

CLAIMS

1. An isolated antibody or antigen-binding fragment thereof, which binds human BMP6 and comprises:

- (a) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 69, 70 and 71, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 79, 80 and 81, respectively;
- (b) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 72, 73 and 74, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 82, 83 and 84, respectively;
- (c) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 29, 30 and 31, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 39, 40 and 41, respectively;
- (d) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 32, 33 and 34, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 42, 43 and 44, respectively;
- (e) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 49, 50 and 51, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 59, 60 and 61, respectively;
- (f) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 52, 53 and 54, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 62, 63 and 64, respectively;
- (g) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 9, 10 and 11, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 19, 20 and 21, respectively; or
- (h) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 12, 13 and 14, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 22, 23 and 24, respectively.

2. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising:

- (a) A VH sequence of SEQ ID NO: 75
- (b) A VH sequence of SEQ ID NO: 35
- (c) A VH sequence of SEQ ID NO: 55 or
- (d) A VH sequence of SEQ ID NO: 15.

3. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising:

- (e) A VL sequence of SEQ ID NO: 85
- (f) A VL sequence of SEQ ID NO: 45
- (g) A VL sequence of SEQ ID NO: 65 or
- (h) A VL sequence of SEQ ID NO: 25.

4. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising:

- (i) A VH sequence of SEQ ID NO: 75; and a VL sequence of SEQ ID NO: 85
- (j) A VH sequence of SEQ ID NO: 35; and a VL sequence of SEQ ID NO: 45
- (k) A VH sequence of SEQ ID NO: 55; and a VL sequence of SEQ ID NO: 65 or
- (l) A VH sequence of SEQ ID NO: 15; and a VL sequence of SEQ ID NO: 25.

5. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising:

- (a) A heavy chain sequence of SEQ ID NO: 77;
- (b) A heavy chain sequence of SEQ ID NO: 37;
- (c) A heavy chain sequence of SEQ ID NO: 57; or
- (d) A heavy chain sequence of SEQ ID NO: 17.

6. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising:

- (e) A light chain sequence of SEQ ID NO: 87;
- (f) A light chain sequence of SEQ ID NO: 47;
- (g) A light chain sequence of SEQ ID NO: 67; or
- (h) A light chain sequence of SEQ ID NO: 27.

7. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising:

- (i) A heavy chain sequence of SEQ ID NO: 77; and a light chain sequence of SEQ ID NO: 87;
- (j) A heavy chain sequence of SEQ ID NO: 37; and a light chain sequence of SEQ ID NO: 47;
- (k) A heavy chain sequence of SEQ ID NO: 57; and a light chain sequence of SEQ ID NO: 67; or
- (l) A heavy chain sequence of SEQ ID NO: 17; and a light chain sequence of SEQ ID NO: 27.

8. The isolated antibody or antigen-binding fragment thereof of any of the previous claims, wherein the antibody or antigen-binding fragment thereof binds human BMP6 with a K_D of ≤ 1 nM.
9. The isolated antibody or antigen-binding fragment thereof of any of the previous claims, wherein the antibody or antigen-binding fragment thereof binds human BMP6 with a K_D of ≤ 0.1 nM.
10. The isolated antibody or antigen-binding fragment thereof of any of the previous claims, wherein the antibody or antigen-binding fragment thereof has at least about 100-fold greater affinity for human BMP6 than human BMP7.
11. The isolated antibody or antigen-binding fragment thereof of any of the previous claims, wherein the antibody or antigen-binding fragment thereof has at least about 100-fold greater affinity for human BMP6 than human BMP2, human BMP5, or human BMP7.
12. The isolated antibody or antigen-binding fragment thereof of any of the previous claims, wherein the antibody or antigen-binding fragment thereof has at least about 500-fold greater affinity for human BMP6 than human BMP2, human BMP5, or human BMP7.
13. The isolated antibody or antigen-binding fragment thereof of any of the previous claims, wherein the antibody or antigen-binding fragment thereof has no detectable binding to human BMP2 or BMP7 in an ELISA.
14. The isolated antibody or antigen-binding fragment thereof of any of the previous claims, wherein the isolated antibody or antigen-binding fragment thereof reduces BMP6-induced hepcidin expression in liver cell lines or primary human liver cells *in vitro*.
15. The isolated antibody or antigen-binding fragment thereof of any of the previous claims, wherein the isolated antibody or antigen-binding fragment thereof exhibits at least about a 50% reduction in BMP6-induced hepcidin expression in liver cell lines or primary human liver cells *in vitro*.
16. The isolated antibody or antigen-binding fragment thereof of any of the previous claims,

wherein the isolated antibody or antigen-binding fragment thereof reduces the activity of human BMP6 *in vitro*.

17. The isolated antibody or antigen-binding fragment thereof of any of the previous claims, wherein the isolated antibody or antigen-binding fragment thereof reduces the activity of human BMP6 *in vitro*, as measured in a HEP3B-BRE-Luc reporter gene assay.

18. The isolated antibody or antigen-binding fragment thereof of any of the previous claims, wherein the isolated antibody or antigen-binding fragment comprises a scaffold selected from an IgM and an IgG.

19. The isolated antibody or antigen-binding fragment thereof of any of the previous claims, wherein the isolated antibody or antigen-binding fragment is an IgM and an IgG, wherein the IgG is selected from an IgG1, an IgG2, and IgG3 or an IgG4.

20. The isolated antibody or antigen-binding fragment thereof of any of the previous claims, wherein the isolated antibody or antigen-binding fragment is selected from the group consisting of: a monoclonal antibody, a chimeric antibody, a single chain antibody, a Fab and a scFv.

21. The isolated antibody or antigen-binding fragment thereof of any of the previous claims, wherein the isolated antibody or antigen-binding fragment is a component of an immuno-conjugate.

22. The isolated antibody or antigen-binding fragment thereof of any of the previous claims, which has altered effector function through mutation of the Fc region.

23. An antibody or antigen-binding fragment thereof which cross-blocks an antibody or isolated antigen-binding fragment thereof of any of the previous claims.

24. An isolated antibody or antigen-binding fragment thereof, which binds to a human BMP6 epitope comprising sequence QTLVHLMNPEYVPKP (SEQ ID NO: 92).

25. The isolated antibody or antigen-binding fragment thereof of claim 24, which has at least about 100-fold greater affinity for a human BMP6 epitope comprising sequence

QTLVHLMNPEYVPKP (SEQ ID NO: 92), than to (a) a human BMP7 epitope comprising sequence QTLVHFINPETVPKP (SEQ ID NO: 93) or (b) a human BMP5 epitope comprising sequence QTLVHLMFPDHVPKP (SEQ ID NO: 94).

26. The isolated antibody or antigen-binding fragment thereof of claim 24, which has at least about 500-fold greater affinity for a human BMP6 epitope comprising sequence QTLVHLMNPEYVPKP (SEQ ID NO: 92), than to (a) a human BMP7 epitope comprising sequence QTLVHFINPETVPKP (SEQ ID NO: 93) or (b) a human BMP5 epitope comprising sequence QTLVHLMFPDHVPKP (SEQ ID NO: 94).

27. The isolated antibody or antigen-binding fragment thereof of any of claims 24-26, wherein the isolated antibody or antigen-binding fragment thereof comprises:

- (a) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 69, 70 and 71, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 79, 80 and 81, respectively or
- (b) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 72, 73 and 74, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 82, 83 and 84, respectively.

28. The isolated antibody or antigen-binding fragment thereof of claim 27, comprising the VH sequence of SEQ ID NO: 75; and the VL sequence of SEQ ID NO: 85.

29. An antibody or antigen-binding fragment thereof which cross-blocks an antibody or antigen-binding fragment thereof of any of claims 1-28.

30. A composition comprising an isolated antibody or antigen-binding fragment thereof of any of the previous claims.

31. The composition of claim 30, comprising a pharmaceutically acceptable carrier.

32. The composition of any of claims 30-31, comprising an additional therapeutic agent.

33. The composition of claim 32, wherein the additional therapeutic agent reduces the activity of BMP6.

34. The composition of claim 33, wherein the additional therapeutic agent is a siRNA, antibody or antigen-binding fragment thereof, or small molecule.
35. The composition of any of claims 32-33, wherein the therapeutic agent is an erythropoiesis stimulating agent (ESA) or iron.
36. The composition of claim 35, wherein the therapeutic agent is erythropoiesis stimulating agent (ESA).
37. An isolated polynucleotide comprising sequence encoding the isolated antibody or antigen-binding fragment thereof, which binds human BMP6, of any of claims 1-29.
38. An isolated polynucleotide comprising sequence encoding a VH or a VL sequence of an antibody or antigen-binding fragment thereof, which binds human BMP6, of any of claims 1-29.
39. An isolated polynucleotide comprising a sequence encoding a VH or a VL sequence of an antibody or antigen-binding fragment thereof to human BMP6, wherein the antibody or antigen-binding fragment thereof comprises:
- (a) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 69, 70 and 71, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 79, 80 and 81, respectively;
 - (b) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 72, 73 and 74, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 82, 83 and 84, respectively;
 - (c) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 29, 30 and 31, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 39, 40 and 41, respectively;
 - (d) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 32, 33 and 34, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 42, 43 and 44, respectively;
 - (e) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 49, 50 and 51, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 59, 60 and 61, respectively;
 - (f) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 52, 53 and 54,

respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 62, 63 and 64, respectively;

(g) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 9, 10 and 11, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 19, 20 and 21, respectively; or

(h) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 12, 13 and 14, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 22, 23 and 24, respectively.

40. An isolated polynucleotide encoding a heavy or a light chain of an antibody or antigen-binding fragment thereof to BMP6, the polynucleotide comprising the sequence of any of:

- (a) the heavy chain sequence of SEQ ID NO: 78;
- (b) the VH sequence of SEQ ID NO: 76;
- (c) the light chain sequence of SEQ ID NO: 88;
- (d) the VL sequence of SEQ ID NO: 86.
- (e) the heavy chain sequence of SEQ ID NO: 38;
- (f) the VH sequence of SEQ ID NO: 36;
- (g) the light chain sequence of SEQ ID NO: 48;
- (h) the VL sequence of SEQ ID NO: 46;
- (i) the heavy chain sequence of SEQ ID NO: 58;
- (j) the VH sequence of SEQ ID NO: 56;
- (k) the light chain sequence of SEQ ID NO: 68;
- (l) the VL sequence of SEQ ID NO: 66;
- (m) the heavy chain sequence of SEQ ID NO: 18;
- (n) the VH sequence of SEQ ID NO: 16;
- (o) the light chain sequence of SEQ ID NO: 28; or
- (p) the VL sequence of SEQ ID NO: 26.

41. A vector comprising a polynucleotide of claims 37-40.

42. A host cell comprising a vector of claim 41 or the polynucleotide of claims 37-40.

43. The host cell of claim 42, wherein the cell is a Chinese hamster ovary (CHO) cell.

44. A method of reducing the activity of BMP6 in a cell, comprising the step of contacting the cell with an antibody or antigen-binding fragment thereof of any of claims 1-29, or the

composition of any of claims 30-36.

45. The use of an antibody or antigen-binding fragment thereof of any of claims 1-29, or the composition of any of claims 30-36 in the manufacture of a medicament for inhibiting BMP6 in a patient in need thereof.

46. The use of claim 45, wherein the patient has anemia.

47. The use of claim 46, wherein the anemia is anemia of chronic disease (ACD), anemia of chronic kidney disease (CKD), anemia of cancer, anemia of inflammation, erythropoiesis stimulating agent (ESA) resistant anemia, or iron-restricted anemia.

48. The use of any of claims 45-47, wherein the patient is a chronic hemodialysis patient.

49. The use of any of claims 45-48, wherein the patient has been or is being administered an erythropoiesis stimulating agent (ESA).

50. The use of claim 49, wherein the ESA is erythropoietin (EPO).

51. The antibody or antigen-binding fragment thereof of any of claims 1-29, or the composition of any of claims 30-36, for use in increasing serum iron levels, transferrin saturation (TAST), reticulocyte hemoglobin content (CHr), reticulocyte count, red blood cell count, hemoglobin, or hematocrit in a patient in need thereof.

52. The antibody or antigen-binding fragment thereof of any of claims 1-29, or the composition of any of claims 30-36, for use in reducing the activity or level of Hepcidin in a patient in need thereof.

53. The use of an antibody or antigen-binding fragment thereof of any of claims 1-29, or the composition of any of claims 30-36 in the manufacture of a medicament for reducing the activity or level of Hepcidin in a patient in need thereof.

54. The use of claim 53, wherein the activity or level of Hepcidin is reduced by at least 50%.

55. The antibody or antigen-binding fragment thereof of any of claims 1-29, or the composition of any of claims 30-36, for use in treating anemia in a patient in need thereof.
56. The antibody or antigen-binding fragment thereof of any of claims 1-29, or the composition of any of claims 30-36, for use in increasing or maintaining hemoglobin level in a patient in need thereof.
57. The use of an antibody or antigen-binding fragment thereof of any of claims 1-29, or the composition of any of claims 30-36, in the manufacture of a medicament for increasing or maintaining the hemoglobin level in a patient in need thereof and reducing the patient's iron dose requirement, reducing the patient's EPO dose requirement, or reducing both the patient's iron dose requirement and the patient's EPO dose requirement, relative to said EPO dose requirement and/or iron dose requirement in the absence of treatment with the antibody or antigen-binding fragment thereof of any of claims 1-29 or the composition of any of claims 30-36.
58. The use of claim 57, wherein the patient has anemia.
59. The use of claim 58, wherein the anemia is anemia associated with chronic disease.
60. The use of claim 59, wherein the chronic disease is chronic kidney disease, cancer or inflammation.
61. The use of any of claims 53-54 or 59-60, wherein the patient is being or has been treated with an erythropoiesis stimulating agent (ESA).
62. The use of claim 61, wherein the ESA is erythropoietin (EPO).
63. The use of any of claims 53-54 or 58-62, wherein the anemia is EPO-hyporesponsive anemia.
64. The use of any of claims 53-54 or 58-63, wherein the anemia is iron-restricted anemia.
65. The use of any of claims 53-64, wherein the patient is a chronic hemodialysis patient.

66. The use of any of claims 45-65, wherein the antibody or antigen-binding fragment thereof is administered at a dose ranging from 0.001 mg/kg to 0.1 mg/kg.

67. The use of claim 66, wherein the antibody or antigen-binding fragment thereof is administered at a dose ranging from 0.0063 to 0.1 mg/kg.

68. The use of any of claims 45-66, wherein the antibody or antigen-binding fragment thereof is administered at a dose of 0.001 mg/kg, 0.0016 mg/kg, 0.0025 mg/kg, 0.0040 mg/kg, 0.0063 mg/kg, 0.01 mg/kg, 0.016 mg/kg, 0.025 mg/kg, 0.040 mg/kg, 0.063 mg/kg, or 0.1 mg/kg.

69. The use of any of claims 45-68, wherein the antibody or antigen-binding fragment thereof is formulated for intravenous or subcutaneous administration.

70. The use of claim 69, wherein the antibody or antigen-binding fragment thereof is formulated for intravenous administration.

71. The use of any of claims 45-50, 53-54 or 57-70, wherein the anemia is functional iron-deficiency anemia.

72. The use of a polynucleotide of any of claims 37-40, a vector of claim 41, or a host cell of any of claims 42-43, in the manufacture of a medicament for inhibiting BMP6.

73. The antibody or antigen-binding fragment thereof of any of claims 1-29 or a composition of any of claims 30-36, for use as a medicament.