Claims

1. A T cell activating bispecific antigen binding molecule comprising a first and a second antigen binding moiety, one of which is a Fab molecule capable of specific binding to an activating T cell antigen and the other one of which is a Fab molecule capable of specific binding to a target cell antigen, and an Fc domain composed of a first and a second subunit capable of stable association;

wherein the first antigen binding moiety is

(a) a single chain Fab molecule wherein the Fab light chain and the Fab heavy chain are connected by a peptide linker, or

(b) a crossover Fab molecule wherein either the variable or the constant regions of the Fab light chain and the Fab heavy chain are exchanged, and

wherein the first and the second antigen binding moiety are fused to each other, optionally via a peptide linker.

2. The T cell activating bispecific antigen binding molecule of claim 1, comprising not more than one antigen binding moiety capable of specific binding to an activating T cell antigen.

~~3. The T cell activating bispecific antigen binding molecule of claim 1 or 2, wherein the first and the second antigen binding moiety are fused to each other, optionally via a peptide linker.~~

43. The T cell activating bispecific antigen binding molecule of ~~any one of~~ claims 1 ~~to 3~~or 2, 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.

54. The T cell activating bispecific antigen binding molecule of ~~any one of~~ claims 1 ~~to 3~~or 2, 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.

65. The T cell activating bispecific antigen binding molecule of claim ~~4~~ 3 or ~~5~~4, wherein the first antigen binding moiety is a crossover Fab molecule and 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.

~~7~~6. The T cell activating bispecific antigen binding molecule of ~~any one of~~ claims 1 ~~to 3~~or 2, wherein the second antigen binding moiety of the T cell activating bispecific antigen binding molecule is

fused at the C-terminus of the Fab light chain to the N-terminus of the Fab light chain of the first antigen binding moiety.

~~8~~7. The T cell activating bispecific antigen binding molecule of any one of claims 1 ~~to 3, 5~~, 2, 4 or ~~7~~6, wherein the second antigen binding moiety of the T cell activating bispecific antigen binding molecule 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.

~~9~~8. The T cell activating bispecific antigen binding molecule of any one of claims 1 to 43, 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.

~~10. The T cell activating bispecific antigen binding molecule of claim 1 or 2, 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.~~

~~11~~9. The T cell activating bispecific antigen binding molecule of any one of claims 1 to ~~10~~8, comprising a third antigen binding moiety which is a Fab molecule capable of specific binding to a target cell antigen.

~~12~~10. The T cell activating bispecific antigen binding molecule of claim ~~11~~9, wherein the 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.

~~13~~11. The T cell activating bispecific antigen binding molecule of claim ~~11~~9 or ~~12~~10, 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.

~~14~~12. The T cell activating bispecific antigen binding molecule of claim ~~11~~9 or ~~12~~10, 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.

~~15~~13. The T cell activating bispecific antigen binding molecule of claim ~~13~~11, wherein the second and the third antigen binding moiety and the Fc domain are part of an immunoglobulin molecule, particularly an IgG class immunoglobulin.

14. A T cell activating bispecific antigen binding molecule comprising a first antigen binding moiety, a second antigen binding moiety, a third antigen binding moiety, and an Fc domain composed of a first and a second subunit capable of stable association, wherein

(i) the first antigen binding moiety is a Fab molecule capable of specific binding to an activating T cell antigen, and the second and the third antigen binding moiety are each a Fab molecule capable of specific binding to a target cell antigen,

(ii) 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; and

(iii) 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, or

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.

~~16~~15. The T cell activating bispecific antigen binding molecule of any one of the preceding claims, wherein the Fc domain is an IgG, specifically an IgG_1 or IgG_4, Fc domain.

~~17~~16. The T cell activating bispecific antigen binding molecule of any one of the preceding claims, wherein the Fc domain is a human Fc domain.

~~18~~17. The T cell activating bispecific antigen binding molecule of any one of the preceding claims, wherein the Fc domain comprises a modification promoting the association of the first and the second subunit of the Fc domain.

~~19~~18. The T cell activating bispecific antigen binding molecule of claim ~~18~~17, 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.

19. The T cell activating bispecific antigen binding molecule of claim 17 or 18, wherein in the CH3 domain of the first subunit of the Fc domain the threonine residue at position 366 is replaced with a tryptophan residue (T366W), and in the CH3 domain of the second subunit of the Fc domain the tyrosine residue at position 407 is replaced with a valine residue (Y407V), and optionally in the second subunit of the Fc domain additionally the threonine residue at position 366 is replaced with a serine residue (T366S) and the leucine residue at position 368 is replaced with an alanine residue (L368A) (EU numbering).

~~20. The T cell activating bispecific antigen binding molecule of 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 IgG1 Fc domain.~~

~~21~~20. The T cell activating bispecific antigen binding molecule of 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~~21. The T cell activating bispecific antigen binding molecule of claim ~~21~~20, wherein said one or more amino acid substitution is at one or more position selected from the group of L234, L235, and P329 (EU numbering).

~~23~~22. The T cell activating bispecific antigen binding molecule of claim ~~22~~21, 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 amino acid substitutions are L234A, L235A and P329G (EU numbering).

~~24~~23. The T cell activating bispecific antigen binding molecule of any one of claims 20 to ~~23~~22, wherein the Fc receptor is an Fcγ receptor.

~~25~~24. The T cell activating bispecific antigen binding molecule of any one of claims 20 to ~~23~~22, wherein the effector function is antibody-dependent cell-mediated cytotoxicity (ADCC).

~~26~~25. The T cell activating bispecific antigen binding molecule of any one of the preceding claims, wherein the activating T cell antigen is CD3.

~~27~~26. The T cell activating bispecific antigen binding molecule of any one of the preceding claims, wherein the target cell antigen is selected from the group consisting of: Melanoma-associated Chondroitin Sulfate Proteoglycan (MCSP), Epidermal Growth Factor Receptor (EGFR), CD19, CD20, CD33, Carcinoembryonic Antigen (CEA) and Fibroblast Activation Protein (FAP).

~~28~~27. An isolated polynucleotide encoding the T cell activating bispecific antigen binding molecule of any one of claims 1 to ~~27~~26 or a fragment thereof.

~~29. A polypeptide encoded by the isolated polynucleotide of claim 28.~~

~~30~~28. A vector, particularly an expression vector, comprising the isolated polynucleotide of claim ~~28~~27.

~~31~~29. A host cell comprising the isolated polynucleotide of claim 28 or the expression vector of claim ~~30~~28.

~~32~~30. A method of producing the T cell activating bispecific antigen binding molecule of any one of claims 1 to ~~27~~26, comprising the steps of a) culturing the host cell of claim ~~31~~29 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.

~~33. A T cell activating bispecific antigen binding molecule produced by the method of claim 32.~~

~~34~~31. A pharmaceutical composition comprising the T cell activating bispecific antigen binding molecule of any one of claims 1 to ~~27~~26 and a pharmaceutically acceptable carrier.

~~35~~32. The T cell activating bispecific antigen binding molecule of any one of claims 1 to ~~27~~26 or the pharmaceutical composition of claim ~~34~~31 for use as a medicament.

~~36~~33. The T cell activating bispecific antigen binding molecule of any one of claims 1 to ~~27~~26 or the pharmaceutical composition of claim ~~34~~31 for use in the treatment of a disease in an individual in need thereof.

~~37~~34. The T cell activating bispecific antigen binding molecule or the pharmaceutical composition of claim ~~36~~33, wherein the disease is cancer.

~~38~~35. Use of the T cell activating bispecific antigen binding molecule of any one of claims 1 to ~~27~~26 for the manufacture of a medicament for the treatment of ~~a disease in an individual in need thereof~~cancer.

~~39. The use of claim 38, wherein said disease is cancer.~~

~~40~~36. A T cell activating bispecific antigen binding molecule of any one of claims 1-~~27~~26 for use in inducing lysis of a target cell, wherein said target cell is contacted with said T cell activating bispecific antigen binding molecule in the presence of a T cell.