

CLAIMS

What is claimed is:

1. A method of treating a subject having myelofibrosis, the method comprising:
administering to the subject an effective amount of the isolated antibody that binds to human hemojuvelin (HJV), wherein the antibody comprises:
a heavy chain complementary determining region 1 (HC CDR1) set forth as X₁YGMN (SEQ ID NO: 105), in which X₁ can be N or Y;
a heavy chain complementary determining region 2 (HC CDR2) set forth as MIYYDSSX₂KHYADSVKG (SEQ ID NO: 106), in which X₂ can be E or D;
a heavy chain complementary determining region 3 (HC CDR3) set forth as GX₃TPDX₄ (SEQ ID NO: 107), in which X₃ can be T or S, and X₄ can be Y, V, or K; and/or
a light chain complementary determining region 1 (LC CDR1) set forth as RSSQSLX₅X₆SDGX₇TFLX₈ (SEQ ID NO: 108), in which X₅ can be A or E, X₆ can be T, S, E, or D, X₇ can be D, Y, or G, and X₈ can be E or H,
a light chain complementary determining region 2 (LC CDR2) set forth as X₉VSX₁₀RFS (SEQ ID NO: 109), in which X₉ can be E, D or A, and X₁₀ can be N, S, T, E or H,
a light chain complementary determining region 3 (LC CDR3) set forth as X₁₁QX₁₂TX₁₃DPX₁₄X₁₅ (SEQ ID NO: 110), in which X₁₁ can be F or M, X₁₂ can be V or A, X₁₃ can be H or Y, X₁₄ can be M, L or V, and X₁₅ can be T or S.
2. The method of claim 1, wherein the subject is administered via subcutaneous injection.
3. The method of claim 1 or claim 2, wherein the subject having myelofibrosis has anemia resulting from hepcidin expression that is induced by pro-inflammatory cytokines, and wherein the administration of the antibody reduces the anemia.
4. The method of claim 3, wherein the pro-inflammatory cytokines comprises Interleukin-6 (IL-6).

5. The method of any one of claims 1-4, wherein the antibody comprises a HC CDR1 of SEQ ID NO: 1, a HC CDR2 of SEQ ID NO: 2, a HC CDR3 of SEQ ID NO: 3, and a LC CDR1 of SEQ ID NO: 17, a LC CDR2 of SEQ ID NO: 5, a LC CDR3 of SEQ ID NO: 27.
6. The method of any one of claims 1-5, wherein the antibody comprises a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO: 38, and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO: 39.
7. The method of any one of claims 1-6, wherein the antibody is a humanized antibody comprising a humanized VH and/or a humanized VL.
8. The method of any one of claims 1-7, wherein the antibody is selected from the group consisting of a full-length IgG, a Fab fragment, a F(ab') fragment, a F(ab')₂ fragment, a scFv, and a Fv.
9. The method of any one of claims 1-8, wherein the antibody is a full-length IgG comprising a heavy chain constant region of the isotype IgG1, IgG2, IgG3, or IgG4.
10. The method of claim 9, wherein the antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 61 or 117, and a light chain comprising an amino acid sequence of SEQ ID NO: 62.
11. The method of claim 9, wherein the antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 63 or 118, and a light chain comprising an amino acid sequence of SEQ ID NO: 62.
12. The method of any one of claims 1-11, wherein the subject has myelofibrosis initiating mutations in JAK2, MPL, ASXL1, TET2, NFE2, SH2B3, SF3B1, or CALR.
13. The method of any one of claims 1-12, wherein the subject has primary myelofibrosis.
14. The method of any one of claims 1-13, wherein the subject has a DIPSS score of more than 1.

15. The method of any one of claims 1-14, wherein the subject presents with a serum hemoglobin level of less than 10 g/dL
16. The method of any one of claims 1-15, wherein the subject presents with a serum hemoglobin level of less than 8 g/dL.
17. The method of any one of claims 1-16, wherein the subject is erythrocyte-transfusion dependent.
18. The method of any one of claims 1-17, wherein the subject has previously received a selective JAK-STAT inhibitor selected from the group consisting of ruxolitinib, fedratinib, pacritinib, INCB039110, AG490, and PpYLKTK.
19. An isolated antibody that binds to human hemojuvelin (HJV), wherein the antibody comprises a VH comprising an amino acid sequence of SEQ ID NO: 38, and/or a VL comprising an amino acid sequence of SEQ ID NO: 39.
20. The isolated antibody of claim 19, wherein the antibody is a humanized antibody.
21. The isolated antibody of claims 19 or 20, wherein the antibody is selected from the group consisting of a full-length IgG, a Fab fragment, a F(ab') fragment, a F(ab')₂ fragment, a scFv, and a Fv.
22. The isolated antibody of claim 21, wherein the antibody is a full-length IgG comprising a heavy chain constant region of the isotype IgG1, IgG2, IgG3, or IgG4.
23. The isolated antibody of claim 22, wherein the antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 61 or 117, and a light chain comprising an amino acid sequence of SEQ ID NO: 62.
24. The isolated antibody of claim 22, wherein the antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 63 or 118, and a light chain comprising an amino acid sequence of SEQ ID NO: 62.

25. A method of treating a subject having myelofibrosis, the method comprising:
administering to the subject by subcutaneous administration an effective amount of the isolated antibody that binds to human hemojuvelin (HJV), wherein the antibody comprises:
a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO: 38, and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO: 39.
26. A method of inhibiting HJV activity in a subject having myelofibrosis, the method comprising:
administering to the subject by subcutaneous administration an effective amount of the isolated antibody that binds to human hemojuvelin (HJV), wherein the antibody comprises:
a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO: 38, and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO: 39.
27. A method of reducing hepcidin-25 in a subject having myelofibrosis, the method comprising: administering to the subject an effective amount of the isolated antibody that binds to human hemojuvelin (HJV), wherein the antibody comprises:
a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO: 38, and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO: 39.
28. The method of claim 27, wherein the subject is administered via subcutaneous injection.
29. The method of claim 27 or claim 28, wherein the administration reduces hepcidin-25 with 4 hours, 6 hours, 8 hours, 12 hours, 28 hours, 24 hours, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, or two weeks of administration.
30. The method of any one of claims 27-29, wherein the administration reduces hepcidin-25 by at least 30%, least 40%, least 50%, least 60%, least 70%, least 80%, least 90%, or least 95% of hepcidin compared to the hepcidin level in the subject prior to administration.

31. An isolated antibody that binds to human hemojuvelin (HJV) for use in a method of treating a subject having myelofibrosis, wherein the antibody comprises a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO: 38, and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO: 39.
32. The isolated antibody for use according to claim 31, wherein the subject is administered by subcutaneous administration.
33. The isolated antibody for use according to claims 31 or 32, wherein the subject having myelofibrosis has anemia resulting from hepcidin expression that is induced by pro-inflammatory cytokines, and wherein the administration of the antibody reduces the anemia.
34. The isolated antibody for use according to claim 33, wherein the pro-inflammatory cytokines comprise interleukin-6 (IL-6).
35. The isolated antibody for use according to any one of claims 31-34, wherein the antibody is a humanized antibody comprising a humanized VH and/or a humanized VL.
36. The isolated antibody for use according to any one of claims 31-35, wherein the antibody is selected from the group consisting of a full-length IgG, a Fab fragment, a F(ab') fragment, a F(ab')₂ fragment, a scFv, and a Fv.
37. The isolated antibody for use according to any one of claims 31-36, wherein the antibody is a full-length IgG comprising a heavy chain constant region of the isotype IgG1, IgG2, IgG3, or IgG4.
38. The isolated antibody for use according to claim 37, wherein the antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 61 or 117, and a light chain comprising an amino acid sequence of SEQ ID NO: 62.
39. The isolated antibody for use according to claim 37, wherein the antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 63 or 118, and a light chain comprising an amino acid sequence of SEQ ID NO: 62.

40. The isolated antibody for use according to any one of claims 31-39, wherein the subject has myelofibrosis initiating mutations in JAK2, MPL, ASXL1, TET2, NFE2, SH2B3, SF3B1, CALR, or a combination thereof.
41. The isolated antibody for use according to any one of claims 31-40, wherein the subject has primary myelofibrosis.
42. The isolated antibody for use according to any one of claims 31-41, wherein the subject has a DIPSS score of more than 1, optionally between 1-4, or optionally between 5-6.
43. The isolated antibody for use according to any one of claims 31-42, wherein the subject presents with a serum hemoglobin level of less than 10 g/dL, optionally wherein the subject presents with a serum hemoglobin level of less than 8 g/dL.
44. The isolated antibody for use according to any one of claims 31-43, wherein the subject is erythrocyte-transfusion dependent.
45. The isolated antibody for use according to any one of claims 31-44, wherein the subject has previously received a selective JAK-STAT inhibitor selected from the group consisting of ruxolitinib, fedratinib, pacritinib, INCB039110, AG490, and PpYLKTK.
46. The isolated antibody for use according to any one of claims 31-45, wherein the method further comprises administering to the subject one or more of an erythropoietin stimulating agent, a JAK-STAT inhibitor, a growth factor ligand trap, and an anti-fibrotic agent.
47. An isolated antibody that binds to human hemojuvelin (HJV) for use in a method of treating a subject having myelofibrosis, wherein the subject is administered with the isolated antibody by subcutaneous administration, and wherein the antibody comprises a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO: 38, and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO: 39.

48. An isolated antibody that binds to human hemojuvelin (HJV) for use in a method of inhibiting HJV activity in a subject having myelofibrosis, wherein the subject is administered with the isolated antibody by subcutaneous administration, and wherein the antibody comprises a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO: 38, and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO: 39.

49. An isolated antibody that binds to human hemojuvelin (HJV) for use in a method of reducing hepcidin-25 in a subject having myelofibrosis, wherein the antibody comprises:
a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO: 38, and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO: 39.

50. The isolated antibody for use according to claim 49, wherein the subject is administered via subcutaneous injection.

51. The isolated antibody for use according to claim 49 or claim 50, wherein the administration reduces hepcidin-25 with 4 hours, 6 hours, 8 hours, 12 hours, 28 hours, 24 hours, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, or two weeks of administration.

52. The method of any one of claims 49-51, wherein the administration reduces hepcidin-25 by at least 30%, least 40%, least 50%, least 60%, least 70%, least 80%, least 90%, or least 95% of hepcidin compared to the hepcidin level in the subject prior to administration.

CLAIMS

1. Use of an anti-hemojuvelin (HJV) antibody in the manufacture of a medicament for treating myelofibrosis in a subject, wherein the antibody is to be administered to the subject, and wherein the antibody comprises:

a heavy chain complementary determining region 1 (HC CDR1) set forth as X₁YGMN (SEQ ID NO: 105), in which X₁ can be N or Y;

a heavy chain complementary determining region 2 (HC CDR2) set forth as MIYYDSSX₂KHYADSVKG (SEQ ID NO: 106), in which X₂ can be E or D;

a heavy chain complementary determining region 3 (HC CDR3) set forth as GX₃TPDX₄ (SEQ ID NO: 107), in which X₃ can be T or S, and X₄ can be Y, V, or K; and/or

a light chain complementary determining region 1 (LC CDR1) set forth as RSSQSLX₅X₆SDGX₇TFLX₈ (SEQ ID NO: 108), in which X₅ can be A or E, X₆ can be T, S, E, or D, X₇ can be D, Y, or G, and X₈ can be E or H,

a light chain complementary determining region 2 (LC CDR2) set forth as X₉VSX₁₀RFS (SEQ ID NO: 109), in which X₉ can be E, D or A, and X₁₀ can be N, S, T, E or H, and

a light chain complementary determining region 3 (LC CDR3) set forth as X₁₁QX₁₂TX₁₃DPX₁₄X₁₅ (SEQ ID NO: 110), in which X₁₁ can be F or M, X₁₂ can be V or A, X₁₃ can be H or Y, X₁₄ can be M, L or V, and X₁₅ can be T or S.

2. The use of claim 1, wherein the subject has anemia resulting from hepcidin expression that is induced by pro-inflammatory cytokines, and wherein the administration of the antibody reduces the anemia.

3. The use of claim 2, wherein the pro-inflammatory cytokines comprise interleukin-6 (IL-6).

4. The use of any one of 1-3, wherein the antibody is a humanized antibody comprising a humanized VH and/or a humanized VL.

5. The use of any one of claims 1-4, wherein the antibody is selected from the group consisting of a full-length IgG, a Fab fragment, a F(ab') fragment, a F(ab')₂ fragment, a scFv, and a Fv.
6. The use of any one of claims 1-5, wherein the antibody is a full-length IgG comprising a heavy chain constant region of the isotype IgG1, IgG2, IgG3, or IgG4.
7. The use of any one of claims 1-6, wherein the subject has myelofibrosis initiating mutations in JAK2, MPL, ASXL1, TET2, NFE2, SH2B3, SF3B1, CALR, or a combination thereof.
8. The use of any one of claims 1-7, wherein the subject has primary myelofibrosis.
9. The use of claims any one of claims 1-8, wherein the subject has a DIPSS score of more than 1.
10. The use of any one of claims 1-9, wherein the subject has a DIPSS score between 1-4.
11. The use of any one of claims 1-9, wherein the subject has a DIPSS score between 5-6.
12. The use of any one of claims 1-11, wherein the subject presents with a serum hemoglobin level of less than 10 g/dL.
13. The use of any one of claims 1-12, wherein the subject presents with a serum hemoglobin level of less than 8 g/dL.
14. The use any one of claims 1-13, wherein the subject is erythrocyte-transfusion dependent.

15. The use of any one of claims 1-14, wherein the subject has received a selective JAK-STAT inhibitor selected from the group consisting of ruxolitinib, fedratinib, pacritinib, INCB039110, AG490, and PpYLKTK.
16. The use of any one of claims 1-15, wherein one or more of an erythropoietin stimulating agent, a JAK-STAT inhibitor, a growth factor ligand trap, and an anti-fibrotic agent, is/are to be administered to the subject.
17. The use of any one of claims 1-16, wherein the administration reduces hepcidin-25 in the subject.
18. The use of any one of claims 1-17, wherein the administration reduces hepcidin-25 within 4 hours, 6 hours, 8 hours, 12 hours, 28 hours, 24 hours, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, or two weeks of administration.
19. The use of any one of claims 1-18, wherein the administration reduces hepcidin-25 by at least 30%, least 40%, least 50%, least 60%, least 70%, least 80%, least 90%, or least 95% of hepcidin compared to the hepcidin level in the subject prior to administration.
20. The use of any one of claims 1-19, wherein the administration is via intravenous injection or subcutaneous injection.