

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 BMP2, human BMP5, or 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 500-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 no detectable binding to human BMP2 or BMP7 in an ELISA.
13. 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*.
14. 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*.
15. 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*.

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*, as measured in a HEP3B-BMP responsive element (BRE)-Luc reporter gene assay.

17. 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.

18. 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 or an IgG, wherein the IgG is selected from an IgG1, an IgG2, an IgG3 and an IgG4.

19. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-16, 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.

20. 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.

21. The isolated antibody of any of the previous claims, which has altered effector function through mutation of an Fc region.

22. 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.

23. The isolated antibody or antigen-binding fragment thereof of claim 22, 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 QTLVHFINPETVPKP (SEQ ID NO: 93) or (b) a human BMP5 epitope comprising sequence QTLVHLMFPDHPVPKP (SEQ ID NO: 94).

24. The isolated antibody or antigen-binding fragment thereof of claim 22, 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 QTLVHFINPETVPKP (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 22, comprising the VH sequence of SEQ ID NO: 75; and the VL sequence of SEQ ID NO: 85.

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

27. The composition of claim 26, comprising a pharmaceutically acceptable carrier.

28. The composition of any of claims 26-27, comprising an additional therapeutic agent.

29. The composition of claim 28, wherein the additional therapeutic agent is a siRNA, antibody or antigen-binding fragment thereof, or small molecule.

30. The composition of claim 28, wherein the additional therapeutic agent is an erythropoiesis stimulating agent (ESA) or iron.

31. The composition of claim 30, wherein the additional therapeutic agent is the ESA.

32. An isolated polynucleotide comprising sequence encoding the isolated antibody or antigen-binding fragment thereof, which binds human BMP6, of any of claims 1-25.

33. 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 1-25, or the composition of any of claims 26-31.

34. The use of an antibody or antigen-binding fragment thereof of any of claims 1-25, or the composition of any of claims 26-31, in the manufacture of a medicament for inhibiting BMP6 in a patient with anemia.
35. The use of claim 34, 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, iron-restricted anemia, or functional iron deficiency anemia.
36. The use of any of claims 34-35, wherein the patient is a chronic hemodialysis patient.
37. The use of any of claims 34-36, wherein the patient has been or is being administered an erythropoiesis stimulating agent (ESA).
38. The use of claim 37, wherein the ESA is erythropoietin (EPO).
39. The use of an antibody or antigen-binding fragment thereof of any of claims 1-25, or the composition of any of claims 26-31 in the manufacture of a medicament for reducing the activity or level of Hepcidin in a patient with anemia.
40. The use of claim 39, wherein the activity or level of Hepcidin is reduced by at least 50%.
41. The use of the antibody or antigen-binding fragment thereof of any of claims 1-25, or the composition of any of claims 26-31 in the manufacture of a medicament for treating anemia in a patient .
42. The use of claim 41, wherein the anemia is anemia associated with chronic disease and the chronic disease is chronic kidney disease, cancer or inflammation.
43. The use of any of claims 39-42, wherein the patient is being or has been treated with an erythropoiesis stimulating agent (ESA).
44. The use of claim 43, wherein the ESA is erythropoietin (EPO).
45. The use of any of claims 39-44, wherein the anemia is EPO-hyporesponsive anemia.
46. The use of any of claims 39-45, wherein the anemia is iron-restricted anemia.

47. The use of any of claims 39-46, wherein the patient is a chronic hemodialysis patient.
48. The use of any of claims 41-47 wherein the antibody or antigen-binding fragment thereof is formulated for intravenous or subcutaneous administration.
49. The use of claim 48, wherein the antibody or antigen-binding fragment thereof is formulated for subcutaneous administration.
50. The use of any of claims 48-49, wherein the anemia is functional iron-deficiency anemia.
51. The antibody or antigen-binding fragment thereof of any of claims 1-25 or a composition of any of claims 26-31, for use as a medicament for a patient with anemia.
52. The use of any of claims 39-50, wherein the antibody or antigen-binding fragment thereof is to be administered at a dose ranging from 0.01 mg/kg to 15 mg/kg.
53. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising a VH sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity to SEQ ID NO: 75; and a VL sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity to SEQ ID NO: 85.
54. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising a heavy chain sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity to SEQ ID NO: 77; and a light chain sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity to SEQ ID NO: 87.