

Claims

1. An isolated antibody, or an antigen-binding fragment thereof, that binds specifically to GPRC5D comprising:

a heavy chain complementarity determining region (CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 8, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 12, and

a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 15, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 18, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 21.

2. The isolated antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment comprises a variable heavy chain (VH) region comprising the amino acid sequence of SEQ ID NO: 55 and a variable light chain (VL) region comprising the amino acid sequence of SEQ ID NO: 58.

3. The isolated antibody or antigen-binding fragment of claim 1 or claim 2, further comprising the amino acid sequence of SEQ ID NO: 59.

4. The isolated antibody or antigen-binding fragment of any one of claim 1 to 3, wherein the isolated antibody or antigen-binding fragment binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 22.

5. The isolated antibody or antigen-binding fragment of any one of claim 1 to 4, wherein the antibody or antigen-binding fragment is a human antibody or antigen-binding fragment.

6. The isolated antibody or antigen-binding fragment of any one of claim 1 to 5, wherein the antibody or antigen-binding fragment is recombinant.

7. The isolated antibody or antigen-binding fragment of any one of claim 1 to 6, wherein the antigen binding fragment is a Fab fragment, a Fab2 fragment, or a single chain antibody.

8. The isolated antibody or antigen-binding fragment of any one of claim 1 to 7, wherein the antibody or antigen-binding fragment thereof are of IgG1, IgG2, IgG3, or IgG4 isotype,

optionally wherein the antibody or antigen-binding fragment further comprises an S228P substitution, an L234A substitution, and an L235A substitution in its Fc region.

9. The isolated antibody or antigen-binding fragment of any one of claim 1 to 8, wherein the antibody or antigen-binding fragment is of IgG1 or an IgG4 isotype, optionally wherein;

- i. the IgG1 has a K409R substitution in its Fc region;
- ii. the IgG1 has an F405L substitution in its Fc region; or
- iii. IgG4 has an F405L substitution and an R409K substitution in its Fc region.

10. The isolated antibody or antigen-binding fragment of any one of claims 1 to 9, wherein the antibody or antigen-binding fragment specifically binds human GPRC5D and cross reacts to cynomolgus monkey GPRC5D.

11. The isolated antibody or antigen-binding fragment of any one of claims 1 to 9, wherein the antibody or antigen-binding fragment induces ADCC *in vitro* with an EC50 of less than about 28 nM.

12. An isolated cell expressing the antibody, or antigen-binding fragment thereof, of any one of claims 1 to 11.

13. The isolated cell of claim 12, wherein the cell is a hybridoma.

14. The isolated cell of claim 12 or claim 13, wherein the antibody or antigen-binding fragment thereof, is recombinantly produced.

15. An isolated bispecific GPRC5D x CD3 antibody comprising:

- a) a first heavy chain (HC1);
- b) a second heavy chain (HC2);
- c) a first light chain (LC1); and
- d) a second light chain (LC2),

wherein the HC1 and the LC1 pair to form a first antigen-binding site that specifically binds CD3, and the HC2 and the LC2 pair to form a second antigen-binding site that specifically binds GPRC5D,

wherein the HC1 comprises a VH region comprising the amino acid sequence of SEQ

ID NO: 25 and the LC1 comprises a VL region comprising the amino acid sequence of SEQ ID NO: 26, and wherein the HC2 comprises a VH region comprising the amino acid sequence of SEQ ID NO: 55 and the LC2 comprises a VL region comprising the amino acid sequence of SEQ ID NO: 58.

16. The GPRC5D x CD3 bispecific antibody of claim 15 wherein the GPRC5D binding portion of the bispecific antibody further comprises the amino acid sequence of SEQ ID NO: 59.

17. The GPRC5D x CD3 bispecific antibody of claim 39 or claim 40, wherein the CD3 binding portion of the bispecific antibody further comprises the amino acid sequence of SEQ ID NO: 59 comprising a F405L and a R409K substitution.

18. The GPRC5D x CD3 bispecific antibody of any one of claims 15 to 17, wherein the antibody is of IgG1, IgG2, IgG3, or IgG4 isotype.

19. The GPRC5D x CD3 bispecific antibody of claims 18, wherein, the antibody is of IgG4 isotype.

20. The GPRC5D x CD3 bispecific antibody of any one of claims 15 to 19, wherein the antibody or bispecific binding fragment thereof binds GPRC5D on the surface of human myeloma cells.

21. The GPRC5D x CD3 bispecific antibody of any one of claims 15 to 20, wherein the antibody or bispecific binding fragment thereof binds GPRC5D on the surface of human multiple myeloma cells.

22. The GPRC5D x CD3 bispecific antibody of any one of claims 15 to 21, wherein the antibody or bispecific binding fragment induces human T cell activation *in vitro* with an EC₅₀ of less than about 0.22 nM.

23. The GPRC5D x CD3 bispecific antibody of any one of claims 15 to 22, wherein the antibody or bispecific binding fragment induces T-cell dependent cytotoxicity of GPRC5D-expressing cells *in vitro* with an EC₅₀ of less than about 0.89 nM.

24. An isolated cell expressing the GPRC5D x CD3 bispecific antibody of any one of claims 15 to 23.
25. The isolated cell of claim 24, wherein the cell is a hybridoma.
26. The isolated cell of claim 24 or 25, wherein the antibody is recombinantly produced.
27. Use of the GPRC5D x CD3 bispecific antibody of any one of claims 15 to 23 for the manufacture of a medicament for treating a subject having cancer.
28. Use of a GPRC5D x CD3 bispecific antibody of any one of claims 15 to 23 for the manufacture of a medicament for inhibiting growth or proliferation of cancer cells.
29. Use of the GPRC5D x CD3 bispecific antibody of any one of claims 15 to 23 for the manufacture of a medicament for redirecting a T cell to a GPRC5D-expressing cancer cell.
30. The use of any one of claims 27 to 29, wherein the cancer is a hematological cancer.
31. The use of claim 30, wherein the hematological cancer is a GPRC5D-expressing B cell cancer.
32. The use of claim 31, wherein the GPRC5D-expressing B cell cancer is multiple myeloma.
33. The use of any one of claims 27 to 29, wherein the medicament is adapted to be administrable with a second therapeutic agent.
34. The use of claim 57, wherein the second therapeutic agent is a chemotherapeutic agent or a targeted anti-cancer therapy.
35. The use of claim 34, wherein the chemotherapeutic agent is cytarabine, an anthracycline, histamine dihydrochloride, or interleukin 2.

36. The use of claim 34, wherein the second therapeutic agent is adapted to be administered to said subject simultaneously with, sequentially, or separately from the medicament.
37. A pharmaceutical composition comprising the GPRC5D x CD3 bispecific antibody of any one of claims 15 to 23 and a pharmaceutically acceptable carrier.
38. A method for generating the GPRC5D x CD3 bispecific antibody of any one of claims 15 to 23 by culturing the isolated cell any one of claims 24 to 26.
39. One or more isolated synthetic polynucleotides encoding the HC1, the HC2, the LC1 and the LC2 of the GPRC5D x CD3 bispecific antibody of any one of claims 15 to 23.
40. A kit comprising the GPRC5D x CD3 bispecific antibody of any one of claims 15 to 23 and/or the one or more polynucleotides as defined in claim 39, and packaging for the same.
41. An isolated antibody that binds specifically to GPRC5D comprising:
a heavy chain comprising a variable heavy (VH) chain region comprising the amino acid sequence of SEQ ID NO: 55, and
a light chain comprising a variable light (VL) chain region comprising the amino acid sequence of SEQ ID NO: 58,
wherein the antibody is an IgG4 isotype.
42. The isolated antibody of claim 41, wherein the heavy chain further comprises the amino acid sequence of SEQ ID NO: 59.
43. An isolated GPRC5D x CD3 bispecific antibody comprising:
a GPRC5D binding portion comprising:
a heavy chain comprising a variable heavy (VH) chain region comprising the amino acid sequence of SEQ ID NO: 55, and
a light chain comprising a variable light (VL) chain region comprising the amino acid sequence of SEQ ID NO: 58; and

a CD3 binding portion comprising a heavy chain comprising SEQ ID NO: 99 and a light chain comprising SEQ ID NO: 100, wherein the antibody is an IgG4 isotype.

44. The isolated GPRC5D x CD3 bispecific antibody of claim 43, wherein the GPRC5D heavy chain further comprises the amino acid sequence of SEQ ID NO: 59.