQ ID NO: 19, and a VL comprising a LCDR 1 of SEQ ID NO: 20, a LCDR 2 of SEQ ID NO: 21 and a LCDR 3 of SEQ ID NO: 22; or

(vi) a VH comprising a HCDR 1 of SEQ ID NO: 33, a HCDR 2 of SEQ ID NO: 34, and a HCDR 3 of SEQ ID NO: 35, and a VL comprising a LCDR 1 of SEQ ID NO: 36, a LCDR 2 of SEQ ID NO: 37 and a LCDR 3 of SEQ ID NO: 38.

13. The antibody of claim 12, wherein the third antigen binding domain comprises

(i) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 31, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 32;

(ii) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 7, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 8;

(iii) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 47, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 48;

(iv) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 15, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 16;

(v) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 23, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 24; or

(vi) a VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 39, and/or a VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 40.

14. The antibody of any one of claims 10-13, wherein the third antigen binding domain is identical to the first antigen binding domain.

15. The antibody of any one of the preceding claims, wherein the first, the second and/or the third antigen binding domain is a Fab molecule.

16. The antibody of any one of claims 5-15, wherein the second antigen binding domain is a Fab molecule wherein the variable domains VL and VH or the constant domains CL and CH1, particularly the variable domains VL and VH, of the Fab light chain and the Fab heavy chain are replaced by each other.

17. The antibody of any one of the preceding claims, wherein the first and, where present, the third antigen binding domain is a conventional Fab molecule.

18. The antibody of any one of the preceding claims, wherein the first and, where present, the third antigen binding domain is a Fab molecule wherein in the constant domain CL the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat) and the amino acid at position 123 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat), and in the constant domain CH1 the amino acid at position 147 is substituted independently by glutamic acid (E), or aspartic acid (D) (numbering according to Kabat EU index) and the amino acid at position 213 is substituted independently by glutamic acid (E), or aspartic acid (D) (numbering according to Kabat EU index).

19. The antibody of any one of claims 5-18, wherein the first and the second antigen binding domain are fused to each other, optionally via a peptide linker.

20. The antibody of any one of claims 5-19, wherein the first and the second antigen binding domain are each a Fab molecule and either (i) the first antigen binding domain is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the second antigen binding domain, or (ii) the second antigen binding domain is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the first antigen binding domain.

21. The antibody of any one of the preceding claims, wherein the antibody comprises an Fc domain composed of a first and a second subunit.

22. The antibody of any one of claims 5-21, wherein the first, the second and, where present, the third antigen binding domain are each a Fab molecule and the antibody comprises an Fc domain composed of a first and a second subunit; and either (i) the first antigen binding domain is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the second antigen binding domain and the second antigen binding domain is fused at the C-terminus of the Fab heavy chain to the N-terminus of the first subunit of the Fc domain, or (ii) the second antigen binding domain is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the first antigen binding domain and the first antigen binding domain is fused at the C-terminus of the Fab heavy chain to the N-terminus of the first subunit of the Fc domain; and the third antigen binding domain, where present, is fused at the C-terminus of the Fab heavy chain to the N-terminus of the second subunit of the Fc domain.

23. The antibody of claims 21 or 22, wherein the Fc domain is an IgG, particularly an IgG_1, Fc domain.

24. The antibody of any one of claims 21-23, wherein the Fc domain is a human Fc domain.

25. The antibody of any one of claims 21-24, wherein the Fc domain is a human IgG_1 Fc domain.

26. The antibody of any one of claims 21-25, wherein the Fc domain comprises a modification promoting the association of the first and the second subunit of the Fc domain.

27. The antibody of any one of claims 21-26, wherein an amino acid residue in the CH3 domain of the first subunit of the Fc domain is replaced with an amino acid residue having a larger side chain volume, thereby generating a protuberance within the CH3 domain of the first subunit which is positionable in a cavity within the CH3 domain of the second subunit, and an amino acid residue in the CH3 domain of the second subunit of the Fc domain is replaced with an amino acid residue having a smaller side chain volume, thereby generating a cavity within the CH3 domain of the second subunit within which the protuberance within the CH3 domain of the first subunit is positionable.

28. The antibody of any one of claims 21-27, wherein in the CH3 domain of the first subunit of the Fc domain the threonine residue at position 366 is replaced with a tryptophan residue (T366W), and in the CH3 domain of the second subunit of the Fc domain the tyrosine residue at position 407 is replaced with a valine residue (Y407V), and optionally in the second subunit of the Fc domain additionally the threonine residue at position 366 is replaced with a serine residue (T366S) and the

leucine residue at position 368 is replaced with an alanine residue (L368A) (numbering according to Kabat EU index).

29. The antibody of claim 28, wherein in the first subunit of the Fc domain additionally the serine residue at position 354 is replaced with a cysteine residue (S354C) or the glutamic acid residue at position 356 is replaced with a cysteine residue (E356C), and in the second subunit of the Fc domain additionally the tyrosine residue at position 349 is replaced by a cysteine residue (Y349C) (numbering according to Kabat EU index).

30. The antibody of any one of claims 21-29, wherein the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor and/or effector function.

31. The antibody of claim 30, wherein the one or more amino acid substitution is at a position selected from the group of E233, L234, L235, N297, P331 and P329, particularly a position selected from the group of L234, L235 and P329 (numbering according to Kabat EU index).

32. The antibody of any one of claims 21-31, wherein each subunit of the Fc domain comprises the amino acid substitutions L234A, L235A and P329G (numbering according to Kabat EU index).

33. The antibody of any one of claims 1-32, comprising

a) a first and a third antigen binding domain that binds to HLA-A2/MAGE-A4, wherein the first and the third antigen binding domain are each a (conventional) Fab molecule comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 31 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 32;

b) a second antigen binding domain that binds to CD3, wherein the second antigen binding domain is Fab molecule wherein the variable domains VL and VH of the Fab light chain and the Fab heavy chain are replaced by each other, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 65 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 66;

c) a human IgG_1 Fc domain composed of a first and a second subunit;

wherein

(i) in the constant domain CL of the first and the third antigen binding domain the amino acid at position 124 is substituted by lysine (K) (numbering according to Kabat) and the amino acid at position 123 is substituted by arginine (R) (numbering according to Kabat), and wherein in the constant domain CH1 of the first and the third antigen binding domain the amino acid at position 147 is substituted by glutamic acid (E) (numbering according to Kabat EU index) and the amino acid at position 213 is substituted by glutamic acid (E) (numbering according to Kabat EU index);

(ii) the first antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the second antigen binding moiety, and the second antigen binding moiety and the third antigen binding moiety are each fused at the C-terminus of the Fab heavy chain to the N-terminus of one of the subunits of the Fc domain; and

(iii) the first subunit of the Fc domain comprises amino acid substitutions S354C and T366W, and the second subunit of the Fc domain comprises amino acid substitutions Y349C, T366S, L368A and Y407V, and each subunit of the Fc domain further comprises the amino acid substitutions L234A, L235A and P329G (numbering according to Kabat EU index).

34. The antibody of any one of claims 1-33, comprising a polypeptide comprising an amino acid sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 68, a polypeptide comprising an amino acid sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 69, a polypeptide (particularly two polypeptides) comprising an amino acid sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 70, and a polypeptide comprising an amino acid sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 72.

35. An isolated polynucleotide encoding the antibody of any one of claims 1-34.

36. A host cell comprising the isolated polynucleotide of claim 35.

37. A method of producing an antibody that binds to HLA-A2/MAGE-A4, comprising the steps of (a) culturing the host cell of claim 36 under conditions suitable for the expression of the antibody and optionally (b) recovering the antibody.

38. An antibody that binds to HLA-A2/MAGE-A4, produced by the method of claim 37.

39. A pharmaceutical composition comprising the antibody of any one of claims 1-34 or 38 and a pharmaceutically acceptable carrier.

40. The antibody of any one of claims 1-34 or 38 or the pharmaceutical composition of claim 39 for use as a medicament.

41. The antibody of any one of claims 1-34 or 38 or the pharmaceutical composition of claim 39 for use in the treatment of a disease.

42. The antibody or the pharmaceutical composition for use of claim 41, wherein the disease is cancer.

43. The antibody or the pharmaceutical composition for use of claim 42, wherein the cancer is a cancer expressing HLA-A2/MAGE-A4.

44. The antibody or the pharmaceutical composition for use of claim 42 or 43, wherein the cancer is a cancer selected from the group consisting of lung cancer, head and neck cancer, bladder cancer, esophageal cancer, skin cancer, gastric cancer and ovarian cancer.

45. Use of the antibody of any one of claims 1-34 or 38 or the pharmaceutical composition of claim 39 in the manufacture of a medicament.

46. Use of the antibody of any one of claims 1-34 or 38 or the pharmaceutical composition of claim 39 in the manufacture of a medicament for the treatment of a disease, particularly cancer.

47. The use of claim 46, wherein the cancer is a cancer expressing HLA-A2/MAGE-A4.

48. The use of claim 46 or 47, wherein the cancer is a cancer selected from the group consisting of lung cancer, head and neck cancer, bladder cancer, esophageal cancer, skin cancer, gastric cancer and ovarian cancer.