

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

GPRC5D is an orphan receptor with no known ligand and largely unknown biology in men in general and in cancer specifically. The GPRC5D encoding gene, which is mapped on chromosome 12p13.3, contains three exons 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. 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.

Given that all standard-of-care treatments are not able to cure multiple myeloma patients, there is a clear need to develop potent and specific new therapies. One of these approaches includes 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. Upon simultaneous binding of such an antibody to both of its targets, a T-cell synapse will be formed, leading to activation of the (cytotoxic) T cell 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 of the Invention

The present inventors have developed bispecific antigen binding molecules that bind to GPRC5D and an activating T cell antigen, incorporating the novel GPRC5D antibody.

~~In a first aspect the~~ The present invention 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 (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; (ii) 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 NO: 89; (iii) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 90, a HCDR 2 of SEQ ID NO: 91, and a HCDR 3 of SEQ ID NO: 93, and a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 94, a LCDR 2 of SEQ ID NO: 95 and a LCDR 3 of SEQ ID NO: 97; (iv) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 90, a HCDR 2 of SEQ ID NO: 91, and a HCDR 3 of SEQ ID NO: 93, and a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 94, a LCDR 2 of SEQ ID NO: 96 and a LCDR 3 of SEQ ID NO: 97; or (v) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 90, a HCDR 2 of SEQ ID NO: 92, and a HCDR 3 of SEQ ID NO: 93, and a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 94, a LCDR 2 of SEQ ID NO: 95 and a LCDR 3 of SEQ ID NO: 97; 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 (i) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (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 light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 32, a LCDR 2 of SEQ ID NO: 33 and a LCDR 3 of SEQ ID NO: 34; (i) 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; or (ii) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 106, a HCDR 2 of SEQ ID NO: 107, and a HCDR 3 of SEQ ID NO: 108, and a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 109, a LCDR 2 of SEQ ID NO: 110 and a LCDR 3 of SEQ ID NO: 111.

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 In another ~~embodiment~~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

that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 14; or (ii) 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: 15, and the VL of the first antigen binding moiety comprises an amino acid sequence
5 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
10 SEQ ID NO: 53; or (iv) wherein 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 wherein 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
15 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
20 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. In another embodiment example, the VH of the second antigen binding moiety comprises an amino acid sequence (i) that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 35, and the VL of the second
25 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: 36; (ii) that is at least about 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 about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ
30 ID NO: 105; or (iii) that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 112, and the VL of the second 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: 113.

In an [embodimentexample](#), the first and/or the second antigen binding moiety is a Fab molecule. This means, either the first antigen binding moiety may be a Fab molecule, or the second antigen binding moiety may be a Fab molecule, or the first antigen binding moiety and the second antigen binding moiety may be Fab molecules. In another [embodimentexample](#), 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. In another [embodimentexample](#), 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). In another [embodimentexample](#), the first and the second antigen binding moiety are fused to each other, optionally via a peptide linker. In another [embodimentexample](#), 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. In another [embodimentexample](#), the bispecific antigen binding molecule comprises a third antigen binding moiety. In another [embodimentexample](#), the third antigen moiety is identical to the first antigen binding moiety. In another [embodimentexample](#), the bispecific antigen binding molecule comprises an Fc domain composed of a first and a second subunit. In another [embodimentexample](#), 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. In another [embodimentexample](#), the

Fc domain is an IgG Fc domain. In another ~~embodiment~~example, the Fc domain is an IgG1 Fc domain. In yet another ~~embodiment~~example, the Fc domain is a human Fc domain. In another ~~embodiment~~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 ~~embodiment~~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 ~~invention~~disclosure provides one or more isolated polynucleotide encoding the bispecific antigen binding molecule as described herein. In a further aspect, the ~~invention~~disclosure provides one or more vector, particularly expression vector, comprising the polynucleotide(s) as described herein. In another aspect, the ~~invention~~disclosure provides a host cell comprising the polynucleotide(s) as described herein or the vector(s) as described herein.

In another aspect, ~~of the invention~~disclosure provides a method of producing a bispecific antigen binding molecule that binds to GPRC5D, 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.

In another aspect, the ~~invention~~disclosure provides a bispecific antigen binding molecule that binds to GPRC5D, produced by the method ~~of claim 24~~as described herein.

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

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

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

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

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

In a further aspect, the ~~invention~~disclosure provides use of a bispecific antigen binding molecule as ~~disclosed~~disclosed herein in the manufacture of a medicament for the treatment of a disease.

~~In another aspect the invention~~ 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 a 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 ~~embodiments~~ 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 two CrossFabs and alternative order of Crossfab and Fab components (“inverted”). (Fig.1O, Fig.1S) Illustration of the “Fab-Crossfab” molecule. (Fig.1P, Fig.1T) Illustration of the “Crossfab-Fab” molecule. (Fig.1Q, Fig.1U) Illustration of the “(Fab)₂-Crossfab” molecule. (Fig.1R, Fig.1V) Illustration of the “Crossfab-(Fab)₂” molecule. (Fig.1W, Fig.1Y) Illustration of the “Fab-(Crossfab)₂” molecule. (Fig.1X, Fig.1Z) Illustration of the “(Crossfab)₂-Fab” molecule. Black dot: optional modification in the Fc domain promoting heterodimerization. ++, --: amino acids of opposite charges optionally introduced in the CH1 and CL domains. Crossfab molecules are depicted as comprising an exchange of VH and VL regions, but may – in embodiments wherein no charge modifications are introduced in CH1 and CL domains – alternatively comprise an exchange of the CH1 and CL domains.

Figure 2. Analysis of gene expression of tumor targets on plasma cells and B-cells by RNAseq.

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

~~(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 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;~~

~~(ii) 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 NO: 89;~~

~~(iii) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 90, a HCDR 2 of SEQ ID NO: 91, and a HCDR 3 of SEQ ID NO: 93, and a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 94, a LCDR 2 of SEQ ID NO: 95 and a LCDR 3 of SEQ ID NO: 97;~~

~~(iv) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 90, a HCDR 2 of SEQ ID NO: 91, and a HCDR 3 of SEQ ID NO: 93, and a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 94, a LCDR 2 of SEQ ID NO: 96 and a LCDR 3 of SEQ ID NO: 97; or~~

~~(v) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 90, a HCDR 2 of SEQ ID NO: 92, and a HCDR 3 of SEQ ID NO: 93, and a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 94, a LCDR 2 of SEQ ID NO: 95 and a LCDR 3 of SEQ ID NO: 97; 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

~~(i) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (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 light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 32, a LCDR 2 of SEQ ID NO: 33 and a LCDR 3 of SEQ ID NO: 34;~~

~~(i) 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; or~~

~~(ii) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 106, a HCDR 2 of SEQ ID NO: 107, and a HCDR 3 of SEQ ID NO: 108, and a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 109, a LCDR 2 of SEQ ID NO: 110 and a LCDR 3 of SEQ ID NO: 111.~~

2. The bispecific antigen binding molecule of claim 1,

~~(i) wherein 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 wherein 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: 14; or~~

~~(ii) wherein 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: 15, and wherein 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)~~ wherein 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 wherein 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

5 ID NO: 53; ~~or~~

~~(iv) wherein 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 wherein 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~~

10 ID NO: 52; ~~or~~

~~(v) wherein 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 wherein 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~~

15 ID NO: 64; ~~or~~

~~(vi) wherein 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 wherein 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~~

20 ID NO: 63.

3. The bispecific antigen binding molecule of claim 1 or 2, wherein the VH of the second antigen binding moiety comprises an amino acid sequence

~~(i) that is at least about 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 about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 36;~~

25

~~(ii) that is at least about 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 about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 105; ~~or~~~~

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~~(iii) that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 112, and the VL of the second 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: 113.~~

- 5 4. The bispecific antigen binding molecule of any one of claims 1 to 3, wherein the first and/or 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
10 chain and the Fab heavy chain are replaced by each other.
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
15 (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).
- 20 7. The bispecific antigen binding molecule of any one of claims 1 to 6, wherein the first and the second antigen binding moiety are fused to each other, optionally via a peptide linker.
8. The bispecific antigen binding molecule of any one of claims 1 to 7, 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
25 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.
9. The bispecific antigen binding molecule of any one of claims 1 to 8, comprising a third antigen binding moiety.

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

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

5 12. The bispecific antigen binding molecule of claim 11, 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
10 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
15 Fab heavy chain to the N-terminus of the second subunit of the Fc domain.

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

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

20 15. The bispecific antigen binding molecule of any one of claims 11 to 14, wherein the Fc domain is a human Fc domain.

16. The bispecific antigen binding molecule of any one of claims 11 to 15, wherein 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
25 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.

17. The bispecific antigen binding molecule of any one of claims 11 to 16, wherein the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor and/or effector function.

18. The bispecific antigen binding molecule of any one of claims 1 to 17, comprising
5 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,
10 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: 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~~19. One or more isolated polynucleotide encoding the bispecific antigen binding molecule of any one of claims 1 to ~~17~~18.

15 ~~19~~20. One or more vector, particularly expression vector, comprising the polynucleotide(s) of claim ~~18~~19.

~~20~~21. A host cell comprising the polynucleotide(s) of claim ~~18-19~~ or the vector(s) of claim ~~19~~20.

~~21~~22. A method of producing a bispecific antigen binding molecule that binds to GPRC5D, comprising the steps of a) culturing the host cell of claim ~~20-21~~ under conditions suitable for the
20 expression of the bispecific antigen binding molecule and b) optionally recovering the bispecific antigen binding molecule.

~~22~~23. A bispecific antigen binding molecule that binds to GPRC5D, produced by the method of claim ~~21~~22.

~~23~~24. A pharmaceutical composition comprising the bispecific antigen binding molecule of any
25 one of claims 1 to ~~17-18~~ or ~~22-23~~ and a pharmaceutically acceptable carrier.

~~24~~25. The bispecific antigen binding molecule of any one of claims 1 to ~~17-18~~ or ~~22-23~~ or the pharmaceutical composition of claim ~~23-24~~ for use as a medicament.

~~2526~~. The bispecific antigen binding molecule of any one of claims 1 to ~~17-18~~ or ~~22-23~~ or the pharmaceutical composition of claim ~~23-24~~ for use in the treatment of a disease.

~~2627~~. The bispecific antigen binding molecule or pharmaceutical composition for use of claim ~~2526~~, wherein the disease is cancer or an autoimmune disease.

5 ~~2728~~. The bispecific antigen binding molecule or pharmaceutical composition for use of claim ~~2526~~, wherein the disease is multiple myeloma.

~~2829~~. Use of the bispecific antigen binding molecule of any one of claims 1 to ~~17-18~~ or ~~22-23~~ in the manufacture of a medicament for the treatment of a disease.

10 ~~29. A method of treating a disease in an individual, comprising administering to said individual a therapeutically effective amount of a composition comprising the bispecific antigen binding molecule of any one of claims 1 to 17 or 22 in a pharmaceutically acceptable form.~~

30. The use of claim ~~2829 or the method of claim 29~~, wherein said disease is cancer or an autoimmune disease.

31. The use of claim ~~2829 or the method of claim 29~~, wherein said disease is multiple myeloma.