

In one 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 GPRC5D and the first antigen binding moiety comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region

5 (HCDR) 1 of SEQ ID NO: 83, a HCDR 2 of SEQ ID NO: 85, and a HCDR 3 of SEQ ID NO: 86, and a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 87, a LCDR 2 of SEQ ID NO: 88 and a LCDR 3 of SEQ ID NO: 89; and

(b) a second antigen binding moiety that binds to a second antigen, wherein the second antigen is

10 CD3 and the second antigen binding moiety comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 98, a HCDR 2 of SEQ ID NO: 99, and a HCDR 3 of SEQ ID NO: 100, and a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 101, a LCDR 2 of SEQ ID NO: 102 and a LCDR 3 of SEQ ID NO: 103,

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

In another example, (i) the VH of the first antigen binding moiety comprises an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 13, and the VL of the first antigen binding moiety comprises an amino acid sequence

Fc domain is an IgG Fc domain. In another example, the Fc domain is an IgG1 Fc domain. In yet another example, the Fc domain is a human Fc domain. In another 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 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 another example, the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor and/or effector function.

In another aspect, the disclosure provides one or more isolated polynucleotide encoding the bispecific antigen binding molecule as described herein. In a further aspect, the disclosure provides one or more vector, particularly expression vector, comprising the polynucleotide(s) as described herein. In another aspect, the disclosure provides a host cell comprising the polynucleotide(s) as described herein or the vector(s) as described herein.

In another aspect, the disclosure provides a method of producing the bispecific antigen binding molecule as described herein, comprising the steps of a) culturing the host cell as described herein under conditions suitable for the expression of the bispecific antigen binding molecule and b) optionally recovering the bispecific antigen binding molecule.

The disclosure provides a bispecific antigen binding molecule that binds to GPRC5D, produced by the method as described herein.

In another aspect, the disclosure provides a pharmaceutical composition comprising the bispecific antigen binding molecule as described herein and a pharmaceutically acceptable carrier.

In another aspect, the disclosure provides the bispecific antigen binding molecule as disclosed herein or the pharmaceutical composition as disclosed herein for use as a medicament.

In another aspect, the disclosure provides the bispecific antigen binding molecule as disclosed herein or the pharmaceutical composition as disclosed herein for use in the treatment of a disease.

In another example, the disclosure provides a bispecific antigen binding molecule or pharmaceutical composition as disclosed herein, wherein the disease is cancer or an autoimmune disease.

In another example, the disclosure provides a bispecific antigen binding molecule or pharmaceutical composition as disclosed herein, wherein the disease is multiple myeloma.

In a further aspect, the disclosure provides use of a bispecific antigen binding molecule as disclosed herein in the manufacture of a medicament for the treatment of a disease selected from cancer or an autoimmune disease.

Claims

1. A bispecific antigen binding molecule, comprising
 - (a) a first antigen binding moiety that binds to a first antigen,
5 wherein the first antigen is GPRC5D and the first antigen binding moiety comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 83, a HCDR 2 of SEQ ID NO: 85, and a HCDR 3 of SEQ ID NO: 86, and a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 87, a LCDR 2 of SEQ ID NO: 88 and a LCDR 3 of SEQ ID
10 NO: 89; and
 - (b) a second antigen binding moiety that binds to a second antigen, wherein the second antigen is CD3 and the second antigen binding moiety comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 98, a HCDR 2 of SEQ ID NO: 99, and a HCDR 3 of SEQ ID NO: 100, and a light chain variable
15 region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 101, a LCDR 2 of SEQ ID NO: 102 and a LCDR 3 of SEQ ID NO: 103, wherein the first and the second antigen binding moiety are fused to each other via a peptide linker.
2. The bispecific antigen binding molecule of claim 1, wherein the VH of the first antigen
20 binding moiety comprises an amino acid sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 48, and wherein the VL of the first antigen binding moiety comprises an amino acid sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 53.
3. The bispecific antigen binding molecule of claim 1 or 2, wherein the VH of the second antigen
25 binding moiety comprises an amino acid sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 104, and the VL of the second antigen binding moiety comprises an amino acid sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 105.
4. The bispecific antigen binding molecule of any one of claims 1 to 3, wherein the first and/or
30 the second antigen binding moiety is a Fab molecule.

5. The bispecific antigen binding molecule of any one of claims 1 to 4, wherein 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.

5 6. The bispecific antigen binding molecule of any one of claims 1 to 5, 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 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
10 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).

7. The bispecific antigen binding molecule of any one of claims 1 to 6, wherein the first and the
15 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.

20 8. The bispecific antigen binding molecule of any one of claims 1 to 7, comprising a third antigen binding moiety.

9. The bispecific antigen binding molecule of claim 8, wherein the third antigen moiety is identical to the first antigen binding moiety.

10. The bispecific antigen binding molecule of any one of claims 1 to 9, comprising an Fc
25 domain composed of a first and a second subunit.

11. The bispecific antigen binding molecule of claim 10, 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
30 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;

5 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.

12. The bispecific antigen binding molecule of claim 10 or 11, wherein the Fc domain is an IgG Fc domain.

13. The bispecific antigen binding molecule of claim 12, wherein the Fc domain is an IgG₁ Fc
10 domain.

14. The bispecific antigen binding molecule of any one of claims 10 to 13, wherein the Fc domain is a human Fc domain.

15. The bispecific antigen binding molecule of any one of claims 10 to 14, wherein an amino acid residue in the CH3 domain of the first subunit of the Fc domain is replaced with an amino
15 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 generating a cavity within the CH3 domain of the second subunit within which the protuberance
20 within the CH3 domain of the first subunit is positionable.

16. The bispecific antigen binding molecule of any one of claims 10 to 15, wherein the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor and/or effector function.

17. The bispecific antigen binding molecule of any one of claims 1 to 16, comprising
25 a polypeptide comprising an amino acid sequence that is at least 95%, 96%, 97%, 98%, or 99% identical to the sequence of SEQ ID NO: 122,
a polypeptide comprising an amino acid sequence that is at least 95%, 96%, 97%, 98%, or 99% identical to the sequence of SEQ ID NO: 123,
a polypeptide comprising an amino acid sequence that is at least 95%, 96%, 97%, 98%, or 99%
30 identical to the sequence of SEQ ID NO: 124, and

a polypeptide comprising an amino acid sequence that is at least 95%, 96%, 97%, 98%, or 99% identical to the sequence of SEQ ID NO: 125.

18. The bispecific antigen binding molecule of any one of claims 1 to 17, comprising a polypeptide comprising the amino acid sequence of SEQ ID NO: 122, a polypeptide comprising
5 the amino acid sequence of SEQ ID NO: 123, a polypeptide comprising the amino acid sequence of SEQ ID NO: 124 and a polypeptide comprising the amino acid sequence of SEQ ID NO: 125.

19. One or more isolated polynucleotide encoding the bispecific antigen binding molecule of any one of claims 1 to 18.

20. One or more vector, particularly expression vector, comprising the polynucleotide(s) of claim
10 19.

21. A host cell comprising the polynucleotide(s) of claim 19 or the vector(s) of claim 20.

22. A method of producing the bispecific antigen binding molecule of any one of claims 1 to 18, comprising the steps of a) culturing the host cell of claim 21 under conditions suitable for the expression of the bispecific antigen binding molecule and b) optionally recovering the bispecific
15 antigen binding molecule.

23. A pharmaceutical composition comprising the bispecific antigen binding molecule of any one of claims 1 to 18 and a pharmaceutically acceptable carrier.

24. The bispecific antigen binding molecule of any one of claims 1 to 18 or the pharmaceutical composition of claim 23 for use as a medicament.

20 25. The bispecific antigen binding molecule of any one of claims 1 to 18 or the pharmaceutical composition of claim 23 for use in the treatment of a disease.

26. The bispecific antigen binding molecule or pharmaceutical composition for use of claim 25, wherein the disease is cancer or an autoimmune disease.

27. The bispecific antigen binding molecule or pharmaceutical composition for use of claim 25,
25 wherein the disease is multiple myeloma.

28. Use of the bispecific antigen binding molecule of any one of claims 1 to 18 in the manufacture of a medicament for the treatment of a disease selected from cancer or an autoimmune disease.

29. The use of claim 28, wherein said disease is multiple myeloma.