cell activation and re-direction that combine good efficacy and produceability with low toxicity and favorable pharmacokinetic properties.

Summary

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

(i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3, comprising at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6 and at least one light chain CDR selected from the group of SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10;

(ii) a second antigen binding moiety which is a Fab molecule capable of specific binding to a target cell antigen.

~~In one aspect, there is provided a T cell activating bispecific antigen binding molecule comprising~~

~~(i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3, comprising the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 4, the heavy chain CDR 2 of SEQ ID NO: 5, the heavy chain CDR 3 of SEQ ID NO: 6, the light chain CDR 1 of SEQ ID NO: 8, the light chain CDR 2 of SEQ ID NO: 9 and the light chain CDR 3 of SEQ ID NO: 10;~~

~~(ii) a second antigen binding moiety which is a Fab molecule capable of specific binding to a target cell antigen.~~

In one embodiment the first antigen binding moiety which is a Fab molecule capable of specific binding to CD3 comprises a heavy chain variable region comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to an amino acid sequence selected from the group of: SEQ ID NO: 3, SEQ ID NO: 32 and SEQ ID NO: 33 and a variable light chain comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to an amino acid sequence selected from the group of: SEQ ID NO: 7 and SEQ ID NO: 31.

within the CH3 domain of the second subunit within which the protuberance within the CH3 domain of the first subunit is positionable.

In a particular embodiment 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. In certain embodiments the Fc domain is engineered to have reduced binding affinity to an Fc receptor and/or reduced effector function, as compared to a non-engineered Fc domain. In one embodiment, the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor and/or effector function. In one embodiment, the one or more amino acid substitution in the Fc domain that reduces binding to an Fc receptor and/or effector function is at one or more position selected from the group of L234, L235, and P329 (EU numbering). In particular embodiments, each subunit of the Fc domain comprises three amino acid substitutions that reduce binding to an Fc receptor and/or effector function wherein said amino acid substitutions are L234A, L235A and P329G. In one such embodiment, the Fc domain is an IgG_1 Fc domain, particularly a human IgG_1 Fc domain. In other embodiments, each subunit of the Fc domain comprises two amino acid substitutions that reduce binding to an Fc receptor and/or effector function wherein said amino acid substitutions are L235E and P329G. In one such embodiment, the Fc domain is an IgG_4 Fc domain, particularly a human IgG_4 Fc domain. In one embodiment, the Fc domain of the T cell activating bispecific antigen binding molecule is an IgG_4 Fc domain and comprises the amino acid substitutions L235E and S228P (SPLE).

In one embodiment the Fc receptor is an Fcγ receptor. In one embodiment the Fc receptor is a human Fc receptor. In one embodiment, the Fc receptor is an activating Fc receptor. In a specific embodiment, the Fc receptor is human FcγRIIa, FcγRI, and/or FcγRIIIa. In one embodiment, the effector function is antibody-dependent cell-mediated cytotoxicity (ADCC).

In ~~another~~ one aspect, there is provided a T cell activating bispecific antigen binding molecule comprising

(i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3, comprising the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 4, the heavy chain CDR 2 of SEQ ID NO: 5, the heavy chain CDR 3 of SEQ ID NO: 6, the light chain CDR 1 of SEQ ID NO: 8, the light chain CDR 2 of SEQ ID NO: 9 and the light chain CDR 3 of SEQ ID NO: 10, wherein the first antigen binding moiety is a crossover Fab molecule wherein either the variable or the constant regions, particularly the constant regions, of the Fab light chain and the Fab heavy chain are exchanged;

(ii) a second and a third antigen binding moiety each of which is a Fab molecule capable of specific binding to CEA comprising the heavy chain CDR 1 of SEQ ID NO: 24, the heavy chain CDR 2 of SEQ ID NO: 25, the heavy chain CDR 3 of SEQ ID NO: 26, the light chain CDR 1 of SEQ ID NO: 28, the light chain CDR 2 of SEQ ID NO: 29 and the light chain CDR3 of SEQ ID NO: 30;

(iii) an Fc domain composed of a first and a second subunit capable of stable association,

wherein 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, and wherein the third antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the second subunit of the Fc domain.

~~In another aspect, there is provided a T cell activating bispecific antigen binding molecule comprising~~

~~(i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3, comprising the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 4, the heavy chain CDR 2 of SEQ ID NO: 5, the heavy chain CDR 3 of SEQ ID NO: 6, the light chain CDR 1 of SEQ ID NO: 8, the light chain CDR 2 of SEQ ID NO: 9 and the light chain CDR 3 of SEQ ID NO: 10, wherein the first antigen binding moiety is a crossover Fab molecule wherein either the variable or the constant regions, particularly the constant regions, of the Fab light chain and the Fab heavy chain are exchanged;~~

~~(ii) a second and a third antigen binding moiety each of which is a Fab molecule capable of specific binding to MCSP comprising comprising the heavy chain CDR 1 of SEQ ID NO: 14, the heavy chain CDR 2 of SEQ ID NO: 15, the heavy chain CDR 3 of SEQ ID NO: 16, the light chain CDR 1 of SEQ ID NO: 18, the light chain CDR 2 of SEQ ID NO: 19 and the light chain CDR3 of SEQ ID NO: 20.~~

According to another aspect, there is provided an isolated polynucleotide encoding a T cell activating bispecific antigen binding molecule of the disclosure ~~or a fragment thereof~~. ~~In another aspect, there is~~The disclosure also ~~provided~~ provides a polypeptide encoded by the polynucleotide of the disclosure. In another aspect, there is provided a vector, particularly an expression vector, comprising the polynucleotide of the disclosure. In another aspect, there is provided a host cell comprising the polynucleotide or the vector of the disclosure. In some embodiments the host cell is a eukaryotic cell, particularly a mammalian cell.

In another aspect, there is provided a method of producing the T cell activating bispecific antigen binding molecule capable of specific binding to CD3 and a target cell antigen, 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 T cell activating bispecific antigen binding molecule produced by the method of the disclosure.

In another aspect, there is provided a pharmaceutical composition comprising the T cell activating bispecific antigen binding molecule of the disclosure and a pharmaceutically acceptable carrier.

Also encompassed by the disclosure are methods of using the T cell activating bispecific antigen binding molecule and pharmaceutical composition of the dislcosure. ~~In another aspect, there is provided~~The disclosure provides a T cell activating bispecific antigen binding molecule or a pharmaceutical composition of the disclosure for use as a medicament. In another aspect, there is provided a T cell activating bispecific antigen binding molecule or a pharmaceutical composition according to the disclosure for use in the treatment of a disease in an individual in need thereof. In a specific embodiment the disease is cancer.

~~In another aspect, there is~~ The disclosure provide~~d~~s the use of a T cell activating bispecific antigen binding molecule of the disclosure in the manufacture of a medicament for the treatment of a disease in an individual in need thereof. 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 T cell activating bispecific antigen binding molecule according to the disclosure in a pharmaceutically acceptable form. In a specific embodiment the disease is cancer. In another aspect, there is provided use of a T cell activating bispecific antigen binding molecule of the disclosure in the manufacture of a medicament for the treatment of cancer in an individual in need thereof. In any of the above embodiments the individual preferably is a mammal, particularly a human.

~~In another aspect, there is~~The disclosure also provides a method for inducing lysis of a target cell comprising contacting a target cell with a T cell activating bispecific antigen binding molecule of the disclosure in the presence of a T cell. The target cell may be a tumor cell. The T cell may be a cytotoxic T cell.

Brief Description of the Drawings

FIGURE 1. Exemplary configurations of the T cell activating bispecific antigen binding molecules (TCBs) of the invention. (A) Illustration of the "1+1 IgG Crossfab" molecule. (B) Illustration of the "2+1 IgG Crossfab" molecule. (C) Illustration of the "2+1 IgG Crossfab" molecule with alternative order of Crossfab and Fab components ("inverted"). (D) Illustration of the "1+1 CrossMab" molecule. (E) Illustration of the "2+1 IgG Crossfab, linked light chain" molecule. (F) Illustration of the "1+1 IgG Crossfab, linked light chain" molecule. (G) Illustration of the "2+1 IgG Crossfab, inverted, linked light chain" molecule. (H) Illustration of the "1+1 IgG

Claims

1. A T cell activating bispecific antigen binding molecule comprising

(i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3, comprising the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 4, the heavy chain CDR 2 of SEQ ID NO: 5, the heavy chain CDR 3 of SEQ ID NO: 6, the light chain CDR 1 of SEQ ID NO: 8, the light chain CDR 2 of SEQ ID NO: 9 and the light chain CDR 3 of SEQ ID NO: 10;

(ii) a second antigen binding moiety which is a Fab molecule capable of specific binding to a target cell antigen.

2. The T cell activating bispecific antigen binding molecule of claim 1, wherein the first antigen binding moiety comprises a heavy chain variable region comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to an amino acid sequence selected from the group of: SEQ ID NO: 3, SEQ ID NO: 32 and SEQ ID NO: 33, and a light chain variable region comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to an amino acid sequence selected from the group of: SEQ ID NO: 7 and SEQ ID NO: 31.

3. The T cell activating bispecific antigen binding molecule of any of claims 1 or 2, wherein the first antigen binding moiety comprises a heavy chain variable region 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: 3 and a light chain variable region 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.

4. The T cell activating bispecific antigen binding molecule of any of claims 1 to 3, wherein the second antigen binding moiety is capable of specific binding to Carcinoembryonic Antigen (CEA) and comprises the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 24, the heavy chain CDR 2 of SEQ ID NO: 25, the heavy chain CDR 3 of SEQ ID NO: 26, the light chain CDR 1 of SEQ ID NO: 28, the light chain CDR 2 of SEQ ID NO: 29 and the light chain CDR 3 of SEQ ID NO: 30.

5. The T cell activating bispecific antigen binding molecule of claim 4, wherein the second antigen binding moiety comprises a heavy chain variable region 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 light chain variable region 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: 27.

6. The T cell activating bispecific antigen binding molecule of any of claims 1 to 3, wherein the second antigen binding moiety is capable of specific binding to Melanoma-associated Chondroitin Sulfate Proteoglycan (MCSP) and comprises at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 40, and at least one light chain CDR selected from the group of SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 48, SEQ ID NO: 49 and SEQ ID NO: 50.

7. The T cell activating bispecific antigen binding molecule of claim 6, wherein the second antigen binding moiety comprises the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 14, the heavy chain CDR 2 of SEQ ID NO: 15, the heavy chain CDR 3 of SEQ ID NO: 16, the light chain CDR 1 of SEQ ID NO: 18, the light chain CDR 2 of SEQ ID NO: 19 and the light chain CDR 3 of SEQ ID NO: 20.

8. The T cell activating bispecific antigen binding molecule of claim 6 or 7, wherein the second antigen binding moiety is capable of specific binding to MCSP and comprises a heavy chain variable region comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to an amino acid sequence selected from the group of SEQ ID NO: 13, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 39 and SEQ ID NO: 41, and a light chain variable region comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to an amino acid sequence selected from the group of SEQ ID NO: 17, SEQ ID NO: 43, SEQ ID NO: 46, SEQ ID NO: 47 and SEQ ID NO: 51.

9 .The T cell activating bispecific antigen binding molecule of any one of claims 6 to 8, wherein the second antigen binding moiety comprises a heavy chain variable region 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: 13 and a light chain variable region 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: 17.

10. The T cell activating bispecific antigen binding molecule of any of claims 1 to 9, wherein the first antigen binding moiety is a crossover Fab molecule wherein either the variable or the constant regions of the Fab light chain and the Fab heavy chain are exchanged.

11. The T cell activating bispecific antigen binding molecule of claim 10, wherein the first antigen binding moiety is a crossover Fab molecule wherein the constant regions of the Fab light chain and the Fab heavy chain are exchanged.

12. The T cell activating bispecific antigen binding molecule of any of claims 1 to 11, wherein the second antigen binding moiety is a conventional Fab molecule.

13. The T cell activating bispecific antigen binding molecule of any one of claims 1 to 12, comprising not more than one antigen binding moiety capable of specific binding to CD3.

14. The T cell activating bispecific antigen binding molecule of any one of claims 1 to 13, comprising a third antigen binding moiety which is a Fab molecule capable of specific binding to a target cell antigen.

15. The T cell activating bispecific antigen binding molecule of claim 14, wherein the third antigen binding moiety is a conventional Fab molecule.

16. The T cell activating bispecific antigen binding molecule of claims 14 or 15, wherein the third antigen binding moiety is identical to the second antigen binding moiety.

17. The T cell activating bispecific antigen binding molecule of claim 16, wherein the third antigen binding moiety is an antigen binding moiety capable of specific binding to CEA as defined in claims 4 or 5.

18. The T cell activating bispecific antigen binding molecule of claim 16, wherein the third antigen binding moiety is an antigen binding moiety capable of specific binding to MCSP as defined in any of claims 6 to 9.

19. The T cell activating bispecific antigen binding molecule of any one of claims 1 to 18, wherein the first and the second antigen binding moiety are fused to each other, optionally via a peptide linker.

20. The T cell activating bispecific antigen binding molecule of any one of claims 1 to 19, wherein 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.

21. The T cell activating bispecific antigen binding molecule of any one of claims 1 to 19, wherein 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.

22. The T cell activating bispecific antigen binding molecule of claim 20 or 21, wherein the Fab light chain of the first antigen binding moiety and the Fab light chain of the second antigen binding moiety are fused to each other, optionally via a peptide linker.

23. The T cell activating bispecific antigen binding molecule of any of claims 1 to 22, additionally comprising

(iii) an Fc domain composed of a first and a second subunit capable of stable association.

24. The T cell activating bispecific antigen binding molecule of claim 23, wherein the second antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the first or the second subunit of the Fc domain.

25. The T cell activating bispecific antigen binding molecule of claim 23, wherein the first antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the first or second subunit of the Fc domain.

26. The T cell activating bispecific antigen binding molecule of claim 23, wherein the first and the second 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.

27. The T cell activating bispecific antigen binding molecule of any one of claims 23 to 25, wherein a third antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the first or second subunit of the Fc domain.

28. The T cell activating bispecific antigen binding molecule of claim 27, wherein the second 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 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.~~

~~29. The T cell activating bispecific antigen binding molecule of claim 27, wherein the first 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 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.~~

~~30. The T cell activating bispecific antigen binding molecule of claim 29, wherein the first and the third antigen binding moiety and the Fc domain are part of an immunoglobulin molecule, particularly an IgG class immunoglobulin.~~

Claims

~~3~~1. A T cell activating bispecific antigen binding molecule comprising

(i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3, comprising the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 4, the heavy chain CDR 2 of SEQ ID NO: 5, the heavy chain CDR 3 of SEQ ID NO: 6, the light chain CDR 1 of SEQ ID NO: 8, the light chain CDR 2 of SEQ ID NO: 9 and the light chain CDR 3 of SEQ ID NO: 10, wherein the first antigen binding moiety is a crossover Fab molecule wherein either the variable or the constant regions, particularly the constant regions, of the Fab light chain and the Fab heavy chain are exchanged;

(ii) a second and a third antigen binding moiety each of which is a Fab molecule capable of specific binding to CEA comprising the heavy chain CDR 1 of SEQ ID NO: 24, the heavy chain CDR 2 of SEQ ID NO: 25, the heavy chain CDR 3 of SEQ ID NO: 26, the light chain CDR 1 of SEQ ID NO: 28, the light chain CDR 2 of SEQ ID NO: 29 and the light chain CDR3 of SEQ ID NO: 30;

(iii) an Fc domain composed of a first and a second subunit capable of stable association,

wherein 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, and wherein the third antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the second subunit of the Fc domain.

~~32~~2. The T cell activating bispecific antigen binding molecule of claim ~~31~~1, wherein the first antigen binding moiety comprises a heavy chain variable region 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: 3 and a light chain variable region 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.

~~33~~3. The T cell activating bispecific antigen binding molecule of claim ~~31~~1 or ~~32~~2, wherein the second and the third antigen binding moiety each comprise a heavy chain variable region 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 light chain variable region 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: 27.

~~34~~4. The T cell activating bispecific antigen binding molecule of any one of claims ~~31~~1 to ~~33~~3, comprising

(i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3 comprising 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, wherein the first antigen binding moiety is a crossover Fab molecule wherein either the variable or the

constant regions, particularly the constant regions, of the Fab light chain and the Fab heavy chain are exchanged;

(ii) a second and a third antigen binding moiety each of which is a Fab molecule capable of specific binding to CEA comprising heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 23 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 27.

~~35. A T cell activating bispecific antigen binding molecule comprising~~

~~(i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3, comprising the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 4, the heavy chain CDR 2 of SEQ ID NO: 5, the heavy chain CDR 3 of SEQ ID NO: 6, the light chain CDR 1 of SEQ ID NO: 8, the light chain CDR 2 of SEQ ID NO: 9 and the light chain CDR 3 of SEQ ID NO: 10, wherein the first antigen binding moiety is a crossover Fab molecule wherein either the variable or the constant regions, particularly the constant regions, of the Fab light chain and the Fab heavy chain are exchanged;~~

~~(ii) a second and a third antigen binding moiety each of which is a Fab molecule capable of specific binding to MCSP comprising comprising the heavy chain CDR 1 of SEQ ID NO: 14, the heavy chain CDR 2 of SEQ ID NO: 15, the heavy chain CDR 3 of SEQ ID NO: 16, the light chain CDR 1 of SEQ ID NO: 18, the light chain CDR 2 of SEQ ID NO: 19 and the light chain CDR3 of SEQ ID NO: 20.~~

~~36. The T cell activating bispecific antigen binding molecule of claim 35, wherein the first antigen binding moiety comprises a heavy chain variable region 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: 3 and a light chain variable region 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.~~

~~37. The T cell activating bispecific antigen binding molecule of claim 35 or 36, wherein the second and the third antigen binding moiety each comprise a heavy chain variable region 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: 13 and a light chain variable region 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: 17.~~

~~38. The T cell activating bispecific antigen binding molecule of any one of claims 35 to 37, comprising~~

~~(i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3 comprising 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, wherein the first antigen binding moiety is a crossover Fab molecule wherein either the variable or the constant regions, particularly the constant regions, of the Fab light chain and the Fab heavy chain are exchanged;~~

~~(ii) a second and a third antigen binding moiety each of which is a Fab molecule capable of specific binding to MCSP comprising a heavy chain variable region comprising~~

~~the amino acid sequence of SEQ ID NO: 13 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 17.~~

~~39. The T cell activating bispecific antigen binding molecule of any of claims 31 to 38, further comprising~~

~~(iii) an Fc domain composed of a first and a second subunit capable of stable association,~~

~~wherein 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, and wherein the third antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the second subunit of the Fc domain.~~

~~40~~5. The T cell activating bispecific antigen binding molecule of any one of claims ~~23~~ 1 to ~~30~~ 4 ~~or 39~~, wherein the Fc domain is an IgG, specifically an IgG_1 or IgG_4, Fc domain.

~~41~~6. The T cell activating bispecific antigen binding molecule of any one of claims ~~23~~ 1 to ~~30~~5, ~~39 or 40~~, wherein the Fc domain is a human Fc domain.

~~42~~7. The T cell activating bispecific antigen binding molecule of any one of claims ~~23~~ 1 to ~~30~~6, ~~39, 40 or 41~~, wherein the Fc domain comprises a modification promoting the association of the first and the second subunit of the Fc domain.

~~43~~8. The T cell activating bispecific antigen binding molecule of claim ~~42~~7, 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.

9. The T cell activating bispecific antigen binding molecule of any one of claims 1 to 8, 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 wherein optionally

(a) 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); and/or

(b) in the first subunit of the Fc domain additionally the serine residue at position 354 is replaced with a cysteine residue (S354C), and in the second subunit of the Fc domain additionally the tyrosine residue at position 349 is replaced by a cysteine residue (Y349C) (EU numbering).

~~44~~10. The T cell activating bispecific antigen binding molecule of any one of claims ~~23~~ 1 to ~~30~~ 9~~or 39 to 43~~, 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.

~~45~~11. The T cell activating bispecific antigen binding molecule of any one of claims ~~23~~ 1 to ~~30~~ 10~~or 39 to 44~~, wherein the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor and/or effector function.

~~46~~12. The T cell activating bispecific antigen binding molecule of claim ~~45~~11, wherein said Fc domain is a human IgG1 Fc domain and said one or more amino acid substitution is at one or more position selected from the group of L234, L235, and P329 (EU numbering).

~~47~~13. The T cell activating bispecific antigen binding molecule of any one of claims ~~46~~1 to 12, wherein each subunit of the Fc domain comprises ~~three amino acid substitutions that reduce binding to an activating Fc receptor and/or effector function wherein said~~the amino acid substitutions ~~are~~ L234A, L235A and P329G (EU numbering).

~~48~~14. The T cell activating bispecific antigen binding molecule of any one of claims ~~44~~ 10 to ~~47~~12, wherein the Fc receptor is an Fcγ receptor.

~~49~~15. The T cell activating bispecific antigen binding molecule of any one of claims ~~44~~ 10 to ~~48~~12, wherein the effector function is antibody-dependent cell-mediated cytotoxicity (ADCC).

~~50~~16. The T cell activating bispecific antigen binding molecule of any one of claims ~~31~~ 1 to ~~34~~ 15~~or 39 to 49~~, comprising a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 22, a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 56, a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 57, and a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 58.

~~51. The T cell activating bispecific antigen binding molecule of any one of claims 35 to 49, comprising a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 12, a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 53, a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 54, and a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 55.~~

~~52~~17. An isolated polynucleotide encoding the T cell activating bispecific antigen binding molecule of any one of claims 1 to ~~51~~ 16~~or a fragment thereof~~.

~~53. A polypeptide encoded by the polynucleotide of claim 52.~~

~~54~~18. A vector, particularly an expression vector, comprising the polynucleotide of claim ~~52~~17.

~~55~~19. A host cell comprising the polynucleotide of claim ~~52~~ 17 or the vector of claim ~~54~~18.

~~56~~20. A method of producing the T cell activating bispecific antigen binding molecule capable of specific binding to CD3 and a target cell antigen, comprising the steps of a) culturing the host cell of claim ~~55~~ 19 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.

~~57~~21. A T cell activating bispecific antigen binding molecule produced by the method of claim ~~56~~20.

~~58~~22. A pharmaceutical composition comprising the T cell activating bispecific antigen binding molecule of any one of claims 1 to ~~51~~ 16 or ~~57~~ 21 and a pharmaceutically acceptable carrier.

~~59. The T cell activating bispecific antigen binding molecule of any one of claims 1 to 51 or 57 or the pharmaceutical composition of claim 58 for use as a medicament.~~

~~60~~23. The T cell activating bispecific antigen binding molecule of any one of claims 1 to ~~51~~16 or ~~57~~21 or the pharmaceutical composition of claim ~~58~~22 for use in the treatment of a disease in an individual in need thereof.

~~61~~24. The T cell activating bispecific antigen binding molecule or the pharmaceutical composition of claim ~~60~~23, wherein the disease is cancer.

~~62~~25. Use of the T cell activating bispecific antigen binding molecule of any one of claims 1 to ~~51~~16 or ~~57~~21 in the manufacture of a medicament for the treatment of ~~a disease~~cancer in an individual in need thereof.

~~63. The use of claim 62, wherein said disease is cancer.~~

~~64. A 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 1-51 or 57 in the presence of a T cell.~~