Claims

1. A bispecific antigen binding molecule, comprising a first Fab fragment which specifically binds to a first antigen, a second Fab fragment which specifically binds to a second antigen, and an Fc domain composed of a first and a second subunit capable of stable association; wherein

a) the bispecific antigen binding molecule provides monovalent binding to the first and/or the second antigen,

b) the first Fab fragment, the second Fab fragment and the first Fc domain subunit are fused to each other, ~~and~~

c) in the first and/or the second Fab fragment one of the following replacements is made: (i) the variable domains VL and VH are replaced by each other, or (ii) the constant domains CL and CH1 are replaced by each other~~, or (iii) both the variable and constant domains VL-CL and VH-CH1 are replaced by each other~~,
provided that not the same replacement is made in the first and the second Fab fragment~~.~~, and

d) the bispecific antigen binding molecule does not comprise a single chain Fab fragment.

2. The bispecific antigen binding molecule of claim 1, wherein the first Fab fragment is fused at its C-terminus to the N-terminus of the second Fab fragment, which is in turn fused at its C-terminus to the N-terminus of the first Fc domain subunit.

3. The bispecific antigen binding molecule of claim 2, wherein the first Fab fragment is fused at the C-terminus of its heavy chain to the N-terminus of the heavy chain of the second Fab fragment, which is in turn fused at the C-terminus of its heavy chain to the N-terminus of the first Fc domain subunit.

4. The bispecific antigen binding molecule of claim 1, wherein the second Fab fragment is fused at its C-terminus to the N-terminus of the first Fab fragment, which is in turn fused at its C-terminus to the N-terminus of the first Fc domain subunit.

5. The bispecific antigen binding molecule of claim 4, wherein the second Fab fragment is fused at the C-terminus of its heavy chain to the N-terminus of the heavy chain of the first Fab fragment, which is in turn fused at the C-terminus of its heavy chain to the N-terminus of the first Fc domain subunit.

6. The bispecific antigen binding molecule of claim 3 or 5, wherein additionally the Fab light chain of the first Fab fragment and the Fab light chain of the second Fab fragment are fused to each other, optionally via a peptide linker.

7. The bispecific antigen binding molecule of claim 1, wherein the second Fab fragment is fused at its C-terminus to the N-terminus of the first Fc domain subunit, which is in turn fused at its C-terminus to the N-terminus of the first Fab fragment.

8. The bispecific antigen binding molecule of any one of the preceding claims, wherein the replacement is made in the first Fab fragment.

9. The bispecific antigen binding molecule of any one of the preceding claims, wherein the replacement is a replacement of the variable domains VL and VH by each other.

10. The bispecific antigen binding molecule of any one of the preceding claims, wherein the replacement is a replacement of the constant domains CL and CH1 by each other.

11. The bispecific antigen binding molecule of any one of the preceding claims, ~~essentially~~ consisting of the first Fab fragment, the second Fab fragment, the Fc domain, and optionally one or more peptide linkers.

12. The bispecific antigen binding molecule of any one of claims 1 to 10, comprising a third Fab fragment which specifically binds to the first or the second antigen.

13. The bispecific antigen binding molecule of claim 12, wherein the third Fab fragment is fused to the second Fc domain subunit.

14. The bispecific antigen binding molecule of claim 12 or 13, wherein the third Fab fragment is fused at its C-terminus to the N-terminus of the second Fc domain subunit.

15. The bispecific antigen binding molecule of claim 14, wherein the third Fab fragment is fused at the C-terminus of its heavy chain to the N-terminus of the second Fc domain subunit.

16. The bispecific antigen binding molecule of any one of claims 12 to 15, wherein the third Fab fragment specifically binds to the second antigen.

17. The bispecific antigen binding molecule of any one of claims 12 to 16, wherein the second Fab fragment, the third Fab fragment and the Fc domain are part of an immunoglobulin molecule.

18. The bispecific antigen binding molecule of claim 17, wherein the immunoglobulin molecule is an IgG class immunoglobulin molecule.

19. The bispecific antigen binding molecule of claim 17 or 18, wherein the immunoglobulin molecule is an IgG1 or IgG4 subclass immunoglobulin molecule.

20. The bispecific antigen binding molecule of any one of claims 17 to 19, wherein the immunoglobulin molecule is a human immunoglobulin molecule.

21. The bispecific antigen binding molecule of any one of claims 12 to 20, ~~essentially~~ consisting of a first Fab fragment which specifically binds to the first antigen, an immunoglobulin

molecule which specifically binds to the second antigen, and optionally one or more peptide linkers.

22. The bispecific antigen binding molecule of any one of ~~the preceding~~ claims 12 to 21, wherein the same replacement is made in Fab fragments that specifically bind to the same antigen.

23. The bispecific antigen binding molecule of any one of the preceding claims, providing monovalent binding to the first antigen.

24. The bispecific antigen binding molecule of any one of the preceding claims, wherein a replacement is made only in the first Fab fragment.

~~25. The bispecific antigen binding molecule of any one of the preceding claims, not comprising a single chain Fab fragment.~~

~~26~~25. The 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 second Fc domain subunit.

~~27. The bispecific antigen binding molecule of claim 26~~, 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.

~~28~~26. The bispecific antigen binding molecule of any one of the preceding claims, wherein the Fc domain is an IgG Fc domain.

~~29~~27. The bispecific antigen binding molecule of any one of the preceding claims, wherein the Fc domain is an IgG1 or IgG4 Fc domain.

~~30~~28. The bispecific antigen binding molecule of any one of the preceding claims, wherein the Fc domain is human.

~~31~~29. The bispecific antigen binding molecule of any one of the preceding claims, wherein the Fc domain is (i) engineered to have ~~altered~~ reduced binding affinity to an Fc receptor and/or ~~altered~~ reduced effector function, as compared to a non-engineered Fc domain, wherein the Fc domain comprises an amino acid substitution at a position selected from the group of E233, L234, L235, N297, P331 and P329 (EU numbering); or (ii) engineered to have increased binding affinity to an Fc receptor and/or increased effector function, as compared to a non-engineered Fc domain, wherein the Fc domain comprises an increased

proportion of non-fucosylated oligosaccharides as compared to a non-engineered Fc domain.

~~32~~30. An isolated polynucleotide encoding the bispecific antigen binding molecule of any one of claims 1 to ~~31~~29 ~~or a fragment thereof~~.

~~33~~31. An expression vector comprising the isolated polynucleotide of claim ~~32~~30.

~~34~~32. A host cell comprising the isolated polynucleotide of claim ~~32~~30 or the expression vector of claim ~~33~~31.

~~35~~33. A method for producing ~~the~~ a bispecific antigen binding molecule ~~of any one of claims 1 to 31~~, comprising the steps of a) culturing the host cell of claim ~~30~~32 under conditions suitable for the expression of the bispecific antigen binding molecule and b) recovering the bispecific antigen binding molecule.

~~36~~34. A pharmaceutical composition comprising the bispecific antigen binding molecule of any one of claims 1 to ~~31~~29 and a pharmaceutically acceptable carrier.

~~37~~35. The bispecific antigen binding molecule of any one of claims 1 to ~~31~~29 or the pharmaceutical composition of claim ~~36~~34 for use as a medicament.

~~38~~36. The bispecific antigen binding molecule of any one of claims 1 to ~~31~~29 or the pharmaceutical composition of claim ~~36~~34 for use in the treatment of a disease in an individual in need thereof.

~~39~~37. The bispecific antigen binding molecule or the pharmaceutical composition of claim ~~38~~36, wherein the disease is cancer.

~~40~~38. Use of the bispecific antigen binding molecule of any one of claims 1 to ~~31~~29 for the manufacture of a medicament for the treatment of a disease in an individual in need thereof.

~~41~~39. The use of claim ~~40~~38, wherein said disease is cancer.