

Claims:

1. An isolated antibody, or an antigen-binding fragment thereof, that binds specifically to GPRC5D comprising a heavy chain CDR1 having the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 8, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 12, and a light chain CDR1 having the amino acid sequence of SEQ ID NO: 15, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 18, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 21.
2. The antibody of claim 1, wherein the antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region of SEQ ID NO: 55 and a variable light (VL) chain region of SEQ ID NO: 58.
3. The antibody or antigen-binding fragment of any one of claims 1 or 2 wherein;
 - a. the antibody or antigen-binding fragment thereof binds to a polypeptide having the amino acid sequence of SEQ ID NO: 22;
 - b. the antibody or antigen-binding fragment is a human antibody or antigen-binding fragment;
 - c. the antibody or antigen-binding fragment is recombinant;
 - d. the antigen binding fragment is a Fab fragment, a Fab2 fragment, or a single chain antibody;
 - e. the antibody or antigen-binding fragment thereof are of IgG1, IgG2, IgG3, or IgG4 isotype;
 - f. the antibody or antigen-binding fragment is an 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;

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

h. the antibody or antigen-binding fragment thereof specifically binds human GPRC5D and cross reacts to cynomolgus monkey GPRC5D; and/or

i. the antibody or antigen-binding fragment induces ADCC *in vitro* with an EC₅₀ of less than about 28 nM.

4. An isolated GPRC5D x CD3 bispecific 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, or a GPRC5D x CD3 -bispecific binding fragment thereof, wherein HC1 comprises SEQ ID NO: 25 and LC1 comprises SEQ ID NO: 26, and wherein HC2 comprises SEQ ID NO: 55 and LC2 comprises SEQ ID NO: 58.

5. The GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 4 wherein:

a. the antibody or bispecific binding fragment are of IgG1, IgG2, IgG3, or IgG4 isotype; optionally wherein, the antibody or bispecific binding fragment is IgG4 isotype;

b. the antibody or bispecific binding fragment thereof binds GPRC5D on the surface of human myeloma cells;

c. the antibody or bispecific binding fragment thereof binds GPRC5D on the surface of human multiple myeloma cells;

d. the antibody or bispecific binding fragment induces human T cell activation *in vitro* with an EC₅₀ of less than about 0.22 nM; and/or

- e. 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.
6. An isolated cell expressing the antibody or bispecific binding fragment or antigen binding fragment of any one of claims 1 to 5, optionally wherein;
- a. the cell is a hybridoma; or
 - b. the antibody or bispecific binding fragment or antigen binding fragment is recombinantly produced.
7. A GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 4 for use in the treatment of cancer, wherein a patient is administered a therapeutically effective amount of the GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 4 for a time sufficient to treat cancer.
8. A GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 4 for use in a method for inhibiting growth or proliferation of cancer cells, said method comprising:
- administering a therapeutically effective amount of the GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 4 to inhibit the growth or proliferation of cancer cells.
9. A GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 4 for use in a method of redirecting a T cell to a GPRC5D-expressing cancer cell, said method comprising:
- administering a therapeutically effective amount of the GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 4 to redirect a T cell to a cancer.
10. The GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 4 for use in the method according to claims 7, 8, or 9 wherein the cancer is a hematological cancer, optionally wherein the hematological cancer is a GPRC5D-expressing B cell cancer, such as wherein the GPRC5D-expressing B cell cancer is multiple myeloma.
11. The GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 4 for use according to claim 7 comprising administering a second therapeutic agent; optionally wherein the second therapeutic agent is a chemotherapeutic agent or a targeted anti-cancer therapy, such as wherein:

- a. the chemotherapeutic agent is cytarabine, an anthracycline, histamine dihydrochloride, or interleukin 2; and/or
 - b. the second therapeutic agent is administered to said subject simultaneously with, sequentially, or separately from the bispecific antibody.
12. A pharmaceutical composition comprising the GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 4 and a pharmaceutically acceptable carrier.
13. A method for generating the GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 4 by culturing the cell of claim 6.
14. One or more isolated synthetic polynucleotides encoding the HC1, the HC2, the LC1 and the LC2 of the GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 4.
15. A kit comprising the GPRC5D x CD3 bispecific antibody or bispecific binding fragment as defined in claim 4 and/or the one or more polynucleotides as defined in claim 14 and packaging for the same.
16. The antibody or antigen-binding fragment of any of claims 1 to 9 is an IgG1 or an IgG4 isotype.
17. The antibody of claim 16 wherein the IgG1 has a K409R substitution in its Fc region.
18. The antibody of claim 16 wherein the IgG1 has an F405L substitution in its Fc region.
19. The antibody of claim 16 wherein the IgG4 has an F405L substitution and an R409K substitution in its Fc region.
20. The antibody of claim 16 further comprising an S228P substitution, an L234A substitution, and an L235A substitution in its Fc region.
21. The antibody or antigen-binding fragment of any one of claims 1 to 11 wherein the antibody or antigen-binding fragment thereof specifically binds human GPRC5D and cross reacts to cynomolgus monkey GPRC5D.
22. The antibody or antigen-binding fragment of any one of claims 1 to 11 wherein the antibody or antigen-binding fragment induces ADCC *in vitro* with an EC₅₀ of less than about 28 nM.

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

24. The cell of claim 23 wherein the cell is a hybridoma.

25. The cell of claim 23 wherein the antibody is recombinantly produced.

26. An isolated GPRC5D x CD3 bispecific 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, or a GPRC5D x CD3 -bispecific binding fragment thereof.

27. The GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 26 wherein HC1 comprises SEQ ID NO: 25 and LC1 comprises SEQ ID NO: 26.

28. The GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 27 wherein HC2 comprises SEQ ID NO: 52 and LC2 comprises SEQ ID NO: 56.

29. The GPRC5D x CD3 bispecific antibody or bispecific binding fragment of any one of claims 27 and 28 wherein the antibody or bispecific binding fragment are of IgG1, IgG2, IgG3, or IgG4 isotype.

30. The GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 29 wherein the antibody or bispecific binding fragment is IgG4 isotype.

31. The GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claims 26 to 28 wherein the antibody or bispecific binding fragment thereof binds GPRC5D on the surface of human myeloma cells.

32. The GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claims 26 to 28 wherein the antibody or bispecific binding fragment thereof binds GPRC5D on the surface of human multiple myeloma cells.

33. The GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 26 to 28 wherein the antibody or bispecific binding fragment induces human T cell activation in vitro with an EC₅₀ of less than about 0.22 nM.
34. The GPRC5D x CD3 bispecific antibody or bispecific binding fragment of claim 26 to 28 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.
35. An isolated cell expressing the antibody or bispecific binding fragment of any one of claims 26 to 28.
36. The cell of claim 35 wherein the cell is a hybridoma.
37. The cell of claim 35 wherein the antibody or bispecific binding fragment is recombinantly produced.
38. Use of a GPRC5D x CD3 bispecific antibody or bispecific binding fragment of any one of claims 26 to 28 to a patient in need thereof for a time sufficient to treat the cancer.
39. Use of a GPRC5D x CD3 bispecific antibody or bispecific binding fragment of any one of claims 26 to 28 to inhibit the growth or proliferation of cancer cells.
40. Use of a GPRC5D x CD3 bispecific antibody or bispecific binding fragment of any one of claims 26 to 28 to redirect a T cell to a cancer.
41. The use of claim 38, 39, or 40 wherein the cancer is a hematological cancer.
42. The use of claim 41 wherein the hematological cancer is a GPRC5D-expressing B cell cancer.
43. The use of claim 42 wherein the GPRC5D-expressing B cell cancer is multiple myeloma.
44. The use of claim 38 comprising administering a second therapeutic agent.
45. The use of claim 44 wherein the second therapeutic agent is a chemotherapeutic agent or a targeted anti-cancer therapy.
46. The use of claim 45 wherein the chemotherapeutic agent is cytarabine, an anthracycline, histamine dihydrochloride, or interleukin 2.

47. The use of claim 45 wherein the second therapeutic agent is administered to said subject simultaneously with, sequentially, or separately from the bispecific antibody.
48. A pharmaceutical composition comprising the GPRC5D x CD3 bispecific antibody or bispecific binding fragment of any one of claims 26 to 28 and a pharmaceutically acceptable carrier.
49. A method for generating the GPRC5D x CD3 bispecific antibody or bispecific binding fragment of any one of claims 26 to 28 by culturing the cell of any one of claims 35 to 37.
50. An isolated synthetic polynucleotide encoding the HC1, the HC2, the LC1 or the LC2 of the GPRC5D x CD3 bispecific antibody or bispecific binding fragment of any one of claims 26 to 28.
51. A kit comprising the GPRC5D x CD3 bispecific antibody or bispecific binding fragment as defined in any one of claims 26 to 28 and/or a polynucleotide as defined in claim 49 and packaging for the same.