

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 WT1 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 bispecific antibodies, that bind HLA-A2/WT1 and have particularly favorable properties for therapeutic purposes.

The present inventors have developed novel antibodies with unexpected, improved properties, that bind to HLA-A2/WT1. In particular, the antibody binds HLA-A2/WT1 with good affinity and remarkable specificity. Furthermore, the inventors have developed bispecific antigen binding molecules that bind to HLA-A2/WT1 and an activating T cell antigen, incorporating the novel HLA-A2/WT1 antibody and combine good efficacy and produceability with low toxicity and favorable pharmacokinetic properties.

In one aspect, the present disclosure provides an antibody that binds to HLA-A2/WT1, wherein the antibody binds an epitope of HLA-A2/WT1, particularly HLA-A2/WT1_{RMF}, comprising at least three amino acid residues of the WT1 peptide in HLA-A2/WT1, particularly the WT1_{RMF} peptide.

In another aspect the present disclosure provides an antibody that binds to HLA-A2/WT1, wherein the antibody comprises

(i) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (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 light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 4, a LCDR 2 of SEQ ID NO: 5 and a LCDR 3 of SEQ ID NO:

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(ii) 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;

(iii) 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;

(iv) a VH comprising a 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 VL comprising a LCDR 1 of SEQ ID NO: 28, a LCDR 2 of SEQ ID NO: 29 and a LCDR 3 of SEQ ID NO: 30;

(v) 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;

(vi) 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;

(vii) a VH comprising a HCDR 1 of SEQ ID NO: 49, a HCDR 2 of SEQ ID NO: 50, and a HCDR 3 of SEQ ID NO: 51, and a VL comprising a LCDR 1 of SEQ ID NO: 52, a LCDR 2 of SEQ ID NO: 53 and a LCDR 3 of SEQ ID NO: 54;

(viii) a VH comprising a HCDR 1 of SEQ ID NO: 57, a HCDR 2 of SEQ ID NO: 58, and a HCDR 3 of SEQ ID NO: 59, and a VL comprising a LCDR 1 of SEQ ID NO: 60, a LCDR 2 of SEQ ID NO: 61 and a LCDR 3 of SEQ ID NO: 62; or

(ix) a VH comprising a HCDR 1 of SEQ ID NO: 65, a HCDR 2 of SEQ ID NO: 66, and a HCDR 3 of SEQ ID NO: 67, and a VL comprising a LCDR 1 of SEQ ID NO: 68, a LCDR 2 of SEQ ID NO: 69 and a LCDR 3 of SEQ ID NO: 70.

In one example, the antibody 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: 7, and 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;

(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: 15, and 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;

(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: 23, and 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;

(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: 31, and 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;

(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: 39, and 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;

(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: 47, and 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;

(vii) 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: 55, and 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: 56;

(viii) 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: 63, and 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: 64; or

(ix) 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: 71, and 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: 72.

In one example, the antibody is an IgG, particularly an IgG₁, antibody. In one example, the antibody is a full-length antibody. In another example, the antibody is an antibody fragment selected from the group of an Fv molecule, a scFv molecule, a Fab molecule, and a F(ab')₂ molecule. In one example, the antibody is a multispecific antibody.

In another aspect, the present disclosure provides a bispecific antigen binding molecule, comprising (a) a first antigen binding moiety that binds to a first antigen, wherein the first antigen is HLA-A2/WT1 and the first antigen binding moiety comprises

(i) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (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 light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 4, a LCDR 2 of SEQ ID NO: 5 and a LCDR 3 of SEQ ID NO:

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(ii) 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;

(iii) a VH comprising a HCDR 1 of SEQ ID NO: 17, a HCDR 2 of SEQ ID NO: 18, and a
10 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;

(iv) a VH comprising a 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 VL comprising a LCDR 1 of SEQ ID NO: 28, a LCDR 2 of SEQ ID NO: 29 and a LCDR 3 of SEQ ID NO: 30;

(v) a VH comprising a HCDR 1 of SEQ ID NO: 33, a HCDR 2 of SEQ ID NO: 34, and a HCDR
15 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;

(vi) a VH comprising a HCDR 1 of SEQ ID NO: 41, a HCDR 2 of SEQ ID NO: 42, and a HCDR
20 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;

(vii) a VH comprising a HCDR 1 of SEQ ID NO: 49, a HCDR 2 of SEQ ID NO: 50, and a HCDR 3 of SEQ ID NO: 51, and a VL comprising a LCDR 1 of SEQ ID NO: 52, a LCDR 2 of SEQ ID NO: 53 and a LCDR 3 of SEQ ID NO: 54;

(viii) a VH comprising a HCDR 1 of SEQ ID NO: 57, a HCDR 2 of SEQ ID NO: 58, and a
25 HCDR 3 of SEQ ID NO: 59, and a VL comprising a LCDR 1 of SEQ ID NO: 60, a LCDR 2 of SEQ ID NO: 61 and a LCDR 3 of SEQ ID NO: 62; or

(ix) a VH comprising a HCDR 1 of SEQ ID NO: 65, a HCDR 2 of SEQ ID NO: 66, and a HCDR 3 of SEQ ID NO: 67, and a VL comprising a LCDR 1 of SEQ ID NO: 68, a LCDR 2 of SEQ ID NO: 69 and a LCDR 3 of SEQ ID NO: 70; and

30 (b) a second antigen binding moiety which specifically binds to a second antigen.

In one example, the first antigen binding moiety 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: 7, and 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: 72.

In one example, the second antigen is CD3, particularly CD3 ϵ . In one example, the second antigen binding moiety comprises a VH comprising a HCDR 1 of SEQ ID NO: 115, a HCDR 2 of SEQ ID NO: 116, and a HCDR 3 of SEQ ID NO: 117, and a VL comprising a LCDR 1 of SEQ ID NO: 118, a LCDR 2 of SEQ ID NO: 119 and a LCDR 3 of SEQ ID NO: 120. In one example, the VH of the second antigen binding moiety comprises 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: 121, and the VL of the second antigen binding moiety comprises 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: 122. In one example, the first and/or the second antigen binding moiety is a Fab molecule. In one example, the second antigen binding moiety 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 antigen binding moiety is a Fab molecule wherein in the constant domain 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 moiety are fused to each other, optionally via a peptide linker. In one example, the first and the second antigen binding moiety are each a Fab molecule and either (i) the second 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 first antigen binding moiety, or (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. In one example, the bispecific antigen binding molecule comprises a third antigen binding moiety. In one example, the third antigen moiety is identical to the first antigen binding moiety. In one example, the bispecific antigen binding molecule 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 moiety are each a Fab molecule; and either (i) the second 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 first antigen binding moiety and the first antigen binding moiety 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 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 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 moiety, 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 IgG₁, Fc domain. In one example, the Fc domain is a human Fc domain.

10 In one example, 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

15 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. 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 another aspect of the disclosure there is provided one or more isolated

20 polynucleotide(s) encoding an antibody or bispecific antigen binding molecule of the disclosure. The disclosure further provides one or more expression vector(s) comprising the isolated polynucleotide(s) of the disclosure, and a host cell comprising the isolated polynucleotide(s) or the expression vector(s) of the disclosure. In another aspect, the present disclosure provides one or more vector, particularly expression vector, comprising the polynucleotide(s) of the disclosure.

25 In another aspect, the present disclosure provides a host cell comprising the polynucleotide(s) of the disclosure or the vector(s) of the disclosure. In some examples the host cell is a eukaryotic cell, particularly a mammalian cell.

In another aspect is provided a method of producing an antibody that binds to HLA-A2/WT1, comprising the steps of a) culturing the host cell of the disclosure under conditions suitable for

30 the expression of the antibody and b) recovering the antibody. In another aspect, the disclosure also encompasses an antibody that binds to HLA-A2/WT1 produced by the method of the disclosure.

In another aspect, the disclosure provides a pharmaceutical composition comprising the antibody or bispecific antigen binding molecule of the disclosure and a pharmaceutically acceptable carrier.

- 5 Also encompassed by the disclosure are methods of using the antibody, bispecific antigen binding molecule and pharmaceutical composition of the disclosure. In another aspect the disclosure provides an antibody, bispecific antigen binding molecule or pharmaceutical composition according to the disclosure

for use as a medicament. In one aspect is provided an antibody, bispecific antigen binding molecule or 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, the present disclosure provides the use of an antibody or bispecific antigen binding molecule according to the disclosure in the manufacture of a medicament for the treatment of a disease. There is also provided a method of treating a disease in an individual, comprising administering to said individual a therapeutically effective amount of a composition comprising the antibody or bispecific antigen binding molecule according to the disclosure in a pharmaceutically acceptable form. In a specific example the disease is cancer. In any of the above examples the individual preferably is a mammal, particularly a human.

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 embodiments 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 WT1 binders, EE = 147E, 213E; RK = 123R, 124K).

Claims

1. An antibody that binds to HLA-A2/WT1, wherein the antibody binds an epitope of HLA-A2/WT1, particularly HLA-A2/WT1_{RMF}, comprising at least three amino acid residues of the WT1 peptide in HLA-A2/WT1, particularly the WT1_{RMF} peptide.
- 5 2. The antibody of claim 1, wherein said at least three amino acid residues are selected from the amino acid residues corresponding to amino acid residues R1, M2, P4, N5, A6 and Y8 of the WT1_{RMF} peptide.
3. An antibody that binds to HLA-A2/WT1, wherein the antibody comprises
 - (i) a heavy chain variable region (VH) comprising a heavy chain complementary determining
10 region (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 light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 4, a LCDR 2 of SEQ ID NO: 5 and a LCDR 3 of SEQ ID NO: 6;
 - (ii) a VH comprising a HCDR 1 of SEQ ID NO: 9, a HCDR 2 of SEQ ID NO: 10, and a HCDR 3
15 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;
 - (iii) 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;
 - 20 (iv) a VH comprising a 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 VL comprising a LCDR 1 of SEQ ID NO: 28, a LCDR 2 of SEQ ID NO: 29 and a LCDR 3 of SEQ ID NO: 30;
 - (v) 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
25 NO: 37 and a LCDR 3 of SEQ ID NO: 38;
 - (vi) 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;

(vii) a VH comprising a HCDR 1 of SEQ ID NO: 49, a HCDR 2 of SEQ ID NO: 50, and a HCDR 3 of SEQ ID NO: 51, and a VL comprising a LCDR 1 of SEQ ID NO: 52, a LCDR 2 of SEQ ID NO: 53 and a LCDR 3 of SEQ ID NO: 54;

(viii) a VH comprising a HCDR 1 of SEQ ID NO: 57, a HCDR 2 of SEQ ID NO: 58, and a HCDR 3 of SEQ ID NO: 59, and a VL comprising a LCDR 1 of SEQ ID NO: 60, a LCDR 2 of SEQ ID NO: 61 and a LCDR 3 of SEQ ID NO: 62; or

(ix) a VH comprising a HCDR 1 of SEQ ID NO: 65, a HCDR 2 of SEQ ID NO: 66, and a HCDR 3 of SEQ ID NO: 67, and a VL comprising a LCDR 1 of SEQ ID NO: 68, a LCDR 2 of SEQ ID NO: 69 and a LCDR 3 of SEQ ID NO: 70.

10 4. The antibody of claim 3, wherein the antibody 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: 7, and 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;

15 (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: 15, and 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;

(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: 23, and 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;

20 (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: 31, and 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;

(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: 39, and 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;

30 (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: 47, and 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;

(vii) 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: 55, and 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: 56;

(viii) 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: 63, and 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: 64; or

(ix) 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: 71, and 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: 72.

5. The antibody of any one of claims 1 to 4, wherein the antibody is an IgG, particularly an IgG₁, antibody.

6. The antibody of any one of claims 1 to 5, wherein the antibody is a full-length antibody.

7. The antibody of any one of claims 1 to 5, wherein the antibody is an antibody fragment selected from the group of an Fv molecule, a scFv molecule, a Fab molecule, and a F(ab')₂ molecule.

8. The antibody of any one of claims 1 to 7, wherein the antibody is a multispecific antibody.

9. A bispecific antigen binding molecule, comprising

(a) a first antigen binding moiety that binds to a first antigen, wherein the first antigen is HLA-A2/WT1 and the first antigen binding moiety comprises

(i) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (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 light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 4, a LCDR 2 of SEQ ID NO: 5 and a LCDR 3 of SEQ ID NO:

6;

- (ii) 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;
- (iii) 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;
- (iv) a VH comprising a 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 VL comprising a LCDR 1 of SEQ ID NO: 28, a LCDR 2 of SEQ ID NO: 29 and a LCDR 3 of SEQ ID NO: 30;
- (v) 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;
- (vi) 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;
- (vii) a VH comprising a HCDR 1 of SEQ ID NO: 49, a HCDR 2 of SEQ ID NO: 50, and a HCDR 3 of SEQ ID NO: 51, and a VL comprising a LCDR 1 of SEQ ID NO: 52, a LCDR 2 of SEQ ID NO: 53 and a LCDR 3 of SEQ ID NO: 54;
- (viii) a VH comprising a HCDR 1 of SEQ ID NO: 57, a HCDR 2 of SEQ ID NO: 58, and a HCDR 3 of SEQ ID NO: 59, and a VL comprising a LCDR 1 of SEQ ID NO: 60, a LCDR 2 of SEQ ID NO: 61 and a LCDR 3 of SEQ ID NO: 62; or
- (ix) a VH comprising a HCDR 1 of SEQ ID NO: 65, a HCDR 2 of SEQ ID NO: 66, and a HCDR 3 of SEQ ID NO: 67, and a VL comprising a LCDR 1 of SEQ ID NO: 68, a LCDR 2 of SEQ ID NO: 69 and a LCDR 3 of SEQ ID NO: 70, and
- (b) a second antigen binding moiety which specifically binds to a second antigen.

10. The bispecific antigen binding molecule of claim 9, wherein the first antigen binding moiety 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: 7, and 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;

(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: 15, and 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;

5 (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: 23, and 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;

10 (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: 31, and 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;

15 (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: 39, and 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;

20 (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: 47, and 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;

(vii) 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: 55, and 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: 56;

25 (viii) 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: 63, and 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: 64; or

30 (ix) 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: 71, and 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: 72.

11. The bispecific antigen binding molecule of claim 9 or 10, wherein the second antigen is CD3, particularly CD3ε.

12. The bispecific antigen binding molecule of claim 11, wherein the second antigen binding moiety comprises

- 5 (i) a VH comprising a HCDR 1 of SEQ ID NO: 115, a HCDR 2 of SEQ ID NO: 116, and a HCDR 3 of SEQ ID NO: 117, and a VL comprising a LCDR 1 of SEQ ID NO: 118, a LCDR 2 of SEQ ID NO: 119 and a LCDR 3 of SEQ ID NO: 120; or
- (ii) a VH comprising a HCDR 1 of SEQ ID NO: 130, a HCDR 2 of SEQ ID NO: 131, and a HCDR 3 of SEQ ID NO: 132, and a VL comprising a LCDR 1 of SEQ ID NO: 133, a LCDR 2
- 10 of SEQ ID NO: 134 and a LCDR 3 of SEQ ID NO: 135.

13. The bispecific antigen binding molecule of claim 12, wherein the second antigen binding moiety 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: 21, and a VL comprising an amino
- 15 acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 22; 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: 136, and a VL comprising an amino
- 20 acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 137.

14. The bispecific antigen binding molecule of any one of claims 9 to 13, wherein the first and/or the second antigen binding moiety is a Fab molecule.

15. The bispecific antigen binding molecule of any one of claims 9 to 14, wherein the second antigen binding moiety is a Fab molecule wherein the variable domains VL and VH or the

25 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.

16. The bispecific antigen binding molecule of any one of claims 9 to 15, wherein the first antigen binding moiety is a Fab molecule wherein in the constant domain the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering

30 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).

17. The bispecific antigen binding molecule of any one of claims 9 to 16, wherein the first and the second antigen binding moiety are fused to each other, optionally via a peptide linker.

18. The bispecific antigen binding molecule of any one of claims 9 to 17, wherein the first and the second antigen binding moiety are each a Fab molecule and wherein either (i) the second 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 first antigen binding moiety, or (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.

19. The bispecific antigen binding molecule of any one of claims 9 to 18, comprising a third antigen binding moiety.

20. The bispecific antigen binding molecule of claim 19, wherein the third antigen moiety is identical to the first antigen binding moiety.

21. The bispecific antigen binding molecule of any one of claims 9 to 20, comprising an Fc domain composed of a first and a second subunit.

22. The bispecific antigen binding molecule of claim 21, wherein the first, the second and, where present, the third antigen binding moiety are each a Fab molecule; and wherein either (i) the second 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 first antigen binding moiety and the first antigen binding moiety 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 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 is fused at the C-terminus of the Fab heavy chain to the N-terminus of the first subunit of the Fc domain; and wherein the third antigen binding moiety, 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 bispecific antigen binding molecule of claim 21 or 22, wherein the Fc domain is an IgG, particularly an IgG₁, Fc domain.

24. The bispecific antigen binding molecule of any one of claims 21 to 23, wherein the Fc domain is a human Fc domain.

5 25. The bispecific antigen binding molecule of any one of claims 21 to 24, 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
10 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.

26. The bispecific antigen binding molecule of any one of claims 21 to 25, wherein in the CH3 domain of the first subunit of the Fc domain the threonine residue at position 366 is
15 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).

20 27. The bispecific antigen binding molecule of claim 26, 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).

25 28. The bispecific antigen binding molecule of any one of claims 21 to 27, wherein the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor and/or effector function.

29. The bispecific antigen binding molecule of claim 28, wherein the one or more amino acid substitution is at a position selected from the group of E233, L234, L235, N297, P331 and P329
30 (numbering according to Kabat EU index).

30. The bispecific antigen binding molecule of any one of claims 21 to 29, wherein each subunit of the Fc domain comprises the amino acid substitutions L234A, L235A and P329G (numbering according to Kabat EU index).

31. The bispecific antigen binding molecule of any one of claims 9 to 30, comprising

- 5 a) a first and a third antigen binding moiety that binds to a first antigen; wherein the first antigen is HLA-A2/WT1 and wherein the first and the second antigen binding moiety are each a (conventional) Fab molecule comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 15 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 16;
- 10 b) a second antigen binding moiety that binds to a second antigen; wherein the second antigen is CD3 and wherein the second antigen binding moiety 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: 136 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 137;
- 15 c) a human IgG₁ 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 moiety under a) 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
- 20 in the constant domain CH1 of the first and the third antigen binding moiety under a) 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 under a) 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 under b), and the
- 25 second antigen binding moiety under b) and the third antigen binding moiety under a) 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 under c); and
- (iii) the first subunit of the Fc domain comprises amino acid substitutions S354C and T366W,
- 30 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 (numberings according to Kabat EU index).

32. The bispecific antigen binding molecule of any one of claims 8 to 31, 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: 123, 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: 125, 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: 139, 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: 140.
33. One or more isolated polynucleotide encoding the antibody or bispecific antigen binding molecule of any one of claims 1 to 32.
34. One or more vector, particularly expression vector, comprising the polynucleotide(s) of claim 33.
35. A host cell comprising the polynucleotide(s) of claim 33 or the vector(s) of claim 34.
36. A method of producing an antibody that binds to HLA-A2/WT1, comprising the steps of
a) culturing the host cell of claim 35 under conditions suitable for the expression of the antibody and b) optionally recovering the antibody.
37. An antibody that binds to HLA-A2/WT1, produced by the method of claim 36.
38. A pharmaceutical composition comprising the antibody or bispecific antigen binding molecule of any one of claims 1 to 32 or 37 and a pharmaceutically acceptable carrier.
39. The antibody or bispecific antigen binding molecule of any one of claims 1 to 32 or 37 or the pharmaceutical composition of claim 38 for use as a medicament.
40. The antibody or bispecific antigen binding molecule of any one of claims 1 to 32 or 37 or the pharmaceutical composition of claim 38 for use in the treatment of a disease.
41. The antibody, bispecific antigen binding molecule or pharmaceutical composition of claim 40, wherein the disease is cancer.
42. Use of the antibody or bispecific antigen binding molecule of any one of claims 1 to 32 or 37 in the manufacture of a medicament for the treatment of a disease.

43. The use of claim 42, wherein said disease is cancer.