

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; or
- (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.

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; or
- (c) A VH sequence of SEQ ID NO: 55.

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

- (a) A VL sequence of SEQ ID NO: 85;
- (b) A VL sequence of SEQ ID NO: 45; or
- (c) A VL sequence of SEQ ID NO: 65.

4. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising:
 - (a) A VH sequence of SEQ ID NO: 75; and a VL sequence of SEQ ID NO: 85;
 - (b) A VH sequence of SEQ ID NO: 35; and a VL sequence of SEQ ID NO: 45; or
 - (c) A VH sequence of SEQ ID NO: 55; and a VL sequence of SEQ ID NO: 65.
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; or
 - (c) A heavy chain sequence of SEQ ID NO: 57.
6. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising:
 - (a) A light chain sequence of SEQ ID NO: 87;
 - (b) A light chain sequence of SEQ ID NO: 47; or
 - (c) A light chain sequence of SEQ ID NO: 67.
7. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising:
 - (a) A heavy chain sequence of SEQ ID NO: 77; and a light chain sequence of SEQ ID NO: 87;
 - (b) A heavy chain sequence of SEQ ID NO: 37; and a light chain sequence of SEQ ID NO: 47; or
 - (c) A heavy chain sequence of SEQ ID NO: 57; and a light chain sequence of SEQ ID NO: 67.
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 KD 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 KD 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 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 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 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 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-BMP responsive element (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 comprises an IgM or an IgG, wherein the IgG is selected from an IgG1, an IgG2, an 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 of any of the previous claims, which has altered effector function through mutation of an Fc region.

23. An isolated antibody or antigen-binding fragment thereof, wherein the isolated antibody or antigen-binding fragment thereof:

(a) binds to a human BMP6 epitope comprising sequence QTLVHLMNPEYVPKP (SEQ ID NO: 92); and

(b) comprises:

(i) 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

(ii) 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.

24. The isolated antibody or antigen-binding fragment thereof of claim 23, which has at least 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 QTLVHFNPETVPKP (SEQ ID NO: 93) or (b) a human BMP5 epitope comprising sequence QTLVHLMFPDHPVPKP (SEQ ID NO: 94).

25. The isolated antibody or antigen-binding fragment thereof of claim 23, which has at least 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 QTLVHFNPETVPKP (SEQ ID NO: 93) or (b) a human BMP5 epitope comprising sequence QTLVHLMFPDHPVPKP (SEQ ID NO: 94).
26. The isolated antibody or antigen-binding fragment thereof of claim 23, comprising the VH sequence of SEQ ID NO: 75; and the VL sequence of SEQ ID NO: 85.
27. A composition comprising an isolated antibody or antigen-binding fragment thereof of any of the previous claims.
28. The composition of claim 27, comprising a pharmaceutically acceptable carrier.
29. The composition of any of claims 27-28, comprising an additional therapeutic agent.
30. The composition of claim 29, wherein an additional therapeutic agent is a siRNA, antibody or antigen-binding fragment thereof, or small molecule.
31. The composition of claim 29, wherein the therapeutic agent is an erythropoiesis stimulating agent (ESA) or iron.
32. The composition of claim 31, wherein the therapeutic agent is the ESA.
33. An isolated polynucleotide comprising sequence encoding the isolated antibody or antigen-binding fragment thereof, which binds human BMP6, of any of claims 1-26.
34. A method of reducing the activity of BMP6 in a cell in vitro, comprising the step of contacting the cell with an antibody or antigen-binding fragment thereof of any of claims 1-26, or the composition of any of claims 27-32.
35. The use of an antibody or antigen-binding fragment thereof of any of claims 1-26, or the composition of any of claims 27-32, in the manufacture of a medicament for inhibiting BMP6 in a patient with anemia.

36. The use of claim 35, 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.
37. The use of any of claims 35-36, wherein the patient is a chronic hemodialysis patient.
38. The use of any of claims 35-37, wherein the patient has been or is being administered an erythropoiesis stimulating agent (ESA).
39. The use of claim 38, wherein the ESA is erythropoietin (EPO).
40. The antibody or antigen-binding fragment thereof of any of claims 1-26, or the composition of any of claims 27-32, 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 with anemia.
41. The antibody or antigen-binding fragment thereof of any of claims 1-26, or the composition of any of claims 27-32, for use in reducing the activity or level of Hepcidin in a patient with anemia.
42. The use of an antibody or antigen-binding fragment thereof of any of claims 1-26, or the composition of any of claims 27-32 in the manufacture of a medicament for reducing the activity or level of Hepcidin in a patient with anemia.
43. The use of claim 42, wherein the activity or level of Hepcidin is reduced by at least 50%.
44. The antibody or antigen-binding fragment thereof of any of claims 1-26, or the composition of any of claims 27-32, for use in treating anemia in a patient in need thereof.
45. The antibody or antigen-binding fragment thereof of any of claims 1-26, or the composition of any of claims 27-32, for use in increasing or maintaining hemoglobin level in a patient with anemia.

46. The use of the antibody or antigen-binding fragment thereof of any of claims 1-26 in the manufacture of a medicament for a patient with anemia, wherein the anemia is anemia associated with chronic disease.
47. The use of claim 46, wherein the chronic disease is chronic kidney disease, cancer or inflammation.
48. The use of any of claims 42-43 or 46-47, wherein the patient is being or has been treated with an erythropoiesis stimulating agent (ESA).
49. The use of claim 48, wherein the ESA is erythropoietin (EPO).
50. The use of any of claims 42-43 or 46-49, wherein the anemia is EPO-hyporesponsive anemia.
51. The use of any of claims 42-43 or 46-50, wherein the anemia is iron-restricted anemia.
52. The use of any of claims 42-43 or 46-51, wherein the patient is a chronic hemodialysis patient.
53. The use of the antibody or antigen-binding fragment thereof of any of claims 1-26 in the manufacture of a medicament for the patient with anemia, wherein the antibody or antigen-binding fragment thereof is administered at a dose ranging from 0.001 mg/kg to 0.1 mg/kg.
54. The use of claim 53, wherein the antibody or antigen-binding fragment thereof is administered at a dose ranging from 0.0063 to 0.1 mg/kg.
55. The use of claim 53, 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.
56. The use of any of claims 46-55, wherein the antibody or antigen-binding fragment thereof is formulated for intravenous or subcutaneous administration.

57. The use of claim 56, wherein the antibody or antigen-binding fragment thereof is formulated for intravenous administration.

58. The use of any of claims 53-57, wherein the anemia is functional iron-deficiency anemia.

59. The antibody or antigen-binding fragment thereof of any of claims 1-26 or a composition of any of claims 27-32, for use as a medicament for a patient with anemia.