comprising the amino acid sequence of SEQ ID NO: 50 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 51;

(b) a second Fab molecule which specifically binds to CD3, wherein the second Fab molecule comprises a heavy chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 5, a heavy chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 6, a light chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 8, a light chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 9 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 10, wherein the variable domains VL and VH of the Fab light chain and the Fab heavy chain of the second Fab molecule, respectively, are replaced by each other, and

(c) a third Fab molecule which specifically binds to CD20, wherein the third Fab molecule comprises a heavy chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 46, a heavy chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 47, a heavy chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 48, a light chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 49, a light chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 50 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 51; and

(d) an Fc domain comprising a first and a second subunit capable of stable association;

wherein:

in the constant domain CL of the first Fab molecule and the third molecule, the amino acid at position 124, according to Kabat, is substituted by lysine (K), arginine (R), or histidine (H), and, in the constant domain CH1 of the first Fab molecule and the third Fab molecule, one or both of the amino acids at positions 147 and 213, according to Kabat EU index, are substituted by glutamic acid (E), or aspartic acid (D); and

wherein in the CH3 domain of the first subunit of the Fc domain, an amino acid residue 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 in the CH3 domain of the second subunit of the Fc domain an amino acid residue 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; and

wherein

(i) the C-terminus of the Fab heavy chain of the first Fab molecule is fused to the N-terminus of the Fab heavy chain of the second Fab molecule, and the C-terminus of the Fab heavy chain of the second Fab molecule and the C-terminus of the Fab heavy chain of the third Fab molecule are each fused to the N-terminus of one of the subunits of the Fc domain, or

(ii) the C-terminus of the Fab heavy chain of the second Fab molecule is fused to the N-terminus of the Fab heavy chain of the first Fab molecule, and the C-terminus of the Fab heavy chain of the first Fab molecule and the C-terminus of the Fab heavy chain of the third Fab molecule are each fused to the N-terminus of one of the subunits of the Fc domain.

According to the disclosure, the second Fab molecule is a crossover Fab molecule wherein the variable regions of the Fab light chain and the Fab heavy chain are exchanged. In particular embodiments, the first (and the third, if any) Fab molecule is a conventional Fab molecule. In a further particular embodiment, not more than one Fab molecule capable of specific binding to an activating T cell antigen is present in the T cell activating bispecific antigen binding molecule

In another aspect, the present disclosure provides a T cell activating bispecific antigen binding molecule comprising:

(a) a first Fab molecule which specifically binds to CD20, wherein the first Fab molecule comprises a heavy chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 46, a heavy chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 47, a heavy chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 48, a light chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 49, a light chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 50 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 51;

(b) a second Fab molecule which specifically binds to CD3, wherein the second Fab molecule comprises a heavy chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 5, a heavy chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 6, a light chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 8, a light chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 9 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 10, and wherein the variable domains VL and VH of the Fab light chain and the Fab heavy chain of the second Fab molecule, respectively, are replaced by each other;

(c) a third Fab molecule which specifically binds to CD20, wherein the third Fab molecule comprises a heavy chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 46, a heavy chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 47, a heavy chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 48, a light chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 49, a light chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 50 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 51; and

(d) an Fc domain comprising a first and a second subunit capable of stable association,

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

wherein in the CH3 domain of the first subunit of the Fc domain, an amino acid residue 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 in the CH3 domain of the second subunit of the Fc domain an amino acid residue 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; and

wherein:

(i) the C-terminus of the Fab heavy chain of the first Fab molecule is fused to the N-terminus of the Fab heavy chain of the second Fab molecule, and the C-terminus of the Fab heavy chain of the second Fab molecule and the C-terminus of the Fab heavy chain of the third Fab molecule are each fused to the N-terminus of one of the subunits of the Fc domain, or

(ii) the C-terminus of the Fab heavy chain of the second Fab molecule is fused to the N-terminus of the Fab heavy chain of the first Fab molecule, and the C-terminus of the Fab heavy chain of the first Fab molecule and the C-terminus of the Fab heavy chain of the third Fab molecule are each fused to the N-terminus of one of the subunits of the Fc domain.

In an even more particular embodiment, the disclosure provides a T cell activating bispecific antigen binding molecule comprising

a) a first Fab molecule which specifically binds to a first antigen;

comprising the amino acid sequence of SEQ ID NO: 48, a light chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 49, a light chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 50 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 51; and

(d) an Fc domain comprising a first and a second subunit capable of stable association,

wherein,

in the constant domain CL of the first Fab molecule and the third Fab molecule, the amino acid at position 124, according to Kabat, is substituted by lysine (K) and the amino acid at position 123, according to Kabat, is substituted by lysine (K) or arginine (R), and in the constant domain CH1 of the first Fab molecule and the third Fab molecule, the amino acids at positions 147 and 213, according to the Kabat EU index, are each substituted by glutamic acid (E); and

wherein in the CH3 domain of the first subunit of the Fc domain, an amino acid residue 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 in the CH3 domain of the second subunit of the Fc domain an amino acid residue 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; and

wherein

the C-terminus of the Fab heavy chain of the first Fab molecule is fused to the N-terminus of the Fab heavy chain of the second Fab molecule, and the C-terminus of the Fab heavy chain of the second Fab molecule and the third Fab molecule are each fused to the N-terminus of one of the subunits of the Fc domain.

The disclosure also provides a T cell activating bispecific antigen binding molecule comprising

a) a first Fab molecule which specifically binds to a first antigen;

b) a second Fab molecule which specifically binds to a second antigen, and wherein the variable domains VL and VH of the Fab light chain and the Fab heavy chain are replaced by each other;

c) a third Fab molecule which specifically binds to the first antigen; and

d) an Fc domain composed of a first and a second subunit capable of stable association;

wherein

(i) the first antigen is CD20 and the second antigen is CD3, particularly CD3 epsilon;

(ii) the first Fab molecule under a) and the third Fab molecule under c) each comprise the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 46, the heavy chain CDR 2 of SEQ ID NO: 47, the heavy chain CDR 3 of SEQ ID NO: 48, the light chain CDR 1 of SEQ ID NO: 49, the light chain CDR 2 of SEQ ID NO: 50 and the light chain CDR 3 of SEQ ID NO: 51, and the second Fab molecule under b) comprises the heavy chain CDR 1 of SEQ ID NO: 4, the heavy chain CDR 2 of SEQ ID NO: 67, the heavy chain CDR 3 of SEQ ID NO: 6, the light chain CDR 1 of SEQ ID NO: 68, the light chain CDR 2 of SEQ ID NO: 9 and the light chain CDR 3 of SEQ ID NO: 10;

(iii) in the constant domain CL of the first Fab molecule under a) and the third Fab molecule under c) 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 lysine (K) or arginine (R), particularly by arginine (R) (numbering according to Kabat), and wherein in the constant domain CH1 of the first Fab molecule under a) and the third Fab molecule under c) 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); and

(iv) the first Fab molecule 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 Fab molecule under b), and the second Fab molecule under b) and the third Fab molecule under c) 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 d).

According to another aspect of the disclosure there is provided one or more isolated polynucleotide(s) encoding a T cell activating 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. According to another aspect of the disclosure, there is provided one or more vector, particularly expression vector, comprising the polynucleotide(s) as defined herein. According to another aspect of the disclosure, there is provided a host cell comprising the polynucleotide(s) as defined herein or the vector(s) as defined herein. In some embodiments the host cell is a eukaryotic cell, particularly a mammalian cell.
There is also provided a method of producing the T cell activating bispecific antigen binding molecule of the disclosure, comprising the steps of a) culturing the host cell of the disclosure under conditions suitable for the expression of the T cell activating bispecific antigen binding molecule and b) recovering the T cell activating bispecific antigen binding molecule. In another aspect, there is provided a method of producing a T cell activating bispecific antigen binding molecule as defined herein, comprising the steps of a) culturing the host cell as defined herein under conditions suitable for the expression of the T cell activating bispecific antigen binding molecule and b) recovering the T cell activating bispecific antigen binding molecule.

Claims

1. A T cell activating bispecific antigen binding molecule comprising:

(a) a first Fab molecule which specifically binds to CD20, wherein the first Fab molecule comprises a heavy chain complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO: 46, a heavy chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 47, a heavy chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 48, a light chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 49, a light chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 50 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 51;

(b) a second Fab molecule which specifically binds to CD3, wherein the second Fab molecule comprises a heavy chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 5, a heavy chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 6, a light chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 8, a light chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 9 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 10, wherein the variable domains VL and VH of the Fab light chain and the Fab heavy chain of the second Fab molecule, respectively, are replaced by each other, and

(c) a third Fab molecule which specifically binds to CD20, wherein the third Fab molecule comprises a heavy chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 46, a heavy chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 47, a heavy chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 48, a light chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 49, a light chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 50 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 51; and

(d) an Fc domain comprising a first and a second subunit capable of stable association;

wherein:

in the constant domain CL of the first Fab molecule and the third Fab molecule, the amino acid at position 124, according to Kabat, is substituted by lysine (K), arginine (R), or histidine (H), and, in the constant domain CH1 of the first Fab molecule and the third Fab molecule, one or both of the amino acids at positions 147 and 213, according to Kabat EU index, are substituted by glutamic acid (E), or aspartic acid (D); and

wherein in the CH3 domain of the first subunit of the Fc domain, an amino acid residue 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 in the CH3 domain of the second subunit of the Fc domain an amino acid residue 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; and

wherein

(i) the C-terminus of the Fab heavy chain of the first Fab molecule is fused to the N-terminus of the Fab heavy chain of the second Fab molecule, and the C-terminus of the Fab heavy chain of the second Fab molecule and the C-terminus of the Fab heavy chain of the third Fab molecule are each fused to the N-terminus of one of the subunits of the Fc domain, or

(ii) the C-terminus of the Fab heavy chain of the second Fab molecule is fused to the N-terminus of the Fab heavy chain of the first Fab molecule, and the C-terminus of the Fab heavy chain of the first Fab molecule and the C-terminus of the Fab heavy chain of the third Fab molecule are each fused to the N-terminus of one of the subunits of the Fc domain.

2. The T cell activating bispecific antigen binding molecule according to claim 1, wherein, in the constant domain CL of the first Fab molecule, the amino acid at position 124, according to Kabat, is substituted by lysine (K), arginine (R) or histidine (H); and

in the constant domain CH1 of the first Fab molecule, one or both of the amino acids at positions 147 and 213, according to Kabat EU index, are substituted by glutamic acid (E), or aspartic acid (D).

3. The T cell activating bispecific antigen binding molecule according to claim 1 or 2, wherein, in the constant domain CH1 of the first Fab molecule, the amino acid at position 147, according to Kabat EU index, is substituted by glutamic acid (E), or aspartic acid (D).

4. The T cell activating bispecific antigen binding molecule according to any one of claims 1-3, wherein, the amino acid at position 123, according to Kabat, is substituted by lysine (K), arginine (R) or histidine (H) in the constant domain CL of the first Fab molecule, and the amino acid at position 213, according to the Kabat EU index, of the constant domain CH1 of the first Fab molecule is substituted by glutamic acid (E), or aspartic acid (D).

5. The T cell activating bispecific antigen binding molecule according to claim 4, wherein, in the constant domain CL of the first Fab molecule, the amino acid at position 124, according to Kabat, is substituted by lysine (K) and the amino acid at position 123, according to Kabat, is substituted by arginine (R), and in the constant domain CH1 of the first Fab molecule, the amino acid at position 147, according to the Kabat EU index, is substituted by glutamic acid (E) and the amino acid at position 213, according to the Kabat EU index, is substituted by glutamic acid (E).

6. The T cell activating bispecific antigen binding molecule according to claim 4, wherein, in the constant domain CL of the first Fab molecule, the amino acid at position 124, according to Kabat, is substituted by lysine (K), and the amino acid at position 123, according to Kabat, is substituted by lysine (K), and in the constant domain CH1 of the first Fab molecule, the amino acid at position 147, according to the Kabat EU index, is substituted by glutamic

7. The T cell activating bispecific antigen binding molecule according to claim 1, wherein the first and the third Fab molecules and the Fc domain are part of an immunoglobulin molecule.

8. A T cell activating bispecific antigen binding molecule comprising:

(a) a first Fab molecule which specifically binds to CD20, wherein the first Fab molecule comprises a heavy chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 46, a heavy chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 47, a heavy chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 48, a light chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 49, a light chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 50 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 51;

(b) a second Fab molecule which specifically binds to CD3, wherein the second Fab molecule comprises a heavy chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 5, a heavy chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 6, a light chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 8, a light chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 9 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 10, and wherein the variable domains VL and VH of the Fab light chain and the Fab heavy chain of the second Fab molecule, respectively, are replaced by each other;

(c) a third Fab molecule which specifically binds to CD20, wherein the third Fab molecule comprises a heavy chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 46, a heavy chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 47, a heavy chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 48, a light chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 49, a light chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 50 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 51; and

(d) an Fc domain comprising a first and a second subunit capable of stable association,

wherein, in the constant domain CL of the first Fab molecule and the third Fab molecule, the amino acid at position 124, according to Kabat, is substituted by lysine (K),

and the amino acid at position 123, according to Kabat, is substituted by arginine (R) or lysine (K), and, in the constant domain CH1 of the first Fab molecule and the third Fab molecule, the amino acid at position 147, according to the Kabat EU index, is substituted by glutamic acid (E) , and the amino acid at position 213, according to the Kabat EU index, is substituted by glutamic acid (E), and

wherein in the CH3 domain of the first subunit of the Fc domain, an amino acid residue 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 in the CH3 domain of the second subunit of the Fc domain an amino acid residue 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; and

wherein:

(i) the C-terminus of the Fab heavy chain of the first Fab molecule is fused to the N-terminus of the Fab heavy chain of the second Fab molecule, and the C-terminus of the Fab heavy chain of the second Fab molecule and the C-terminus of the Fab heavy chain of the third Fab molecule are each fused to the N-terminus of one of the subunits of the Fc domain, or

(ii) the C-terminus of the Fab heavy chain of the second Fab molecule is fused to the N-terminus of the Fab heavy chain of the first Fab molecule, and the C-terminus of the Fab heavy chain of the first Fab molecule and the C-terminus of the Fab heavy chain of the third Fab molecule are each fused to the N-terminus of one of the subunits of the Fc domain.

9. The T cell activating bispecific antigen binding molecule according to any one of the preceding claims, wherein the second Fab molecule comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7.

10. The T cell activating bispecific antigen binding molecule according to claim 8 or 9, wherein the first Fab molecule and the third Fab molecule each comprise a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 30 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 31.

11. A T cell activating bispecific antigen binding molecule comprising:

(a) a first Fab molecule which specifically binds to CD20, wherein the first Fab molecule comprises a heavy chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 46, a heavy chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 47, a heavy chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 48, a light chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 49, a light chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 50 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 51;

b) a second Fab molecule which specifically binds to CD3, wherein the second Fab molecule comprises a heavy chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 5, a heavy chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 6, a light chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 8, a light chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 9 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 10, and wherein the variable domains VL and VH of the Fab light chain and the Fab heavy chain of the second Fab molecule, respectively, are replaced by each other;

(c) a third Fab molecule which specifically binds to CD20, wherein the third Fab molecule comprises a heavy chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 46, a heavy chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 47, a heavy chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 48, a light chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 49, a light chain CDR 2 comprising the amino acid sequence of SEQ ID NO: 50 and a light chain CDR 3 comprising the amino acid sequence of SEQ ID NO: 51; and
(d) an Fc domain comprising a first and a second subunit capable of stable association,

wherein,

in the constant domain CL of the first Fab molecule and the third Fab molecule, the amino acid at position 124, according to Kabat, is substituted by lysine (K) and the amino acid at position 123, according to Kabat, is substituted by lysine (K) or arginine (R), and in the constant domain CH1 of the first Fab molecule and the third Fab molecule, the amino acids at positions 147 and 213, according to the Kabat EU index, are each substituted by glutamic acid (E); and

wherein in the CH3 domain of the first subunit of the Fc domain, an amino acid residue 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 in the CH3 domain of the second subunit of the Fc domain an amino acid residue 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; and

wherein

the C-terminus of the Fab heavy chain of the first Fab molecule is fused to the N-terminus of the Fab heavy chain of the second Fab molecule, and the C-terminus of the Fab heavy chain of the second Fab molecule and the third Fab molecule are each fused to the N-terminus of one of the subunits of the Fc domain.

12. The T cell activating bispecific antigen binding molecule of claim 11, wherein the first Fab molecule and the third Fab molecule each comprise a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 30 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 31.

13. The T cell activating bispecific antigen binding molecule of claim 11, wherein the second Fab molecule comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7.

14. The T cell activating bispecific antigen binding molecule according to any one of the preceding claims, wherein the Fc domain is an IgG.

15. The T cell activating bispecific antigen binding molecule according to any one of the preceding claims, wherein the Fc domain is a human Fc domain.

16. The T cell activating bispecific antigen binding molecule according to any one of the preceding claims, wherein the amino acid residue having a larger side chain volume is selected from the group consisting of arginine (R), phenylalanine (F), tyrosine (Y), and tryptophan (W), and the amino acid residue having a smaller side chain volume is selected from the group consisting of alanine (A), serine (S), threonine (T), and valine (V).

17. The T cell activating bispecific antigen binding molecule according to any one of the preceding claims, wherein, in the CH3 domain of the first subunit of the Fc domain, the threonine residue at position 366, according to the Kabat EU index, 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, according to the Kabat EU index, is replaced with a valine residue (Y407V).

18. The T cell activating bispecific antigen binding molecule according to any one of the preceding claims, wherein, in the first subunit of the Fc domain, the serine residue at position 354, according to the Kabat EU index, is replaced with a cysteine residue (S354C), or the glutamic acid residue at position 356, according to the Kabat EU index, is replaced with a cysteine residue (E356C), and, in the second subunit of the Fc domain, the tyrosine residue at position 349, according to the Kabat EU index, is replaced by a cysteine residue (Y349C).

19. The T cell activating bispecific antigen binding molecule according to any one of the preceding claims, wherein the first subunit of the Fc domain comprises amino acid substitutions S354C and T366W, according to the Kabat EU index, and the second subunit of the Fc domain comprises amino acid substitutions Y349C, T366S, L368A and Y407V.

20. The T cell activating bispecific antigen binding molecule according to any one of the preceding claims, wherein the Fc domain exhibits reduced binding affinity to an Fc receptor and/or reduced effector function, as compared to a native IgG_1 Fc domain.

21. The T cell activating bispecific antigen binding molecule according to any one of the preceding claims, wherein the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor and/or effector function.

22. The T cell activating bispecific antigen binding molecule according to claim 21, wherein the one or more amino acid substitution is at one or more position selected from the group of L234, L235, and P329, according to the Kabat EU index.

23. The T cell activating bispecific antigen binding molecule according to any one of the preceding claims, wherein each subunit of the Fc domain comprises three amino acid substitutions that reduce binding to an activating Fc receptor and/or reduce effector function, wherein the amino acid substitutions are L234A, L235A and P329G, according to the Kabat EU index.

24. The T cell activating bispecific antigen binding molecule of any one of claims 20 to 23, wherein the Fc receptor is an Fcγ receptor.

25. The T cell activating bispecific antigen binding molecule of any one of claims 20 to 24, wherein the effector function is antibody-dependent cell-mediated cytotoxicity (ADCC).

26. The T cell activating bispecific antigen binding molecule according to any one of the preceding claims, wherein the CD3 is CD3 epsilon.

27. The T cell activating bispecific antigen binding molecule according to any one of the preceding claims, wherein the first and the third Fab molecules and the Fc domain are part of an IgG class immunoglobulin.

28. The T cell activating bispecific antigen binding molecule according to claim 11, wherein, in the constant domain CL of the first Fab molecule and the third Fab molecule, the amino acid at position 123, according to Kabat, is substituted by arginine (R).

29. The T cell activating bispecific antigen binding molecule according to claim 14, wherein the Fc domain is an IgG_1 Fc domain or an IgG_4 Fc domain.

30. The T cell activating bispecific antigen binding molecule according to claim 24, wherein, in the second subunit of the Fc domain, the threonine residue at position 366, according to the Kabat EU index, is replaced with a serine residue (T366S), and the leucine residue at position 368, according to the Kabat EU index, is replaced with an alanine residue (L368A).

31. One or more isolated polynucleotide encoding the T cell activating bispecific antigen binding molecule of any one of claims 1 to 30.

32. One or more vector, particularly expression vector, comprising the polynucleotide(s) of claim 31.

33. A host cell comprising the polynucleotide(s) of claim 31 or the vector(s) of claim 32.

34. A method of producing a T cell activating bispecific antigen binding molecule according to any one of claims 1 to 30, comprising the steps of a) culturing the host cell of claim 33 under conditions suitable for the expression of the T cell activating bispecific antigen binding molecule and b) recovering the T cell activating bispecific antigen binding molecule.

35. A pharmaceutical composition comprising the T cell activating bispecific antigen binding molecule of any one of claims 1 to 31 and a pharmaceutically acceptable carrier.

36. The T cell activating bispecific antigen binding molecule of any one of claims 1 to 31or the pharmaceutical composition of claim 50 for use as a medicament.

37. The T cell activating bispecific antigen binding molecule of any one of claims 1 to 31or the pharmaceutical composition of claim 50 for use in the treatment of a disease in an individual in need thereof.

38. The T cell activating bispecific antigen binding molecule or the pharmaceutical composition for use according to claim 37, wherein the disease is cancer.

39. Use of the T cell activating bispecific antigen binding molecule of any one of claims 1 to 31 in the manufacture of a medicament for the treatment of cancer in an individual in need thereof.

40. An *in vitro* method for inducing lysis of a target cell, comprising contacting a target cell with the T cell activating bispecific antigen binding molecule of any one of claims 1-31 in the presence of a T cell.