

2012. 42(9): p. 953-60; and Cohen, Y., et al., GPRC5D is a promising marker for monitoring the tumor load and to target multiple myeloma cells. Hematology, 2013. 18(6): p. 348-51).

GPRC5D is an orphan receptor with no known ligand or function in human and human cancer.

The GPRC5D encoding gene, which is mapped on chromosome 12p13.3, contains three exons

5 and spans about 9.6 kb (Brauner-Osborne, H., et al., Cloning and characterization of a human orphan family C G-protein coupled receptor GPRC5D. Biochim Biophys Acta, 2001. 1518(3): p. 237-48). The large first exon encodes the seven-transmembrane domain. The biology of GPRC5D is however largely unknown. It has been shown that GPRC5D is involved in keratin formation in hair follicles in animals (Gao, Y., et al., Comparative Transcriptome Analysis of Fetal Skin Reveals Key Genes Related to Hair Follicle Morphogenesis in Cashmere Goats. PLoS One, 2016. 11(3): p. e0151118; and Inoue, S., T. Nambu, and T. Shimomura, The RAIG family member, GPRC5D, is associated with hard-keratinized structures. J Invest Dermatol, 2004. 122(3): p. 565-73).

WO 2018/017786 A2 discloses GPRC5D-specific antibodies or antigen-binding fragments.

15 There exists a need for additional drugs to treat cancer, particularly multiple myeloma. Particularly useful drugs for this purpose include antibodies that bind GPRC5D, in particular bispecific antibodies that bind GPRC5D on target cells and an activating T-cell antigen such as CD3 on T-cells. The simultaneous binding of such an antibody to both of its targets will force a temporary interaction between target cell and T cell, causing activation of any cytotoxic T cell
20 and subsequent lysis of the target cell.

The present invention provides novel antibodies, including bispecific antibodies that specifically bind human GPRC5D. Particularly, the T-cell bispecific antibodies according to the invention targeting GPRC5D have the potency to treat multiple myeloma.

Summary

25 The present inventors have developed a novel antibody with unexpected, improved properties that binds to GPRC5D. Furthermore, the inventors have developed bispecific antigen binding molecules that bind to GPRC5D and an activating T cell antigen, incorporating the novel GPRC5D antibody.

The present disclosure provides an antibody that binds to GPRC5D, wherein the antibody
30 comprises (i) 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: 84, and a HCDR 3 of SEQ ID NO: 86, and a light chain variable region (VL) comprising a light

sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 16; or (iii) the VH 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: 48, and the VL comprises 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: 53; or (iv) the VH 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: 49, and the VL comprises 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: 52; or (v) the VH 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: 57, and the VL comprises 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: 64; or (vi) the VH 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: 58, and the VL comprises 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: 63. Thus, in one aspect, the present disclosure provides an antibody that binds to GPRC5D, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), (i) wherein the VH comprises an amino acid sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 13, and the VL 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: 14; or (ii) wherein the VH 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 the VL 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; or (iii) wherein the VH comprises an amino acid sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 49, and the VL 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: 52. In another example (i) the VH comprises the amino acid sequence of SEQ ID NO: 13, and the VL comprises the amino acid sequence of SEQ ID NO: 14; or (ii) the VH comprises the amino acid sequence of SEQ ID NO: 15, and the VL comprises the amino acid sequence of SEQ ID NO: 16; or (iii) the VH comprises

the amino acid sequence of SEQ ID NO: 48, and the VL comprises the amino acid sequence of SEQ ID NO: 53; or (iv) the VH comprises the amino acid sequence of SEQ ID NO: 49, and the VL comprises the amino acid sequence of SEQ ID NO: 52; or (v) the VH comprises the amino acid sequence of SEQ ID NO: 57, and the VL comprises the amino acid sequence of SEQ ID NO: 64; or (vi) the VH comprises the amino acid sequence of SEQ ID NO: 58, and the VL comprises the amino acid sequence of SEQ ID NO: 63. In another example, the antibody is an IgG, particularly an IgG1, antibody. In one example, the antibody is a full-length antibody. In another example, the antibody is an antibody fragment selected from the group of an Fv molecule, a scFv molecule, a Fab molecule, and a F(ab')₂ molecule. In one example, the antibody is a multispecific antibody.

The 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 (i) 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: 84, and a HCDR 3 of SEQ ID NO: 86, and a light chain variable region

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: 15, and the VL 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 amino acid sequence of SEQ ID NO: 16; or (iii) 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: 48, and the VL 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 amino acid sequence of SEQ ID NO: 53; or (iv) 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: 49, and the VL 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 amino acid sequence of SEQ ID NO: 52; or (v) 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: 57, and the VL 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 amino acid sequence of SEQ ID NO: 64; or (vi) 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: 58, and the VL 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 amino acid sequence of SEQ ID NO: 63. Thus, in another 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 an amino acid sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 13, 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: 14; or 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; or an amino acid

sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 49, 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: 52; and (b) a second antigen binding moiety which specifically binds
5 to a second antigen. In an example, (i) the VH of the first antigen binding moiety comprises an amino acid sequence of SEQ ID NO: 13, and the VL of the first antigen binding moiety comprises an amino acid sequence of SEQ ID NO: 14; or (ii) the VH of the first antigen binding moiety comprises an amino acid sequence of SEQ ID NO: 15, and the VL of the first antigen binding moiety comprises an amino acid sequence of SEQ ID NO: 16; or (iii) the VH of the first
10 antigen binding moiety comprises an amino acid sequence of SEQ ID NO: 48, and the VL of the first antigen binding moiety comprises an amino acid sequence of SEQ ID NO: 53; or (iv) the VH of the first antigen binding moiety comprises an amino acid sequence of SEQ ID NO: 49, and the VL of the first antigen binding moiety comprises an amino acid sequence of SEQ ID NO: 52; or (v) the VH of the first antigen binding moiety comprises an amino acid sequence of
15 SEQ ID NO: 57, and the VL of the first antigen binding moiety comprises an amino acid sequence of SEQ ID NO: 64; or (vi) the VH of the first antigen binding moiety comprises an amino acid sequence of SEQ ID NO: 58, and the VL of the first antigen binding moiety comprises an amino acid sequence of SEQ ID

suitable for the expression of the antibody and b) optionally recovering the antibody. The disclosure provides an antibody that binds to GPRC5D, produced by the method as described herein. Another aspect of the disclosure relates to a pharmaceutical composition comprising the antibody or bispecific antigen binding molecule as described herein and a pharmaceutically acceptable carrier. Another aspect of the disclosure relates to the antibody or bispecific antigen binding molecule as described herein or the pharmaceutical composition as described herein for use as a medicament. Another aspect of the disclosure relates the antibody or bispecific antigen binding molecule as described herein or the pharmaceutical composition as described herein for use in the treatment of a disease. In an example, the disease is cancer, particularly multiple myeloma. Alternatively, the disease is an autoimmune disease, such as systemic lupus erythematosus and/or rheumatoid arthritis.

The disclosure provides the use of the antibody or bispecific antigen binding molecule as described herein in the manufacture of a medicament for the treatment of a disease. The disease is particularly cancer, more particularly multiple myeloma. Alternatively, the disease is an autoimmune disease, such as systemic lupus erythematosus and/or rheumatoid arthritis. Thus, in another aspect, the present disclosure provides use of the antibody or bispecific antigen binding molecule as described herein in the manufacture of a medicament for the treatment of a disease, wherein said disease is cancer, an autoimmune disease, or multiple myeloma.

The disclosure relates to a method of treating a disease, particularly cancer, more particularly multiple myeloma, in an individual, comprising administering to said individual a therapeutically effective amount of a composition comprising the antibody or bispecific antigen binding molecule as described herein in a pharmaceutically acceptable form. Alternatively, the disease is an autoimmune disease, such as systemic lupus erythematosus and/or rheumatoid arthritis. In any of the above examples the individual preferably is a mammal, particularly a human.

Brief Description of the Drawings

Figures 1A-Z. Exemplary configurations of the bispecific antigen binding molecules of the invention. (Fig.1A, Fig.2D) Illustration of the “1+1 CrossMab” molecule. (Fig.1B, Fig.1E) Illustration of the “2+1 IgG Crossfab” molecule with alternative

order of Crossfab and Fab components (“inverted”). (Fig.1C, Fig.1F) Illustration of the “2+1 IgG Crossfab” molecule. (Fig.1G, Fig.1K) Illustration of the “1+1 IgG Crossfab” molecule with alternative order of Crossfab and Fab components (“inverted”). (Fig.1H, Fig.1L) Illustration of the “1+1 IgG Crossfab” molecule. (Fig.1I, Fig.1M) Illustration of the “2+1 IgG Crossfab” molecule with two CrossFabs. (Fig.1J, Fig.1N) Illustration of the “2+1 IgG Crossfab” molecule with

Claims

1. An antibody that binds to GPRC5D, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL),

(i) wherein the VH comprises an amino acid sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 13, and the VL 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: 14; or

(ii) wherein the VH 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 the VL 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; or

(iii) wherein the VH comprises an amino acid sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 49, and the VL 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: 52.

2. The antibody of claim 1, wherein the antibody is an IgG antibody.

3. The antibody of claim 2, wherein the antibody is an IgG1 antibody.

4. The antibody of any one of claims 1 to 3, wherein the antibody is a full-length antibody.

5. The antibody of any one of claims 1 to 3, wherein the antibody is an antibody fragment selected from the group of an Fv molecule, a scFv molecule, a Fab molecule, and a F(ab')₂ molecule.

6. The antibody of any one of claims 1 to 5, wherein the antibody is a multispecific antibody.

7. 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 an amino acid sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 13, 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: 14; or 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; or an amino acid sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 49, 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: 52; and

10 (b) a second antigen binding moiety which specifically binds to a second antigen.

8. The bispecific antigen binding molecule of claim 7, wherein the second antigen is CD3.

9. The bispecific antigen binding molecule of claim 8, wherein the second antigen is CD3ε.

10. The bispecific antigen binding molecule of claim 8 or 9, wherein the second antigen binding moiety comprises a VH comprising a HCDR 1 of SEQ ID NO: 29, a HCDR 2 of SEQ ID NO: 30, and a HCDR 3 of SEQ ID NO: 31, and a VL comprising a LCDR 1 of SEQ ID NO: 32, a LCDR 2 of SEQ ID NO: 33 and a LCDR 3 of SEQ ID NO: 34.

11. The bispecific antigen binding molecule of claim 10, wherein the VH 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: 35, 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: 36.

12. The bispecific antigen binding molecule of any one of claims 7 to 11, wherein the first and/or the second antigen binding moiety is a Fab molecule.

13. The bispecific antigen binding molecule of any one of claims 7 to 12, 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.

14. The bispecific antigen binding molecule of any one of claims 7 to 13, 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 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).

15. The bispecific antigen binding molecule of any one of claims 7 to 14, wherein the first and the second antigen binding moiety are fused to each other, optionally via a peptide linker.

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

17. The bispecific antigen binding molecule of any one of claims 7 to 16, comprising a third antigen binding moiety.

18. The bispecific antigen binding molecule of claim 17, wherein the third antigen moiety is identical to the first antigen binding moiety.

19. The bispecific antigen binding molecule of any one of claims 7 to 18, comprising an Fc domain composed of a first and a second subunit.

20. The bispecific antigen binding molecule of claim 19, 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 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;

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.

21. The bispecific antigen binding molecule of claim 19 or 20, wherein the Fc domain is an IgG Fc domain.

5 22. The bispecific antigen binding molecule of claim 21, wherein the Fc domain is an IgG₁ Fc domain.

23. The bispecific antigen binding molecule of any one of claims 19 to 22, wherein the Fc domain is a human Fc domain.

24. The bispecific antigen binding molecule of any one of claims 19 to 23, wherein an amino
10 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
15 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.

25. The bispecific antigen binding molecule of any one of claims 19 to 24, wherein the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor and/or effector function.

20 26. One or more isolated polynucleotide encoding the antibody or bispecific antigen binding molecule of any one of claims 1 to 25.

27. One or more vector, particularly expression vector, comprising the polynucleotide(s) of claim 26.

28. A host cell comprising the polynucleotide(s) of claim 26 or the vector(s) of claim 27.

25 29. A method of producing an antibody that binds to GPRC5D, comprising the steps of a) culturing the host cell of claim 28 under conditions suitable for the expression of the antibody and b) optionally recovering the antibody.

30. A pharmaceutical composition comprising the antibody or bispecific antigen binding molecule of any one of claims 1 to 25 and a pharmaceutically acceptable carrier.

31. The antibody or bispecific antigen binding molecule of any one of claims 1 to 25 or the pharmaceutical composition of claim 30 for use as a medicament.

5 32. The antibody or bispecific antigen binding molecule of any one of claims 1 to 25 or the pharmaceutical composition of claim 30 for use in the treatment of a disease.

33. The antibody, bispecific antigen binding molecule or pharmaceutical composition for use according to claim 32, wherein the disease is cancer or an autoimmune disease.

10 34. The antibody, bispecific antigen binding molecule or pharmaceutical composition for use according to claim 33, wherein the disease is multiple myeloma.

35. Use of the antibody or bispecific antigen binding molecule of any one of claims 1 to 25 in the manufacture of a medicament for the treatment of a disease, wherein said disease is cancer, an autoimmune disease, or multiple myeloma.