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(54) Title: ANTI-HEMOJUVELIN (HJV) ANTIBODIES FOR TREATING MYELOFIBROSIS

(57) Abstract: Aspects of the application provide anti-hemojuvelin antibodies and methods of using the same in treating myelofibrosis and/or conditions associated with myelofibrosis.

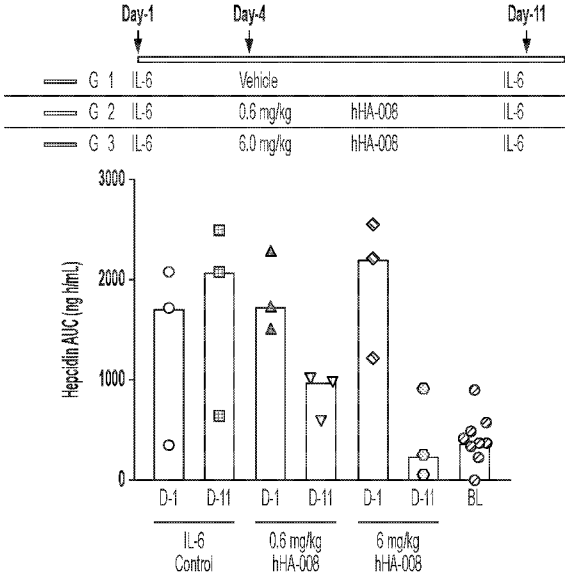


FIG. 13

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[Continued on next page]

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ANTI-HEMOJUVELIN (HJV) ANTIBODIES FOR TREATING MYELOFIBROSIS

RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119(e) of U.S. provisional application serial numbers 63/024,416, filed May 13, 2020, entitled "ANTI-HEMOJUVELIN (HJV) ANTIBODIES FOR TREATING MYELOFIBROSIS," 63/035,649, filed June 5, 2020, entitled "ANTI-HEMOJUVELIN (HJV) ANTIBODIES FOR TREATING MYELOFIBROSIS," 63/047,828, filed July 2, 2020, entitled "ANTI-HEMOJUVELIN (HJV) ANTIBODIES FOR TREATING MYELOFIBROSIS," and 63/164,294, filed March 22, 2021, entitled "ANTI-HEMOJUVELIN (HJV) ANTIBODIES FOR TREATING MYELOFIBROSIS," the entire contents of each of which are incorporated herein by reference.

BACKGROUND

[0002] Iron is a key component of oxygen-transporting storage molecules, such as hemoglobin and myoglobin. Iron deficiency results in anemia, while iron overload leads to tissue damage and fibrosis. Hepcidin is a key peptide hormonal regulator of systemic iron homeostasis. It exerts its regulatory function by binding to the cellular iron exporter ferroportin, a transmembrane protein present on hepatocytes, enterocytes in the duodenum, macrophages, and adipocytes. The binding of hepcidin promotes ferroportin degradation, preventing the export of iron from cells and release of iron into the plasma.

SUMMARY

[0003] Aspects of the disclosure provide methods for treating high hepcidin disorders, such as myelofibrosis, myeloma, Waldenstrom macroglobulinemia, chronic kidney disease, anemias of chronic disease or iron restricted anemias that result in functional iron deficiency. In certain embodiments, methods are provided for treating myelofibrosis, which is generally characterized as a myeloproliferative disease associated with chronic inflammation and progressive marrow fibrosis. Anemia is a major clinical problem in myelofibrosis and is associated with negative outcomes. Such anemia is generally caused by, or associated with, bone marrow failure, splenomegaly and/or functional iron deficiency, which may contribute to inflammation. Moreover, in myelofibrosis, pro-inflammatory cytokines that induce hepcidin synthesis, such as IL-6 and oncostatin-M, are typically increased and associated

with iron sequestration, macrophage iron loading, as well as myeloid proliferation and macrophage activation (See, *e.g.*, FIG. 11). The resulting increases in hepcidin levels are associated with anemia and negative outcome.

[0004] Aspects of the present disclosure relates to effective bioavailability being achieved by subcutaneous administration of an isolated antibody that binds to hemojuvelin (HJV) to a subject having myelofibrosis together with beneficially low maximum serum concentrations (C_{max}). In some embodiments, subcutaneous administration of an anti-HJV antibody yields comparable pharmacodynamics effects (e.g., decreased circulating hepcidin-25 levels, increased TSAT%, and/or increased serum iron levels) at lower maximum concentration (C_{max}) of the anti-HJV antibody compared to intravenous administration of the same antibody. C_{max} is the maximum (or peak) serum concentration that a drug (e.g., an anti-HJV antibody) after the agent/antibody has been administered and before the administration of a second dose. In some embodiments, achieving a low C_{max} within a short period of time (e.g., within 12 hours, within 24 hours, etc) after administration of an anti-HJV antibody minimizes undesirable increases in serum iron response, and/or minimizes chances of off-target effects of the antibody (e.g., binding to RGMa). In some embodiments, blunting C_{max} by subcutaneous administration of an anti-HJV antibody avoids an undesirably sharp increase in serum iron response. In some embodiments, blunting C_{max} by subcutaneous administration of an anti-HJV antibody reduces the off-target effects of the antibody.

[0005] Aspects of the disclosure also relates to an isolated antibody that binds to human hemojuvelin (HJV) for use in a method of treating a subject having myelofibrosis, in which 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.

[0006] Aspects of the disclosure also relates to an isolated antibody that binds to human hemojuvelin (HJV) for use in a method of inhibiting HJV activity in a subject having myelofibrosis, in which 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.

[0007] In some embodiments, the administration (e.g., intravenous injection or subcutaneous injection) of an anti-HJV antibody reduces circulating hepcidin-25 (e.g., serum or plasma hepcidin-25), which is the active form of hepcidin.

[0008] In some aspects, the present disclosure provides a method for 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. In some aspects, the present disclosure provides an isolated antibody that binds to 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. In some embodiments, the subject is administered via subcutaneous injection. In some embodiments, 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. In some embodiments, 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.

[0009] Certain aspects of this disclosure relate to an observation that hemojuvelin (HJV) is a regulator of hepcidin synthesis and that loss of hemojuvelin function may be associated with iron overload. For example, in some embodiments, homozygous HJV knockdown animals fail to amplify hepcidin synthesis in response to IL-6 and are unable to mount an effective hypoferremic response to acute inflammation. Accordingly, in some embodiments, methods provided herein involve administering to a subject in need thereof a hepcidin antagonist, which may be a hemojuvelin antagonist, in an amount effective to treat a high-hepcidin disorder. In some embodiments, the hemojuvelin antagonist is an anti-hemojuvelin antibody. In some embodiments, the anti-hemojuvelin antibody binds RGMc as its primary mode of action (as compared with RGMa and RGMb). Accordingly, in some embodiments, the anti-hemojuvelin antibody preferentially binds RGMc versus RGMa and/or RGMb. In some embodiments, the anti-hemojuvelin antibody binds RGMc with an equilibrium dissociation constant (K_D) less than one hundred nanomolar (nM) ($K_D < 100$ nM). However, in some embodiments, the anti-hemojuvelin antibody binds RGMc with a similar affinity as RGMa and/or RGMb.

[00010] In some aspects, the present disclosure provides a method of treating a subject having myelofibrosis. In some embodiments, the method comprises: 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 X_1YGMN (SEQ ID NO: 105), in which X_1 can be N or Y; a heavy chain complementary determining region 2 (HC CDR2) set forth as MIYYDSSX_2KHYADSVKG (SEQ ID NO: 106), in which X_2 can be E or D; a heavy chain complementary determining region 3 (HC CDR3) set forth as GX_3TPDX_4 (SEQ ID NO: 107), in which X_3 can be T or S, and X_4 can be Y, V, or K; and/or a light chain complementary determining region 1 (LC CDR1) set forth as RSSQSLX_5X_6SDGX_7TFLX_8 (SEQ ID NO: 108), in which X_5 can be A or E, X_6 can be T, S, E, or D, X_7 can be D, Y, or G, and X_8 can be E or H, a light chain complementary determining region 2 (LC CDR2) set forth as X_9VSX_{10}RFS (SEQ ID NO: 109), in which X_9 can be E, D or A, and X_{10} can be N, S, T, E or H, a light chain complementary determining region 3 (LC CDR3) set forth as X_{11}QX_{12}TX_{13}DP$X_{14}X_{15}$ (SEQ ID NO: 110), in which X_{11} can be F or M, X_{12} can be V or A, X_{13} can be H or Y, X_{14} can be M, L or V, and X_{15} can be T or S.

[00011] In some embodiments, the antibody comprises a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 38, and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 39. In some embodiments, the antibody comprises a VH comprising an amino acid sequence of SEQ ID NO: 38, and a VL comprising an amino acid sequence of SEQ ID NO: 39.

[00012] In some embodiments, the antibody is a humanized antibody. In some embodiments, the humanized antibody comprises a humanized VH and/or a humanized VL.

[00013] In some embodiments, 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.

[00014] In some embodiments, the antibody is a full-length IgG. In some embodiments, the antibody comprises a heavy chain constant region of the isotype IgG1, IgG2, IgG3, or IgG4. In some embodiments, the antibody further comprises a heavy chain constant region set forth in SEQ ID NOs: 46, 48, 112 or 113. In some embodiments, the antibody further comprises a light chain constant region set forth in SEQ ID NO: 47. In some embodiments, the antibody comprises: (i) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 61 or 117, and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 62; or (ii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 63 or 118, and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 62. In some embodiments, 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. In some embodiments, 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.

[00015] In some embodiments, the subject has myelofibrosis initiating mutations in JAK2, MPL, ASXL1, TET2, NFE2, SH2B3, SF3B1, or CALR. In some embodiments, the myelofibrosis is associated with increased levels of pro-inflammatory cytokines (e.g., IL-6, oncostatin-M) in the subject. In some embodiments, the subject presents with a serum hemoglobin level of less than 10 g/dL. In some embodiments, the subject presents with a serum hemoglobin level of less than 8 g/dL. In some embodiments, the subject is erythrocyte-transfusion dependent. In some embodiments, the subject is anemic.

[00016] In some embodiments, the subject has previously received an erythropoietin stimulating agent, a JAK-STAT inhibitor, a growth factor ligand trap, or an anti-fibrotic agent.

[00017] In some embodiments, the method described herein further comprising 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. In some embodiments, the erythropoietin stimulating agent is selected from the group consisting of danazol, prednisone, thalidomide, lenalidomide, and pomalidomide. In some embodiments, the JAK-STAT inhibitor is selected from the group consisting of ruxolitinib, fedratinib, momelotinib, pacritinib, INCB039110, AG490, and PpYLKTK. In some embodiments, the growth factor ligand trap is sotatercept or luspatercept. In some embodiments, the anti-fibrotic agent is PRM-151.

[00018] In some aspects, the present disclosure also provides an isolated antibody that binds to human hemojuvelin (HJV) and compositions comprising the same. In some embodiments, the antibody comprises: a heavy chain complementary determining region 1 (HC CDR1) set forth as X_1YGMN (SEQ ID NO: 105), in which X_1 can be N or Y; and/or a heavy chain complementary determining region 2 (HC CDR2) set forth as MIYYDSSX_2KHYADSVKG (SEQ ID NO: 106), in which X_2 can be E or D; and/or a heavy chain complementary determining region 3 (HC CDR3) set forth as GX_3TPDX_4 (SEQ ID NO: 107), in which X_3 can be T or S, and X_4 can be Y, V, or K. In some embodiments, a light chain complementary determining region 1 (LC CDR1) set forth as RSSQSLX_5X_6SDGX_7TFLX_8 (SEQ ID NO: 108), in which X_5 can be A or E, X_6 can be T, S, E, or D, X_7 can be D, Y, or G, and X_8 can be E or H; and/or a light chain complementary determining region 2 (LC CDR2) set forth as X_9VSX_{10}RFS (SEQ ID NO: 109), in which X_9 can be E, D or A, and X_{10} can be N, S, T, E or H; and/or a light chain complementary determining region 3 (LC CDR3) set forth as

$X_{11}QX_{12}TX_{13}DPX_{14}X_{15}$ (SEQ ID NO: 110), in which X_{11} can be F or M, X_{12} can be V or A, X_{13} can be H or Y, X_{14} can be M, L or V, and X_{15} can be T or S.

[00019] In some aspects, the present disclosure also provides an isolated antibody that binds to human hemojuvelin (HJV), in which the antibody comprises: (i) a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 7; and/or (ii) a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 8. In some embodiments, 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/or a LC CDR1 of SEQ ID NO: 4, a LC CDR2 of SEQ ID NO: 5, a LC CDR3 of SEQ ID NO: 6. In some embodiments, the antibody comprises a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 7, and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 8.

[00020] In some aspects, the present disclosure provides an isolated antibody that binds to human hemojuvelin (HJV), in which the antibody comprises: (i) a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 7; and/or (ii) a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 30. In some embodiments 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/or a LC CDR1 of SEQ ID NO: 4, a LC CDR2 of SEQ ID NO: 49, a LC CDR3 of SEQ ID NO: 24. In some embodiments, the antibody comprises a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 7, and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 30.

[00021] In some aspects, the present disclosure provides an isolated antibody that binds to hemojuvelin (HJV), in which the antibody comprises: (i) a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of a heavy

chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 7; (ii) and/or a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 31. In some embodiments, 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/or a LC CDR1 of SEQ ID NO: 4, a LC CDR2 of SEQ ID NO: 18, a LC CDR3 of SEQ ID NO: 25. In some embodiments, the antibody comprises a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 7, and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 8.

[00022] In some aspects, the present disclosure provides an isolated antibody that binds to human hemojuvelin (HJV), in which the antibody comprises: (i) a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 7; and/or (ii) a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of a light chain variable region comprising the amino acid sequence of SEQ ID NO: 32. In some embodiments, 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/or a LC CDR1 of SEQ ID NO: 14, a LC CDR2 of SEQ ID NO: 19, a LC CDR3 of SEQ ID NO: 25. In some embodiments, the antibody comprises a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 7, and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 32.

[00023] In some aspects, the present disclosure provides an isolated antibody that binds to human hemojuvelin (HJV), in which the antibody comprises: (i) a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 7; and/or (ii) a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of a light chain variable region comprising the amino acid sequence of SEQ ID NO: 33. In some embodiments, 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/or a LC

CDR1 of SEQ ID NO: 15, a LC CDR2 of SEQ ID NO: 20, a LC CDR3 of SEQ ID NO: 26. In some embodiments, the antibody comprises a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 7, and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 33.

[00024] In some aspects, the present disclosure provide an isolated antibody that binds to human hemojuvelin (HJV), in which the antibody comprises: (i) a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 34; and/or (ii) a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 35. In some embodiments, the antibody comprises: a HC CDR1 of SEQ ID NO: 9, a HC CDR2 of SEQ ID NO: 2, a HC CDR3 of SEQ ID NO: 3, and/or a LC CDR1 of SEQ ID NO: 16, a LC CDR2 of SEQ ID NO: 21, a LC CDR3 of SEQ ID NO: 27. In some embodiments, the antibody comprises a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 34, and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 35.

[00025] In some aspects, the present disclosure provides an isolated antibody that binds to human hemojuvelin (HJV), in which the antibody comprises: (i) a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 36; and/or (ii) a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 37. In some embodiments, the antibody comprises: a HC CDR1 of SEQ ID NO: 1, a HC CDR2 of SEQ ID NO: 10, a HC CDR3 of SEQ ID NO: 11, and/or a LC CDR1 of SEQ ID NO: 17, a LC CDR2 of SEQ ID NO: 18, a LC CDR3 of SEQ ID NO: 28. In some embodiments, the antibody comprises a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 36, and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 37.

[00026] In some aspects, the present disclosure provides an isolated antibody that binds to human hemojuvelin (HJV), in which the antibody comprises: (i) a heavy chain

complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 38; and/or (ii) a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of a light chain variable region comprising the amino acid sequence of SEQ ID NO: 39. In some embodiments, 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/or a LC CDR1 of SEQ ID NO: 17, a LC CDR2 of SEQ ID NO: 5, a LC CDR3 of SEQ ID NO: 27. In some embodiments, the antibody comprises a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 38, and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 39.

[00027] In some aspects, the present disclosure provides an isolated antibody that binds to human hemojuvelin (HJV), in which the antibody comprises: (i) a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 38; and/or (ii) a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of a light chain variable region comprising the amino acid sequence of SEQ ID NO: 41. In some embodiments, 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/or a LC CDR1 of SEQ ID NO: 50, a LC CDR2 of SEQ ID NO: 22, a LC CDR3 of SEQ ID NO: 28. In some embodiments, the antibody comprises a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 38, and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 41.

[00028] In some aspects, the present disclosure provides an isolated antibody that binds to human hemojuvelin (HJV), in which the antibody comprises: (i) a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 42; and/or (ii) a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of a light chain variable region (VL) comprising the amino

acid sequence of SEQ ID NO: 43. In some embodiments, 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: 12, and/or a LC CDR1 of SEQ ID NO: 15, a LC CDR2 of SEQ ID NO: 23, a LC CDR3 of SEQ ID NO: 27. In some embodiments, the antibody comprises a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 42, and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 43.

[00029] In some aspects, the present disclosure provides an isolated antibody that binds to human hemojuvelin (HJV), in which the antibody comprises: (i) a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 44; and/or (ii) a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 45. In some embodiments, 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: 13, and/or a LC CDR1 of SEQ ID NO: 16, a LC CDR2 of SEQ ID NO: 21, a LC CDR3 of SEQ ID NO: 29. In some embodiments, the antibody comprises a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 44, and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 45.

[00030] In some aspects, the present disclosure provides an isolated antibody that binds to hemojuvelin (HJV), in which the antibody comprises: a HC CDR1, a HC CDR2, and a HC CDR3, which collectively contains no more than 10 amino acid variations, preferably no more than 8 amino acid variations, more preferably no more than 5 amino acid variations, and more preferably no more than 2 amino acid variation, as compared with the HC CDR1, a HC CDR2, and a HC CDR3 of any one of the antibodies listed in Table 1; and/or wherein the antibody comprises a LC CDR1, a LC CDR2, and a LC CDR3, which collectively contains no more than 10 amino acid variations, preferably no more than 8 amino acids variations, as compared with the a LC CDR1, a LC CDR2, and a LC CDR3 of any one of the antibodies listed in Table 1.

[00031] In some embodiments, any of the antibodies provided herein is a humanized antibody. In some embodiments, the humanized antibody comprises a humanized VH and/or a humanized VL. In some embodiments, 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.

In some embodiments, the antibody is a full-length IgG. In some embodiments, the antibody comprises a heavy chain constant region of the isotype IgG1, IgG2, IgG3, or IgG4. In some embodiments, the antibody further comprises a heavy chain constant region set forth in SEQ ID NOs: 46, 48, 112 or 113. In some embodiments, the antibody further comprises a light chain constant region set forth in SEQ ID NO: 47. In some embodiments, the antibody comprises: (i) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 51 or 114, and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NOs: 52-56; (ii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 57 or 115, and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 58; (iii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 59 or 116, and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 60; (iv) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 61 or 117, and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 62; (v) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 63 or 118, and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 62; (vi) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 61 or 117, and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 65; (vii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 66 or 119, and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 67; or (viii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 68 or 120, and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 69.

[00032] In some embodiments, the antibody binds HJV with an equilibrium dissociation constant (KD) less than 100 nM. In some embodiments, the antibody binds to HJV with an equilibrium dissociation constant (KD) less than 1 nM.

[00033] In some embodiments, the antibody is conjugated to a molecular payload. In some embodiments, the molecular payload is a detectable agent, a diagnostic agent, or a therapeutic agent.

[00034] In some aspects, the present disclosure also provides a nucleic acid encoding the isolated antibody described herein.

[00035] In some aspects, the present disclosure also provides vector comprising the nucleic acid encoding the antibody described herein. In some embodiments, the vector comprises a nucleic acid sequence of nucleic acid sequences as set forth in Table 3.

[00036] In some aspects, the present disclosure also provides a host cell comprising the nucleic acid encoding the isolated antibody described herein of and/or the vectors comprising the same.

[00037] In some aspects, the present disclosure also provides a pharmaceutical composition comprising the anti-HJV antibody described herein, and a pharmaceutically acceptable carrier.

[00038] In some aspects, the present disclosure also provides a method for producing an anti-human hemojuvelin (HJV) antibody, the method comprises: (i) culturing the host cell of claim 44 under conditions allowing for expressing of the antibody that binds human hemojuvelin (HJV); and (ii) harvesting the cultured host cell or culture medium for collection of the antibody that binds human hemojuvelin (HJV). In some embodiments, the method comprising purifying the antibody that binds human hemojuvelin (HJV).

[00039] In some aspects, the present disclosure also provides an isolated antibody that binds to human hemojuvelin (HJV) produced by expressing in a host cell (i) a nucleic acid sequence encoding a heavy chain, in which the nucleic acid sequence is at least 90% identical to SEQ ID NO: 92; and/or (ii) a nucleic acid sequence encoding a light chain, in which the nucleic acid sequence is at least 90% identical to SEQ ID NO: 93. In some aspects, the present disclosure also provides an isolated antibody that binds to human hemojuvelin (HJV) produced by expressing in a host cell (i) a nucleic acid sequence encoding a heavy chain, in which the nucleic acid sequence is at least 90% identical to SEQ ID NO: 94; and/or (ii) a nucleic acid sequence encoding a light chain, in which the nucleic acid sequence is at least 90% identical to SEQ ID NO: 93. In some embodiments, the host cell is Chinese hamster ovary (CHO) cells, dhfr- CHO cell, human embryonic kidney (HEK)-293 cells, verda reno (VERO) cells, nonsecreting null (NS0) cells, human embryonic retinal (PER.C6) cells, Sp2/0 cells, baby hamster kidney (BHK) cells, Madin-Darby Canine Kidney (MDCK) cells, Madin-Darby Bovine Kidney (MDBK) cells, or monkey kidney CV1 line transformed by SV40 (COS) cells.

[00040] In some aspects, the present disclosure provides 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.

[00041] In some embodiments, the subject having myelofibrosis has anemia resulting from hepcidin synthesis that is induced by pro-inflammatory cytokines, and wherein the administration of the antibody reduces the anemia.

[00042] In some embodiments, the pro-inflammatory cytokines comprises interleukin-6 (IL-6).

[00043] The foregoing and other aspects, implementations, acts, functionalities, features and embodiments of the present teachings can be more fully understood from the following description in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[00044] The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate certain embodiments, and together with the written description, serve to provide non-limiting examples of certain aspects of the compositions and methods disclosed herein.

[00045] **FIGs. 1A-1G** are graphs showing generation and characterization of anti-HJV antibodies. FIG. 1A shows a schematic process of generation of the anti-hemojuvelin antibody, humanization, and affinity maturation. FIGs. 1B-1G shows the sensorgrams by BIAcore analysis of antibodies HA, hHA-004, hHA-008, hHA-009 and hHA-011.

[00046] **FIGs. 2A-2C** are graphs showing the BMP reporter gene assay for anti-HJV antibodies. FIG. 2A shows the general principle of HJV BMP reporter assay. FIG. 2B shows the effect of anti-HJV antibodies in inhibiting RGMc BMP signaling. FIG. 2C shows the effect of anti-HJV antibodies in inhibiting RGMa BMP signaling.

[00047] **FIG. 3** is a graph showing anti-HJV antibodies non-specific binding to HEK293 cells. Bars from left to right in each group: 100 μg/ml, 10 μg/ml, and 1 μg/ml.

[00048] **FIGs. 4A-4C** are schematic illustrations showing the structure and designs of hHA-008 and hHA-008-QL. FIG. 4A shows the structure of hHA-008. FIG. 4B shows the structure of hHA-008-QL. FIG. 4C shows a comparison in antibody structure between hHA-008 and hHA-008-QL.

[00049] **FIG. 5** is a graph showing the CD4+ T cell response peripheral blood mononuclear cells (PBMCs) challenged with hHA-008 or hHA-008-QL.

[00050] **FIGs. 6A-6C** are graphs showing PK/PD analysis of hHA-008 in rats and Cynomolgus macaque (cyno). FIG. 6A shows maximal effect of hHA-008 measured by TSAT% occurred between 4-8 days post treatment. FIG. 6B shows hHA-008 reached

maximum effect as measured by TSAT% about 1-4 days after injection in female cynos. FIG. 6C shows hHA-008 reached maximum effect as measured by TSAT% about 1-4 days after injection in male cynos, but one of the males did not respond to hHA-008 treatment.

[00051] **FIGs. 7A-7F** shows PK/PD correlation in Cynos with single IV dose of 6 mpk. FIG. 7A shows the maximum TSAT% increase occurred 1-4 days after injection (T_{max}=1-4 days), and one of the animals tested had a drastic decline of TSAT around day 34. FIG. 7B shows plasma hepcidin-25 concentration changes over time after hHA-008 injection. FIG. 7C shows plasma hHA-008 concentration changes over time after hHA-008 injection. FIGs. 7D-7F show that hHA-008 had robust PK/PD correlation of PK (plasma antibody concentration) to TSAT% and plasma hepcidin-25 concentration. The results of each tested Cyno are shown in FIG. 7D (Cyno 1), FIG. 7E (Cyno 2), and FIG. 7F (Cyno 3).

[00052] **FIGs. 8A-8C** show that hHA-008 antibody modulates TSAT% in a dose-dependent manner. FIG. 8A shows TSAT% and hHA-008 concentrations after animals were treated with either 0 (vehicle control) or 0.6 mpk hHA-008. FIG. 8B shows TSAT% and hHA-008 concentrations after animals were treated with either 0 (vehicle control) or 3 mpk hHA-008. FIG. 8C shows TSAT% and hHA-008 concentrations after animals were treated with either 0 (vehicle control) or 60 mpk hHA-008.

[00053] **FIGs. 9A-9C** are graphs showing the PK/PD comparison between hHA-008 and hHA-008-QL. FIG. 9A shows TSAT% changes over time in Cynos post treatment of hHA-008 or hHA-008-QL. FIG. 9A shows TSAT% changes over time in Cynos post treatment of hHA-008 or hHA-008-QL. FIG. 9B shows plasma concentration of the antibodies over time in Cynos post treatment of hHA-008 or hHA-008-QL. FIG. 9C shows a time course of decline of plasma concentration of hHA-008 and hHA-008-QL.

[00054] **FIGs. 10A-10B** are graphs showing binding of FcRn of hHA-008 and hHA-008-QL at pH 6.0 or 7.4. FIG. 10A shows binding of FcRn of hHA-008 and hHA-008-QL at pH 6.0. FIG. 10B shows binding of FcRn of hHA-008 and hHA-008-QL at pH 7.4. X axis: Time. Y Axis: Response.

[00055] **FIG. 11** depicts a myeloproliferation cycle characteristic certain high hepcidin disorders.

[00056] **FIG. 12** depicts the hepcidin stimulatory pathway and the physiological regulation of iron homeostasis by hepcidin.

[00057] **FIG. 13** is a graph showing that IL-6 induces hepcidin expression in Cynos, and hHA-008 treatment prevents inflammation-induced (IL 6) hepcidin-25 increase in a dose-dependent manner in cynos.

[00058] **FIG. 14** shows hHA-008 interacts with amino acids 170-183 (SSPMALGANATATR (SEQ ID NO: 121)) on 3720-RG-050**.** The interaction happens on amino acids 170, 171, 180, 182, 183 on 3720-RG-050.

[00059] **FIG. 15** shows the interaction of 3720-RG-050 and hHA-008. A 3720-RG-050 PDB structure was generated by homology using Swiss Model software. 3720-RG-050 amino acids 170-183 (SSPMALGANATATR (SEQ ID NO: 121)) are shown in A, B, C, D, E: ribbon/surface representation of front view (A); back view (B), side view 1 (C), side view 2 (D) and top view (E). F, G, H, I, J: ribbon representation of front view (F); back view (G), side view 1 (H), side view 2 (I) and top view (J).

[00060] **FIG. 16** shows hHA-008-QL interacts with amino acids 169-182 (TSSPMALGANATAT (SEQ ID NO: 122)) and 289-300 (SQRLSRSERNRR (SEQ ID NO: 127)) of 3720-RG-050. The interaction happens on amino acids 169, 171, 180, 182; 289, 293, 294, 295, 297, 300 on 3720-RG-050.

[00061] **FIG. 17** shows the interaction 3720-RG-050/hHA-008-QL. A 3720-RG-050 PDB structure was generated by homology using Swiss Model software. 3720-RG-050 amino acids 169-182 (TSSPMALGANATAT (SEQ ID NO: 122)) and 289-291 (SQR) are shown in A, B, C, D, E: ribbon/surface representation of front view (A); back view (B), side view 1 (C), side view 2 (D) and top view (E). F, G, H, I, J: ribbon representation of front view (F); back view (G), side view 1 (H), side view 2 (I) and top view (J).

[00062] **FIG. 18** shows that hHA-008 was effective in preventing IL-6-induced serum iron suppression in a dose-dependent manner in cynomolgus monkeys.

[00063] **FIG. 19** shows that decline in PD response (e.g., Hepcidin-25 concentration and TSAT%) was consistent with the decrease of hHA-008 serum concentration (FIG .19) after subcutaneous administration of hHA-008 to Sprague-Dawley Rats.

[00064] **FIGs. 20A-20D** show PK/PD analysis in cynomolgus monkeys after subcutaneous administration of hHA-008. FIG. 20A shows serum concentration-time profiles became indistinguishable between SC injection and IV injection 4 days after administration. FIGs. 20B-20D show the return of serum iron to baseline levels was consistent with the decline in hHA-008 serum concentrations after 0.3 mpk, 0.6 mpk and 1 mpk injection of hHA-008 either by subcutaneous injection or intravenous injection.

DETAILED DESCRIPTION

[00065] The present disclosure, at least in part, is based on the development of anti-Hemojuvelin (HJV) antibodies, *e.g.*, antibodies listed in Table 1 and their variants, which showed high binding affinity and specificity to human hemojuvelin. Also provided are the use of the anti-HJV antibodies and their variants in research, diagnostic/detection, and therapeutic applications. In some embodiments, the disclosure provides anti-Hemojuvelin (HJV) antibodies for targeting hepcidin pathway that are effective for inhibiting hepcidin function and/or reducing hepcidin expression in cells, particularly for modulating iron homeostasis for the treatment of myelofibrosis and/or one or more symptoms or complications thereof. Accordingly, in related aspects, the disclosure provides compositions and methods for treating myelofibrosis, including primary myelofibrosis, myelofibrosis arising from a myeloproliferative neoplasm, and/or one or more symptoms or complications thereof, such as myelofibrosis-associated anemia, inflammation, bone marrow failure, splenomegaly, hypercatabolic symptoms, and/or fatigue.

[00066] In some embodiments, anti-hemojuvelin antibodies are provided that bind RGMc as a primary mode of action (as compared with RGMa and RGMb). Accordingly, in some embodiments, an anti-hemojuvelin antibody preferentially binds RGMc versus RGMa and/or RGMb. In some embodiments, an anti-hemojuvelin antibody binds RGMc with an equilibrium dissociation constant (KD) less than one hundred nanomolar (nM) (KD < 100 nM). However, in some embodiments, the anti-hemojuvelin antibody binds RGMc with a similar affinity as RGMa and/or RGMb.

[00067] The foregoing and other aspects, implementations, acts, functionalities, features and embodiments of the present teachings can be more fully understood from the following description in conjunction with the accompanying drawings.

I. Definitions

[00068] **Administering**: As used herein, the terms "administering" or "administration" means to provide a complex to a subject in a manner that is physiologically and/or pharmacologically useful (e.g., to treat a condition in the subject).

[00069] **Affinity Matured Antibody**: "Affinity Matured Antibody" is used herein to refer to an antibody with one or more alterations in one or more CDRs, which result in an improvement in the affinity (i.e. KD, kd or ka) of the antibody for a target antigen compared to a parent antibody, which does not possess the alteration(s). Exemplary affinity matured

antibodies will have nanomolar or even picomolar affinities for the target antigen. A variety of procedures for producing affinity matured antibodies are known in the art, including the screening of a combinatory antibody library that has been prepared using bio-display. For example, Marks et al., BioTechnology, 10: 779-783 (1992) describes affinity maturation by VH and VL domain shuffling. Random mutagenesis of CDR and/or framework residues is described by Barbas et al., Proc. Nat. Acad. Sci. USA, 91: 3809-3813 (1994); Schier et al., Gene, 169: 147-155 (1995); Yelton et al., J. Immunol., 155: 1994-2004 (1995); Jackson et al., J. Immunol., 154(7): 3310-3319 (1995); and Hawkins et al, J. Mol. Biol., 226: 889-896 (1992). Selective mutation at selective mutagenesis positions and at contact or hypermutation positions with an activity-enhancing amino acid residue is described in U.S. Pat. No. 6,914,128 B1.

[00070] Antibody: As used herein, the term "antibody" refers to a polypeptide that includes at least one immunoglobulin variable domain or at least one antigenic determinant, e.g., paratope that specifically binds to an antigen. In some embodiments, an antibody is a full-length antibody. In some embodiments, an antibody is a chimeric antibody. In some embodiments, an antibody is a humanized antibody. However, in some embodiments, an antibody is a Fab fragment, a F(ab')2 fragment, a Fv fragment or a scFv fragment. In some embodiments, an antibody is a nanobody derived from a camelid antibody or a nanobody derived from shark antibody. In some embodiments, an antibody is a diabody. In some embodiments, an antibody comprises a framework having a human germline sequence. In another embodiment, an antibody comprises a heavy chain constant domain selected from the group consisting of IgG, IgG1, IgG2, IgG2A, IgG2B, IgG2C, IgG3, IgG4, IgA1, IgA2, IgD, IgM, and IgE constant domains. In some embodiments, an antibody comprises a heavy (H) chain variable region (abbreviated herein as VH), and/or a light (L) chain variable region (abbreviated herein as VL). In some embodiments, an antibody comprises a constant domain, e.g., an Fc region. An immunoglobulin constant domain refers to a heavy or light chain constant domain. Human IgG heavy chain and light chain constant domain amino acid sequences and their functional variations are known. With respect to the heavy chain, in some embodiments, the heavy chain of an antibody described herein can be an alpha (α), delta (Δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain. In some embodiments, the heavy chain of an antibody described herein can comprise a human alpha (α), delta (Δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain. In a particular embodiment, an antibody described herein comprises a human gamma 1 CH1, CH2, and/or CH3 domain. In some embodiments, the

amino acid sequence of the V_H domain comprises the amino acid sequence of a human gamma (γ) heavy chain constant region, such as any known in the art. Non-limiting examples of human constant region sequences have been described in the art, e.g., see U.S. Pat. No. 5,693,780 and Kabat E A et al., (1991) supra. In some embodiments, the V_H domain comprises an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or at least 99% identical to any of the variable chain constant regions provided herein. In some embodiments, an antibody is modified, e.g., modified via glycosylation, phosphorylation, sumoylation, and/or methylation. In some embodiments, an antibody is a glycosylated antibody, which is conjugated to one or more sugar or carbohydrate molecules. In some embodiments, the one or more sugar or carbohydrate molecule are conjugated to the antibody via N-glycosylation, O-glycosylation, C-glycosylation, glypiation (GPI anchor attachment), and/or phosphoglycosylation. In some embodiments, the one or more sugar or carbohydrate molecule are monosaccharides, disaccharides, oligosaccharides, or glycans. In some embodiments, the one or more sugar or carbohydrate molecule is a branched oligosaccharide or a branched glycan. In some embodiments, the one or more sugar or carbohydrate molecule includes a mannose unit, a glucose unit, an N-acetylglucosamine unit, or a phospholipid unit. In some embodiments, an antibody is a construct that comprises a polypeptide comprising one or more antigen binding fragments of the disclosure linked to a linker polypeptide or an immunoglobulin constant domain. Linker polypeptides comprise two or more amino acid residues joined by peptide bonds and are used to link one or more antigen binding portions. Examples of linker polypeptides have been reported (see e.g., Holliger, P., et al. (1993) Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak, R. J., et al. (1994) Structure 2:1121-1123). Still further, an antibody may be part of a larger immunoadhesion molecule, formed by covalent or noncovalent association of the antibody or antibody portion with one or more other proteins or peptides. Examples of such immunoadhesion molecules include use of the streptavidin core region to make a tetrameric scFv molecule (Kipriyanov, S. M., et al. (1995) Human Antibodies and Hybridomas 6:93-101) and use of a cysteine residue, a marker peptide and a C-terminal polyhistidine tag to make bivalent and biotinylated scFv molecules (Kipriyanov, S. M., et al. (1994) Mol. Immunol. 31:1047-1058).

[00071] Approximately: As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term "approximately" or "about" refers to a range of values that fall within 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated

or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[00072] CDR: As used herein, the term "CDR" refers to the complementarity determining region within antibody variable sequences. A typical antibody molecule comprises a heavy chain variable region (VH) and a light chain variable region (VL), which are usually involved in antigen binding. The VH and VL regions can be further subdivided into regions of hypervariability, also known as "complementarity determining regions" ("CDR"), interspersed with regions that are more conserved, which are known as "framework regions" ("FR"). Each VH and VL is typically composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The extent of the framework region and CDRs can be precisely identified using methodology known in the art, for example, by the Kabat definition, the IMGT definition, the Chothia definition, the AbM definition, and/or the contact definition, all of which are well known in the art. See, e.g., Kabat, E.A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; IMGT®, the international ImMunoGeneTics information system® http://www.imgt.org, Lefranc, M.-P. et al., Nucleic Acids Res., 27:209-212 (1999); Ruiz, M. et al., Nucleic Acids Res., 28:219-221 (2000); Lefranc, M.-P., Nucleic Acids Res., 29:207-209 (2001); Lefranc, M.-P., Nucleic Acids Res., 31:307-310 (2003); Lefranc, M.-P. et al., In Silico Biol., 5, 0006 (2004) [Epub], 5:45-60 (2005); Lefranc, M.-P. et al., Nucleic Acids Res., 33:D593-597 (2005); Lefranc, M.-P. et al., Nucleic Acids Res., 37:D1006-1012 (2009); Lefranc, M.-P. et al., Nucleic Acids Res., 43:D413-422 (2015); Chothia et al., (1989) Nature 342:877; Chothia, C. et al. (1987) J. Mol. Biol. 196:901-917, Al-lazikani et al (1997) J. Molec. Biol. 273:927-948; and Almagro, J. Mol. Recognit. 17:132-143 (2004). ee also hgmp.mrc.ac.uk and bioinf.org.uk/abs. As used herein, a CDR may refer to the CDR defined by any method known in the art. Two antibodies having the same CDR means that the two antibodies have the same amino acid sequence of that CDR as determined by the same method, for example, the IMGT definition.

[00073] Generally, there are three CDRs in each of the variable regions of the heavy chain and the light chain, which are designated CDR1, CDR2 and CDR3, for each of the variable regions. The term "CDR set" as used herein refers to a group of three CDRs that occur in a single variable region capable of binding the antigen. The exact boundaries of these CDRs have been defined differently according to different systems. The system described by Kabat (Kabat *et al.,* Sequences of Proteins of Immunological Interest (National Institutes of Health,

Bethesda, Md. (1987) and (1991)) not only provides an unambiguous residue numbering system applicable to any variable region of an antibody, but also provides precise residue boundaries defining the three CDRs. These CDRs may be referred to as Kabat CDRs. Sub-portions of CDRs may be designated as L1, L2 and L3 or H1, H2 and H3 where the "L" and the "H" designates the light chain and the heavy chains regions, respectively. These regions may be referred to as Chothia CDRs, which have boundaries that overlap with Kabat CDRs. Other boundaries defining CDRs overlapping with the Kabat CDRs have been described by Padlan (FASEB J. 9:133-139 (1995)) and MacCallum (J Mol Biol 262(5):732-45 (1996)). Still other CDR boundary definitions may not strictly follow one of the above systems, but will nonetheless overlap with the Kabat CDRs, although they may be shortened or lengthened in light of prediction or experimental findings that particular residues or groups of residues or even entire CDRs do not significantly impact antigen binding. The methods used herein may utilize CDRs defined according to any of these systems, although preferred embodiments use Kabat or Chothia defined CDRs.

[00074] CDR-grafted antibody: The term "CDR-grafted antibody" refers to antibodies which comprise heavy and light chain variable region sequences from one species but in which the sequences of one or more of the CDR regions of VH and/or VL are replaced with CDR sequences of another species, such as antibodies having murine heavy and light chain variable regions in which one or more of the murine CDRs (*e.g.,* CDR3) has been replaced with human CDR sequences.

[00075] Chimeric antibody: The term "chimeric antibody" refers to antibodies which comprise heavy and light chain variable region sequences from one species and constant region sequences from another species, such as antibodies having murine heavy and light chain variable regions linked to human constant regions.

[00076] Complementary: As used herein, the term “complementary” refers to the capacity for precise pairing between two nucleotides or two sets of nucleotides. In particular, complementary is a term that characterizes an extent of hydrogen bond pairing that brings about binding between two nucleotides or two sets of nucleotides. For example, if a base at one position of an oligonucleotide is capable of hydrogen bonding with a base at the corresponding position of a target nucleic acid (e.g., an mRNA), then the bases are considered to be complementary to each other at that position. Base pairings may include both canonical Watson-Crick base pairing and non-Watson-Crick base pairing (e.g., Wobble base pairing and Hoogsteen base pairing). For example, in some embodiments, for complementary base pairings, adenosine-type bases (A) are complementary to thymidine-

type bases (T) or uracil-type bases (U), that cytosine-type bases (C) are complementary to guanosine-type bases (G), and that universal bases such as 3-nitropyrrole or 5-nitroindole can hybridize to and are considered complementary to any A, C, U, or T. Inosine (I) has also been considered in the art to be a universal base and is considered complementary to any A, C, U or T.

[00077] Conservative amino acid substitution: As used herein, a "conservative amino acid substitution" refers to an amino acid substitution that does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references which compile such methods, e.g. Molecular Cloning: A Laboratory Manual, J. Sambrook, et al., eds., Fourth Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 2012, or Current Protocols in Molecular Biology, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Conservative substitutions of amino acids include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D.

[00078] Cross-reactive: As used herein and in the context of a targeting agent (e.g., antibody), the term "cross-reactive," refers to a property of the agent being capable of specifically binding to more than one antigen of a similar type or class (e.g., antigens of multiple homologs, paralogs, or orthologs) with similar affinity or avidity. For example, in some embodiments, an antibody that is cross-reactive against human and non-human primate antigens of a similar type or class (e.g., a human hemojuvelin and non-human primate hemojuvelin) is capable of binding to the human antigen and non-human primate antigens with a similar affinity or avidity. In some embodiments, an antibody is cross-reactive against a human antigen and a rodent antigen of a similar type or class. In some embodiments, an antibody is cross-reactive against a rodent antigen and a non-human primate antigen of a similar type or class. In some embodiments, an antibody is cross-reactive against a human antigen, a non-human primate antigen, and a rodent antigen of a similar type or class.

[00079] Effective Amount: As used herein, "an effective amount" refers to the amount of each active agent (e.g., anti-HJV antibody) required to confer therapeutic effect on the subject, either alone or in combination with one or more other active agents. In some embodiments, the therapeutic effect is reduced hepcidin level or activity, increased level of transferrin saturation (TSAT%), decreased level of circulating transferrin level, and/or alleviated disease conditions (e.g., reduced anemia or reduce myelofibrosis progression).

[00080] Framework: As used herein, the term "framework" or "framework sequence" refers to the remaining sequences of a variable region minus the CDRs. Because the exact definition of a CDR sequence can be determined by different systems, the meaning of a framework sequence is subject to correspondingly different interpretations. The six CDRs (CDR-L1, CDR-L2, and CDR-L3 of light chain and CDR-H1, CDR-H2, and CDR-H3 of heavy chain) also divide the framework regions on the light chain and the heavy chain into four sub-regions (FR1, FR2, FR3 and FR4) on each chain, in which CDR1 is positioned between FR1 and FR2, CDR2 between FR2 and FR3, and CDR3 between FR3 and FR4. Without specifying the particular sub-regions as FR1, FR2, FR3 or FR4, a framework region, as referred by others, represents the combined FRs within the variable region of a single, naturally occurring immunoglobulin chain. As used herein, a FR represents one of the four sub-regions, and FRs represents two or more of the four sub-regions constituting a framework region. Human heavy chain and light chain acceptor sequences are known in the art. In one embodiment, the acceptor sequences known in the art may be used in the antibodies disclosed herein.

[00081] Hemojuvelin (HJV): As used herein, the term "hemojuvelin (HJV)" (also known as repulsive guidance molecule C (RGMc) or hemochromatosis type 2 protein (HFE2)) refers to a membrane-bound and soluble form protein that regulates hepcidin production through the BMP/SMAD signaling pathway. The *HFE2* gene encodes two known classes of GPI-anchored and glycosylated HJV molecules, which are targeted to the membrane and undergo distinct fates. HJV exists in multiple isoforms, including two soluble isoforms and two membrane-associated isoforms. In some embodiments, a predominant membrane-associated isoform is a disulfide-linked two-chain form composed of N- and C-terminal fragments. In some embodiments, a full-length single-chain isoform associates with the membrane, but is released from the cell surface and accumulates in extracellular fluid. In some embodiments, HJV may be of human (NCBI Gene ID 148738), non-human primate (e.g., NCBI Gene ID 698805), or rodent (e.g., NCBI Gene ID 69585 or NCBI Gene ID 310681) origin. In addition to HJV (RGMc), the repulsive guidance molecule family includes repulsive guidance molecule A (RGMa) and repulsive guidance molecule B (RGMb). RGMa and RGMb are expressed in the central nervous system during development and are thought to be involved in controlling axonal patterning and neuronal survival, while HJV is produced in the liver and in cardiac and skeletal muscle.

[00082] Hepcidin: As used herein, a "hepcidin" refers to an iron-regulating peptide hormone primarily made in the liver that is encoded by the HAMP gene. In some

embodiments, hepcidin controls the delivery of iron to blood plasma from intestinal cells absorbing iron, from erythrocyte-recycling macrophages, and from iron-storing hepatocytes. In some embodiments, hepcidin inhibits iron transport by binding to the iron export channel ferroportin which is located on the basolateral surface of gut enterocytes and the plasma membrane of reticuloendothelial cells (macrophages). In some embodiments, inhibiting ferroportin prevents iron from being exported and the iron is sequestered in the cells. In some embodiments, by inhibiting ferroportin, hepcidin prevents enterocytes from allowing iron into the hepatic portal system, thereby reducing dietary iron absorption. Hepcidin expression involves multiple aspects, including, for example, transcription of the HAMP gene, translation of the transcribed mRNA, and the posttranslational processing of the hepcidin precursor into the bioactive hepcidin-25 peptide (DTHFPICIFCCGCCHRSKCGMCCKT (SEQ ID NO: 129)). In some embodiments, hepcidin expression is modulated via the hemojuvelin-induced BMP signaling pathway. In some embodiments, hepcidin expression is modulated via the IL-6-JAK-STAT signaling pathway.

[00083] HJV-induced BMP signaling: As used herein, the term "HJV-induced BMP signaling" refers to signaling through BMP receptors that is induced by Hemojuvelin (HJV), which is a membrane bound co-receptor for bone morphogenetic protein (BMP) signaling. As discussed in Xia Y, et al., *Hemojuvelin regulates hepcidin expression via a selective subset of BMP ligands and receptors independently of neogenin*, Blood. 2008 May 15; 111(10): 5195–5204, in hepatocytes, HJV-induced BMP signaling positively regulates hepcidin mRNA expression. In some embodiments, HJV binds to BMP2, BMP4, BMP5, or BMP6 to induce BMP signaling, e.g., to positively regulate hepcidin levels in hepatocytes. In some embodiments, cleavage of HJV by matripatase-2 reduces the amount of cell surface HJV available to participate in BMP signaling. In some embodiments, induction of BMP signaling by HJV is independent of neogenin. However, in some embodiments, neogenin facilitates induction of BMP signaling by HJV, as discussed in Zhao et al, *Neogenin Facilitates the Induction of Hepcidin Expression by Hemojuvelin in the Liver*, J Biol Chem. 2016 Jun 3; 291(23): 12322–12335. In some embodiments, BMP6 is responsible for iron-dependent activation of the Smad signaling. In some embodiments, BMP6 is secreted from liver sinusoidal endothelial cells and binds to a BMP receptor (BMPR) on hepatocytes and thereby activates the SMAD signaling cascade. In such embodiments, HJV serves as a co-receptor for such BMP6, e.g., to positively regulate hepcidin levels in hepatocytes. In some embodiments, BMPs transduce signals by binding to one or a combination of type I and II

serine/threonine kinase receptors. BMP type II receptors include BMPRII, ActRIIA, and ActRIIB. BMP type I receptors include ALK3, ALK6, and ALK2. In some embodiments, upon ligand binding, constitutively active type II receptors phosphorylate type I receptors, and type I receptors then phosphorylate intracellular receptor-activated Smads (R-Smads), namely Smad 1, Smad 5 and/or Smad 8. In such embodiments, activated R-Smads complex with the common partner Smad4 and translocate to the nucleus to regulate gene transcription, e.g., induction of hepcidin expression.

[00084] Hepcidin Antagonist: As used herein, a "hepcidin antagonist" refers to an agent that reduces hepcidin expression and/or hepcidin activity (directly or indirectly). In some embodiments, a hepcidin antagonist reduces hepcidin-25 levels and/or activity (directly or indirectly). In some embodiments, a hepcidin antagonist inhibits hepcidin-induced ferroportin degradation. Accordingly, in some embodiments, a hepcidin antagonist targets hepcidin function indirectly through the hepcidin stimulatory pathway to decrease hepcidin expression. In some embodiments, a hepcidin antagonist targets hepcidin function directly, e.g., by binding the hepcidin peptide to sequester free hepcidin or by binding ferroportin to inhibit the hepcidin-ferroportin binding interaction, thereby decreasing hepcidin-induced ferroportin degradation. In some embodiments, a hepcidin antagonist is a ferroportin inhibitor that disrupts ferroportin-hepcidin interactions, such as, for example, as disclosed in Ross SL, et al., *Identification of Antibody and Small Molecule Antagonists of Ferroportin-Hepcidin Interaction*. Front Pharmacol. 2017 Nov 21;8:838; Fung E., et al., *High-Throughput Screening of Small Molecules Identifies Hepcidin Antagonists*. Molecular Pharmacology March 2013, 83 (3) 681-690; and Angeliki Katsarou and Kostas Pantopoulos, *Hepcidin Therapeutics*. Pharmaceuticals (Basel). 2018 Dec; 11(4): 127, the relevant contents of each of which are incorporated herein by reference.

[00085] Human antibody: The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the disclosure may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[00086] Humanized antibody: The term "humanized antibody" refers to antibodies which comprise heavy and light chain variable region sequences from a non-human species (e.g., a mouse) but in which at least a portion of the V_H and/or V_L sequence has been altered to be more "human-like", *i.e.,* more similar to human germline variable sequences. One type of humanized antibody is a CDR-grafted antibody, in which human CDR sequences are introduced into non-human VH and VL sequences to replace the corresponding nonhuman CDR sequences. In one embodiment, humanized anti-hemojuvelin antibodies and antigen binding portions are provided. Such antibodies may be generated by obtaining murine anti-hemojuvelin monoclonal antibodies using traditional hybridoma technology followed by humanization using *in vitro* genetic engineering, such as those disclosed in Kasaian et al PCT publication No. WO 2005/123126 A2.

[00087] Isolated antibody: An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds hemojuvelin is substantially free of antibodies that specifically bind antigens other than hemojuvelin). An isolated antibody that specifically binds hemojuvelin may, however, have cross-reactivity to other antigens, such as other repulsive guidance molecule (RGM) proteins (e.g., RGMa and/or RGMb). Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[00088] JAK-STAT signaling: As used herein, the term "JAK-STAT signaling" refers to signaling through cellular receptors that recruits a Janus Kinase (JAK), such as, for example, Janus Kinase 1 (JAK1) or Janus Kinase 2 (JAK2), to activate a transcription factor signal transducer and activator of transcription (STAT), such as, for example, STAT3. In some embodiments, as discussed in Maliken, BD, et al., *The Hepcidin Circuits Act: Balancing Iron and Inflammation*, Hepatology. 2011 May; 53(5): 1764–1766, JAK-STAT signaling involves binding of the cytokine interleukin-6 (IL-6) to its cognate cellular receptor, which then recruits Janus Kinase 2 (JAK2) to phosphorylate STAT3. In some embodiments, STAT3 is then (following JAK2 activation/phosphorylation) translocated into the nucleus. In some embodiments, activated STAT3 then induces hepcidin transcription, e.g., by binding to the STAT3 binding motif in the hepcidin promoter region. Thus, in some embodiments, hepcidin expression is induced via JAK-STAT signaling during inflammation through activation STAT3 by IL-6.

[00089] Kabat numbering: The terms "Kabat numbering", "Kabat definitions and "Kabat labeling" are used interchangeably herein. These terms, which are recognized in the art, refer

to a system of numbering amino acid residues which are more variable (i.e. hypervariable) than other amino acid residues in the heavy and light chain variable regions of an antibody, or an antigen binding portion thereof (Kabat et al. (1971) Ann. NY Acad, Sci. 190:382-391 and, Kabat, E. A., *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). For the heavy chain variable region, the hypervariable region ranges from amino acid positions 31 to 35 for CDR1, amino acid positions 50 to 65 for CDR2, and amino acid positions 95 to 102 for CDR3. For the light chain variable region, the hypervariable region ranges from amino acid positions 24 to 34 for CDR1, amino acid positions 50 to 56 for CDR2, and amino acid positions 89 to 97 for CDR3.

[00090] Myelofibrosis: As used herein, the term "myelofibrosis" refers to a disorder characterized by pathological myeloproliferation and aberrant cytokine production resulting in progressive fibrosis, inflammation and/or functional compromise of the bone marrow niche of a subject. The fibrosis associated with myelofibrosis often results from a non-clonal fibroblastic response to inflammatory and fibrogenic cytokines produced by aberrant clonal myeloid cells, such as megakaryocytes. Myelofibrosis typically results in bone marrow failure, splenomegaly, hypercatabolic symptoms, and anemia. In some embodiments, myelofibrosis arises in a subject *de novo*. In such embodiments, the myelofibrosis is considered as a "primary" myelofibrosis. However, in some embodiments, the myelofibrosis arises from a preexisting myeloproliferative neoplasm. In some embodiments, the preexisting myeloproliferative neoplasm is a polycythemia. In some embodiments, the preexisting myeloproliferative neoplasm is an essential thrombocytosis.

[00091] Myelofibrosis-Associated Anemia: As used herein, the term "myelofibrosis-associated anemia" refers to a condition arising in the context of, or comorbid with, myelofibrosis and being characterized by a deficiency in the ability of blood to transport oxygen. In some embodiments, myelofibrosis-associated anemia is the result of a deficiency in red blood cells, a deficiency in hemoglobin, and/or a deficiency in total blood volume. In some embodiments, a myelofibrosis-associated anemia is an iron deficiency anemia or a myelophthisic anemia. In some embodiments, myelofibrosis-associated anemia is further associated with chronic inflammatory disease. In some embodiments, a myelofibrosis-associated anemia is associated with high circulating hepcidin level in a subject. In some embodiments, a myelofibrosis-associate anemia is associated with proinflammatory cytokine (e.g., IL-6) induced high circulating hepcidin level in a subject. Examples of anemias other than myelofibrosis-associated anemia include anemias related to rheumatoid arthritis,

anemias of infection, autoimmune hemolytic anemia, aplastic anemia, hypoplastic anemia, pure red cell aplasia and anemia resulting from renal failure or endocrine disorders, megaloblastic anemias, anemia resulting from defects in heme or globin synthesis, anemia caused by a structural defect in red blood cells, e.g., sickle-cell anemia, sideroblastic anemia, anemia associated with chronic infections such as malaria, trypanosomiasis, HIV, hepatitis virus or other viruses, anemias caused by marrow deficiencies in absence of myelofibrosis, and chemotherapy-induced anemia.

[00092] Oligonucleotide: As used herein, the term "oligonucleotide" refers to an oligomeric nucleic acid compound of up to 200 nucleotides in length. Examples of oligonucleotides include, but are not limited to, RNAi oligonucleotides (e.g., siRNAs, shRNAs), microRNAs, gapmers, mixmers, phosphorodiamidite morpholinos, peptide nucleic acids, aptamers, guide nucleic acids (e.g., Cas9 guide RNAs), etc. Oligonucleotides may be single-stranded or double-stranded. In some embodiments, an oligonucleotide may comprise one or more modified nucleotides (e.g. 2′-O-methyl sugar modifications, purine or pyrimidine modifications). In some embodiments, an oligonucleotide may comprise one or more modified internucleotide linkage. In some embodiments, an oligonucleotide may comprise one or more phosphorothioate linkages, which may be in the Rp or Sp stereochemical conformation.

[00093] Recombinant antibody: The term "recombinant human antibody", as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described in more details in this disclosure), antibodies isolated from a recombinant, combinatorial human antibody library (Hoogenboom H. R., (1997) TIB Tech. 15:62-70; Azzazy H., and Highsmith W. E., (2002) Clin. Biochem. 35:425-445; Gavilondo J. V., and Larrick J. W. (2002) BioTechniques 29:128-145; Hoogenboom H., and Chames P. (2000) Immunology Today 21:371-378), antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic for human immunoglobulin genes (see e.g., Taylor, L. D., et al. (1992) Nucl. Acids Res. 20:6287-6295; Kellermann S-A., and Green L. L. (2002) Current Opinion in Biotechnology 13:593-597; Little M. et al (2000) Immunology Today 21:364-370) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to in vitro mutagenesis (or, when an animal transgenic for

human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*. One embodiment of the disclosure provides fully human antibodies capable of binding human hemojuvelin which can be generated using techniques well known in the art, such as, but not limited to, using human Ig phage libraries such as those disclosed in Jermutus et al., PCT publication No. WO 2005/007699 A2.

[00094] Selective: As used herein, the term "selective" or "selectively" refers to the ability of a molecule to produce an effect in relation to its target molecule compared to a reference molecule. For example, a molecule that selectively inhibits its target molecule means that this molecule is capable of inhibiting its target molecule with a degree that is distinguishable from a reference molecule in an inhibition assay or other inhibitory context. For example, with respect to an inhibitor, the term, "selectively inhibits", refers to the ability of the inhibitor to inhibit its target molecule with a degree that is distinguishable from a reference molecule that is not substantially inhibited in an inhibition assay, e.g., to an extent that permit selective inhibition of the target molecule, as described herein. For example, the half maximal inhibitory concentration (IC50) for the target molecule and/or the reference molecule can be tested in a kinase potency assay as described in Asshoff, M. et al., Momelotinib inhibits ACVR1/ALK2, decreases hepcidin production, and ameliorates anemia of chronic disease in rodents. Blood. 2017 Mar 30; 129(13): 1823–1830 (e.g., Kinase potency assay by Carna Biosciences). In this assay, inhibitor solution (e.g., solution containing the selective inhibitor to be tested)/kinase substrate is mixed with target molecule solution (e.g., ALK2) or reference molecule solution (e.g., JAK1 or JAK2), and incubated under room temperature for 1 hour. Once the reaction is terminated, the signal produced by enzymatic activity on the substrate can be measured. The half maximal inhibitor concentration for the target molecule and the reference molecule can be calculated. In some embodiments, a molecule described herein selectively binds to a target molecule. In some embodiments, a molecule described herein selectively inhibits to a target molecule. In some embodiments, a molecule described herein selectively antagonizes to a target molecule. In some embodiments, a molecule described herein selectively neutralizes to a target molecule.

[00095] Specifically binds: As used herein, the term "specifically binds" refers to the ability of a molecule to bind to a binding partner with a degree of affinity or avidity that enables the molecule to be used to distinguish the binding partner from an appropriate control in a binding assay or other binding context. With respect to an antibody, the term,

"specifically binds", refers to the ability of the antibody to bind to a specific antigen with a degree of affinity or avidity, compared with an appropriate reference antigen or antigens, that enables the antibody to be used to distinguish the specific antigen from others, e.g., to an extent that permits preferential targeting to certain cells, e.g., muscle cells, through binding to the antigen, as described herein. In some embodiments, an antibody specifically binds to a target if the antibody has a K_D for binding the target of at least about 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, 10^{-13} M, or less. In some embodiments, an antibody specifically binds to hemojuvelin.

[00096] Subject: As used herein, the term "subject" refers to a mammal. In some embodiments, a subject is non-human primate, or rodent. In some embodiments, a subject is a human. In some embodiments, a subject is a patient, e.g., a human patient that has or is suspected of having a disease. In some embodiments, the subject is a human patient who has or is suspected of having myelofibrosis and/or one or more conditions arising as a result of myelofibrosis.

[00097] Treatment: As used herein, the term "treating" or "treatment" refers to the application or administration of a composition including one or more active agents (e.g., anti-HJV antibodies) to a subject, who has a target disease or disorder, a symptom of the disease/disorder, or a predisposition toward the disease/disorder, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect the disorder, the symptom of the disease, or the predisposition toward the disease or disorder. Alleviating a target disease/disorder includes delaying or preventing the development or progression of the disease, or reducing disease severity.

II. Anti-Hemojuvelin (HJV) Antibodies

[00098] In some embodiments, the hemojuvelin antagonist binds to one or more proteins of the repulsive guidance molecule (RGM) family, including RGMa, RGMb, and RGMc (HJV). In some embodiments, the hemojuvelin antagonist selectively binds hemojuvelin (RGMc) over RGMa and RGMb. In some embodiments, the hemojuvelin antagonist is an antisense oligonucleotide that reduces expression of hemojuvelin (see, e.g., U.S. Patent No. 7,534,764; U.S. Patent Publication No. US 2014/127325; and International Publication No. WO 2016/180784, which are incorporated herein by reference). In some embodiments, the hemojuvelin antagonist is a small molecule compound that inhibits hemojuvelin, e.g., by competitive binding and/or chemical modification of hemojuvelin.

[00099] In some embodiments, the hemojuvelin antagonist is an antibody (e.g., HA001-HA012) specific for hemojuvelin and/or one or more proteins of the RGM protein family (e.g., RGMa, RGMb). Appropriate antibodies specific for hemojuvelin and/or one or more RGM proteins that may be useful in certain methods provided herein are provided for example, in U.S. Patent Nos. 10,118,958; and 8,507,435; U.S. Patent Publication Nos. US 2013/330343; US 2015/166672; and US 2017/029499; and International Publication Nos. WO 2015/171691; and WO 2018/009624, which are incorporated herein by reference. Provided herein, in some aspects, are antibodies that bind to human hemojuvelin (HJV) with high specificity and affinity. In some embodiments, the anti- HJV antibody described herein specifically binds to any extracellular epitope of a HJV or an epitope that becomes exposed to an antibody. In some embodiments, anti- HJV antibodies provided herein bind specifically to HJV from human, non-human primates, mouse, rat, *etc*. In some embodiments, anti- HJV antibodies provided herein bind to human HJV. In some embodiments, the anti- HJV antibody described herein binds to an amino acid segment of a human or non-human primate HJV.

[000100] In some embodiments, the anti-HJV antibody described herein specifically binds to an epitope on human HJV. Human HJV is a 426 amino acid protein with a predicted N-terminal signal peptide of 31 amino acids and a C-terminal GPI-attachment signal of 45 amino acids. An exemplary human HJV amino acid sequence is set forth in SEQ ID NO: 128:

MGEPGQSPSPRSSHGSPPTLSTLTLLLLLCGHAHSQCKILRCNAEYVSSTLSLRGGGSSGAL
RGGGGGGRGGGVGSGGLCRALRSYALCTRRTARTCRGDLAFHSAVHGIEDLMIQHNCSRQGP
TAPPPPRGPALPGAGSGLPAPDPCDYEGRFSRLHGRPPGFLHCASFGDPHVRSFHHHFHTCR
VQGAWPLLDNDFLFVQATSSPMALGANATATRKLTIIFKNMQECIDQKVYQAEVDNLPVAFE
DGSINGGDRPGGSSLSIQTANPGNHVEIQAAYIGTTIIIRQTAGQLSFSIKVAEDVAMAFSA
EQDLQLCVGGCPPSQRLSRSERNRRGAITIDTARRLCKEGLPVEDAYFHSCVFDVLISGDPN
FTVAAQAALEDARAFLPDLEKLHLFPSDAGVPLSSATLLAPLLSGLFVLWLCIQ (SEQ ID NO: 128)

[000101] In some embodiments, the anti-HJV antibody described herein may bind to a fragment of a human HJV. The fragment of HJV may be between about 5 and about 425 amino acids, between about 10 and about 400 amino acids, between about 50 and about 350 amino acids, between about 100 and about 300 amino acids, between about 150 and about 250 amino acids, between about 200 and about 300 amino acids, or between about 75 and about 150 amino acids in length. The fragment may comprise a contiguous number of amino acids from RGMc. An exemplary amino acid of a HJV fragment is set forth in SEQ ID NO: 123:

QCKILRCNAEYVSSTLSLRGGGSSGALRGGGGGGRGGGVGSGGLCRALRSYALCTRRTARTC
RGDLAFHSAVHGIEDLMIQHNCSRQGPTAPPPPRGPALPGAGSGLPAPDPCDYEGRFSRLHG
RPPGFLHCASFGDPHVRSFHHHFHTCRVQGAWPLLDNDFLFVQATSSPMALGANATATRKLT
IIFKNMQECIDQKVYQAEVDNLPVAFEDGSINGGDRPGGSSLSIQTANPGNHVEIQAAYIGT
TIIIRQTAGQLSFSIKVAEDVAMAFSAEQDLQLCVGGCPPSQRLSRSERNRRGAITIDTARR
LCKEGLPVEDAYFHSCVFDVLISGDPNFTVAAQAALEDARAFLPDLEKLHLFPSD (SEQ ID NO: 123)

[000102] In some embodiments, the anti-HJV antibody described herein binds to different epitopes within a human HJV or a human HJV fragment.

[000103] In some embodiments, the anti-HJV antibody interacts with an epitope within amino acids 160-190 of SEQ ID NO: 123. In some embodiments, the anti-HJV antibody interacts with an epitope having an amino acid sequence of amino acids 170-183 of SEQ ID NO: 123. In some embodiments, the anti-HJV antibody interacts with an epitope having the amino acid sequence of SSPMALGANATATR (SEQ ID NO: 121). In some embodiments, the anti-HJV antibody interacts with different segments within SSPMALGANATATR (SEQ ID NO: 121). In some embodiments, the anti-HJV antibody interacts with amino acids 170-171, amino acids 171-180, amino acids 180-182, and amino acids 182-183 of SEQ ID NO: 123. In some embodiments, the antibody interacts with amino acids 170 (S), 171(S), 180 (T), 182 (T) and 183 (R) of SEQ ID NO: 123. In some embodiments, hHA-008 interacts with the epitope SSPMALGANATATR (SEQ ID NO: 121). In some embodiments, hHA-008 interacts with amino acids 170 (S), 171(S), 180 (T), 182 (T) and 183 (R) of SEQ ID NO: 123.

[000104] In some embodiments, the anti-HJV antibody interacts with an epitope within amino acids 160-190 of SEQ ID NO: 123 and/or amino acids 280-310 of SEQ ID NO: 123. In some embodiments, the anti-HJV antibody interacts with an epitope within amino acids 169-182 of SEQ ID NO: 123 and/or amino acids 289-300 of SEQ ID NO: 123. In some embodiments, the anti-HJV antibody interacts with an epitope within amino acids 169-182 of SEQ ID NO: 123 and amino acids 289-300 of SEQ ID NO: 123. In some embodiments, the anti-HJV antibody interacts with an epitope having the amino acid sequence of TSSPMALGANATAT (SEQ ID NO: 122) and amino acid sequence SQRLSRSERNRR (SEQ ID NO: 127). In some embodiments, the anti-HJV antibody interacts with different segments within TSSPMALGANATAT (SEQ ID NO: 122) and SQRLSRSERNRR (SEQ ID NO: 127). In some embodiments, the anti-HJV antibody interacts with amino acids 169-171, amino acids 171-180, and amino acids 180-182 of SEQ ID NO: 123, and amino acids 289-293, amino acids 293-294, amino acids 294-295, amino acids 295-297 and amino acids 297-300 of SEQ ID NO: 123. In some embodiments, the antibody interacts with amino acids 169

(T), 170 (S), 171(S), 180 (T), 182 (T), 289 (S), 293 (S), 294 (R), 295(S), 297(R), and 300 (R) of SEQ ID NO: 123. In some embodiments, hHA-008-QL interacts with different segments within TSSPMALGANATAT (SEQ ID NO: 122) and SQRLSRSERNRR (SEQ ID NO: 127). In some embodiments, hHA-008-QL interacts with amino acids 169 (T), 170 (S), 171(S), 180 (T), 182 (T), 289 (S), 293 (S), 294 (R), 295(S), 297(R), and 300 (R) of SEQ ID NO: 123.

[000105] In some embodiments, the anti-HJV antibodies described herein are affinity matured clones. In some embodiments, an anti- HJV antibody specifically binds a HJV (e.g., a human or non-human primate HJV) with binding affinity (e.g., as indicated by K_D) of at least about 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, 10^{-13} M, or less. For example, the anti-HJV antibodies of the present disclosure can bind to a hemojuvelin protein (*e.g.,* human hemojuvelin) with an affinity between 5 pM and 500 nM, *e.g.*, between 50 pM and 100 nM, *e.g.*, between 500 pM and 50 nM. The disclosure also includes antibodies that compete with any of the antibodies described herein for binding to a hemojuvelin protein (*e.g.,* human hemojuvelin) and that have an affinity of 100 nM or lower (*e.g.*, 80 nM or lower, 50 nM or lower, 20 nM or lower, 10 nM or lower, 500 pM or lower, 50 pM or lower, or 5 pM or lower). The affinity and binding kinetics of the anti-HJV antibody can be tested using any suitable method including but not limited to biosensor technology (*e.g.*, OCTET or BIACORE). In some embodiments, the anti- HJV antibodies described herein binds to HJV with a K_D of sub-nanomolar range. In some embodiments, the anti- HJV antibodies described herein selectively binds to RGMc, but not RGMa or RGMb.

[000106] Binding affinity (or binding specificity) can be determined by a variety of methods including equilibrium dialysis, equilibrium binding, gel filtration, ELISA, surface plasmon resonance (SPR), florescent activated cell sorting (FACS) or spectroscopy (e.g., using a fluorescence assay). Exemplary conditions for evaluating binding affinity are in HBS-P buffer (10 mM HEPES pH7.4, 150 mM NaCl, 0.005% (v/v) surfactant P20) and PBS buffer (10mM PO4-3, 137mM NaCl, and 2.7mM KCl). These techniques can be used to measure the concentration of bound proteins as a function of target protein concentration. The concentration of bound protein ([Bound]) is generally related to the concentration of free target protein ([Free]) by the following equation:

[Bound] = [Free]/(Kd+[Free])

[000107] It is not always necessary to make an exact determination of K_A, though, since sometimes it is sufficient to obtain a quantitative measurement of affinity, e.g., determined using a method such as ELISA or FACS analysis, is proportional to K_A, and thus can be used

for comparisons, such as determining whether a higher affinity is, e.g., 2-fold higher, to obtain a qualitative measurement of affinity, or to obtain an inference of affinity, e.g., by activity in a functional assay, e.g., an in vitro or in vivo assay.

[000108] The heavy chain (HC) and light chain (LC) sequences, heavy chain variable domain (VH) and light chain variable domain (VL), CDR sequences, and heavy chain and light chain constant region sequences of non-limiting examples of anti-HJV antibodies are provided in Table 1.

Table 1. Examples of anti-HJV antibodies (CDRs according to the Kabat definition)

humanized Hemojuvelin Antagonist (HA) Antibody		Sequences	SEQ ID NO
hHA-001	HC CDR1	NYGMN	1
	HC CDR2	MIYYDSSEKHYADSVKG	2
	HC CDR3	GTTPDY	3
	LC CDR1	RSSQSLETSDGDTFLE	4
	LC CDR2	EVSTRFS	5
	LC CDR3	FQVTHDPMT	6
	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSS	7
	VL	DVVLTQSPLSLPVTLGQPASISC**RSSQSLETSDGDTFLE**W FQQRPGQSPRLLIY**EVSTRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQVTHDPMT**FGQGTKLEIK	8
	HC Constant Region (with or without the lysine residue at C-terminal of heavy chain constant region)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPGK	46
		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPG	112
	LC Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC	47
	Heavy Chain (with or without the lysine residue at C-terminal of heavy chain)	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG	51

		SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPGK	
		EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPG	114
	Light Chain	DVVLTQSPLSLPVTLGQPASISC**RSSQSLETSDGDTFLE**W FQQRPGQSPRLLIY**EVSTRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQVTHDPMT**FGQGTKLEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	52
hHA-002	HC CDR1	NYGMN	1
	HC CDR2	MIYYDSSEKHYADSVKG	2
	HC CDR3	GTTPDY	3
	LC CDR1	RSSQSLETSDGDTFLE	4
	LC CDR2	EVSSRFS	49
	LC CDR3	MQVTHDPLT	24
	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSS	7
	VL	DVVLTQSPLSLPVTLGQPASISC**RSSQSLETSDGDTFLE**W FQQRPGQSPRLLIY**EVSSRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**MQVTHDPLT**FGQGTKLEIK	30
	HC Constant Region (with or without the lysine residue at C-terminal of heavy chain constant region)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPGK	46
		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPG	112
	LC Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC	47

	Heavy Chain (with or without the lysine residue at C-terminal of heavy chain)	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPGK	51
		EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPG	114
	Light Chain	DVVLTQSPLSLPVTLGQPASISC**RSSQSLETSDGDTFLE**W FQQRPGQSPRLLIY**EVSSRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**MQVTHDPLT**FGQGTKLEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	53
hHA-003	HC CDR1	NYGMN	1
	HC CDR2	MIYYDSSEKHYADSVKG	2
	HC CDR3	GTTPDY	3
	LC CDR1	RSSQSLETSDGDTFLE	4
	LC CDR2	EVSNRFS	18
	LC CDR3	FQVTHDPVT	25
	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSS	7
	VL	DVVLTQSPLSLPVTLGQPASISC**RSSQSLETSDGDTFLE**W FQQRPGQSPRLLIY**EVSNRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQVTHDPVT**FGQGTKLEIK	31
	HC Constant Region (with or without the lysine residue at C-terminal of heavy chain constant region)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPGK	46
		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPG	112

	LC Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC	47
	Heavy Chain (with or without the lysine residue at C-terminal of heavy chain)	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPGK	51
		EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPG	114
	Light Chain	DVVLTQSPLSLPVTLGQPASISC**RSSQSLETSDGDTFLE**W FQQRPGQSPRLLIY**EVSNRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQVTHDPVT**FGQGTKLEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	54
hHA-004	HC CDR1	NYGMN	1
	HC CDR2	MIYYDSSEKHYADSVKG	2
	HC CDR3	GTTPDY	3
	LC CDR1	RSSQSLESSDGDTFLE	14
	LC CDR2	DVSTRFS	19
	LC CDR3	FQVTHDPVT	25
	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSS	7
	VL	DVVLTQSPLSLPVTLGQPASISC**RSSQSLESSDGDTFLE**W FQQRPGQSPRLLIY**DVSTRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQVTHDPVT**FGQGTKLEIK	32
	HC Constant Region (with or without the lysine residue at C-terminal of heavy chain constant region)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPGK	46
		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE	112

		MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPG	
	LC Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC	47
	Heavy Chain (with or without the lysine residue at C-terminal of heavy chain)	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPGK	51
		EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPG	114
	Light Chain	DVVLTQSPLSLPVTLGQPASISC**RSSQSLESSDGDTFLE**W FQQRPGQSPRLLIY**DVSTRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQVTHDPVT**FGQGTKLEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	55
hHA-005	HC CDR1	NYGMN	1
	HC CDR2	MIYYDSSEKHYADSVKG	2
	HC CDR3	GTTPDY	3
	LC CDR1	RSSQSLEESDGYTFLE	15
	LC CDR2	DVSERFS	20
	LC CDR3	FQATYDPLT	26
	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSS	7
	VL	DVVLTQSPLSLPVTLGQPASISC**RSSQSLEESDGYTFLE**W FQQRPGQSPRLLIY**DVSERFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATYDPLT**FGQGTKLEIK	33
	HC Constant Region (with or without the lysine residue at C-terminal of heavy chain constant region)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPGK	46

		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPG	112
	LC Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC	47
	Heavy Chain (with or without the lysine residue at C-terminal of heavy chain)	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPGK	51
		EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPG	114
	Light Chain	DVVLTQSPLSLPVTLGQPASISC**RSSQSLEESDGYTFLE**W FQQRPGQSPRLLIY**DVSERFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATYDPLT**FGQGTKLEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	56
hHA-006	HC CDR1	YYGMN	9
	HC CDR2	MIYYDSSEKHYADSVKG	2
	HC CDR3	GTTPDY	3
	LC CDR1	RSSQSLEDSDGGTFLE	16
	LC CDR2	DVSSRFS	21
	LC CDR3	FQATHDPLT	27
	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**YYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSS	34
	VL	DVVLTQSPLSLPVTLGQPASISC**RSSQSLEDSDGGTFLE**W FQQRPGQSPRLLIY**DVSSRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATHDPLT**FGQGTKLEIK	35
	HC Constant Region (with or without the lysine residue at C-terminal of	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE	46

	heavy chain constant region)	MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPGK	
		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPG	112
	LC Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC	47
	Heavy Chain (with or without the lysine residue at C-terminal of heavy chain)	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**YYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPGK	57
		EVQLVESGGGLVQPGGSLRLSCAASGFTFS**YYGMN**WIRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPG	115
	Light Chain	DVVLTQSPLSLPVTLGQPASISC**RSSQSLEDSDGGTFLE**W FQQRPGQSPRLLIY**DVSSRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATHDPLT**FGQGTKLEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	58
hHA-007	HC CDR1	NYGMN	1
	HC CDR2	MIYYDSSDKHYADSVKG	10
	HC CDR3	GTTPDV	11
	LC CDR1	RSSQSLEESDGYTFLH	17
	LC CDR2	EVSNRFS	18
	LC CDR3	FQATHDPVT	28
	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSDKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDV**WGQGTMVTVSS	36
	VL	DVVLTQSPLSLPVTLGQPASISC**RSSQSLEESDGYTFLH**W FQQRPGQSPRLLIY**EVSNRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATHDPVT**FGQGTKLEIK	37

	HC Constant Region (with or without the lysine residue at C-terminal of heavy chain constant region)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPGK	46
		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPG	112
	LC Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC	47
	Heavy Chain (with or without the lysine residue at C-terminal of heavy chain)	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSDKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDV**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPGK	59
		EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WIRQA PGKGLEWIG**MIYYDSSDKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDV**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPG	116
	Light Chain	DVVLTQSPLSLPVTLGQPASISC**RSSQSLEESDGYTFLH**W FQQRPGQSPRLLIY**EVSNRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATHDPVT**FGQGTKLEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	60
hHA-008	HC CDR1	NYGMN	1
	HC CDR2	MIYYDSSEKHYADSVKG	2
	HC CDR3	GTTPDY	3
	LC CDR1	RSSQSLEESDGYTFLH	17
	LC CDR2	EVSTRFS	5
	LC CDR3	FQATHDPLT	27
	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WVRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSS	38

	VL	DVVLTQSPLSLPVTLGQPASISC**RSSQSLEESDGYTFLH**W FQQRPGQSPRLLIY**EVSTRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATHDPLT**FGQGTKLEIK	39
	HC Constant Region (with or without the lysine residue at C-terminal of heavy chain constant region)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPGK	46
		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPG	112
	LC Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC	47
	Heavy Chain (with or without the lysine residue at C-terminal of heavy chain)	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**W**V**RQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPGK	61
		EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**W**V**RQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPG	117
	Light Chain	DVVLTQSPLSLPVTLGQPASISC**RSSQSLEESDGYTFLH**W FQQRPGQSPRLLIY**EVSTRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATHDPLT**FGQGTKLEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	62
hHA-008-QL	HC CDR1	NYGMN	1
	HC CDR2	MIYYDSSEKHYADSVKG	2
	HC CDR3	GTTPDY	3
	LC CDR1	RSSQSLEESDGYTFLH	17
	LC CDR2	EVSTRFS	5
	LC CDR3	FQATHDPLT	27

	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WVRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSS	38
	VL	DVVLTQSPLSLPVTLGQPASISC**RSSQSLEESDGYTFLH**W FQQRPGQSPRLLIY**EVSTRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATHDPLT**FGQGTKLEIK	39
	HC Constant Region (with or without the lysine residue at C-terminal of heavy chain constant region)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**Q**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**L**HEALHNHYT QKSLSLSPGK	48
		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**Q**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**L**HEALHNHYT QKSLSLSPG	113
	LC Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC	47
	Heavy Chain (with or without the lysine residue at C-terminal of heavy chain)	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WVRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**Q**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**L**HEALHNHYTQKSLS LSPGK	63
		EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WVRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**Q**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**L**HEALHNHYTQKSLS LSPG	118
	Light Chain	DVVLTQSPLSLPVTLGQPASISC**RSSQSLEESDGYTFLH**W FQQRPGQSPRLLIY**EVSTRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATHDPLT**FGQGTKLEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	62
hHA-009	HC CDR1	NYGMN	1
	HC CDR2	MIYYDSSEKHYADSVKG	2
	HC CDR3	GTTPDY	3

	LC CDR1	RSSQSLADSDGDTFLH	50
	LC CDR2	AVSHRFS	22
	LC CDR3	FQATHDPVT	28
	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WVRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDY**WGQGTMVTVSS	38
	VL	DVVLTQSPLSLPVTLGQPASISC**RSSQSLADSDGDTFLH**W FQQRPGQSPRLLIY**AVSHRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATHDPVT**FGQGTKLEIK	41
	HC Constant Region (with or without the lysine residue at C-terminal of heavy chain constant region)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPGK	46
		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPG	112
	LC Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC	47
	Heavy Chain (with or without the lysine residue at C-terminal of heavy chain)	EVQLVESGGGLVQPG**G**SLRLSCAASGFTFS**NYGMN**WVRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCA**KGTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPGK	61
		EVQLVESGGGLVQPG**G**SLRLSCAASGFTFS**NYGMN**WVRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCA**KGTTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPG	117
	Light Chain	DVVLTQSPLSLPVTLGQPASISC**RSSQSLADSDGDTFLH**W FQQRPGQSPRLLIY**AVSHRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATHDPVT**FGQGTKLEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	65

hHA-010	HC CDR1	NYGMN	1
	HC CDR2	MIYYDSSEKHYADSVKG	2
	HC CDR3	GTTPDK	12
	LC CDR1	RSSQSLEESDGYTFLE	15
	LC CDR2	EVSHRFS	23
	LC CDR3	FQATHDPLT	27
	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WVRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDK**WGQGTMVTVSS	42
	VL	DVVLTQSPLSLPVTLGQPASISC**RSSQSLEESDGYTFLE**W FQQRPGQSPRLLIY**EVSHRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATHDPLT**FGQGTKLEIK	43
	HC Constant Region (with or without the lysine residue at C-terminal of heavy chain constant region)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPGK	46
		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPG	112
	LC Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC	47
	Heavy Chain (with or without the lysine residue at C-terminal of heavy chain)	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WVRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDK**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPGK	66
		EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WVRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GTTPDK**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPG	119
	Light Chain	DVVLTQSPLSLPVTLGQPASISC**RSSQSLEESDGYTFLE**W FQQRPGQSPRLLIY**EVSHRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATHDPLT**FGQGTKLEIKRTVAAPSV	67

		FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	
hHA-011	HC CDR1	NYGMN	1
	HC CDR2	MIYYDSSEKHYADSVKG	2
	HC CDR3	G**S**TPDY	13
	LC CDR1	RSSQSLEDSDGGTFLE	16
	LC CDR2	DVSSRFS	21
	LC CDR3	FQATHDPLS	29
	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WVRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GSTPDY**WGQGTMVTVSS	44
	VL	DVVLTQSPLSLPVTLGQPASISC**RSSQSLEDSDGGTFLE**W FQQRPGQSPRLLIY**DVSSRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATHDPLS**FGQGTKLEIK	45
	HC Constant Region (with or without the lysine residue at C-terminal of heavy chain constant region)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPGK	46
		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GG PSVFLFPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYT QKSLSLSPG	112
	LC Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC	47
	Heavy Chain (with or without the lysine residue at C-terminal of heavy chain)	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WVRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GSTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPGK	68
		EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGMN**WVRQA PGKGLEWIG**MIYYDSSEKHYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**GSTPDY**WGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFL FPPKPKD**T**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV**M**HEALHNHYTQKSLS LSPG	120

	Light Chain	DVVLTQSPLSLPVTLGQPASISC**RSSQSLEDSDGGTFLE**W FQQRPGQSPRLLIY**DVSSRFS**GVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYC**FQATHDPLS**FGQGTKLEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	69

[000109] In some embodiments, the N-terminal of the heavy chain of the anti-HJV antibody described herein is glutamic acid (E). In some embodiments, the glutamic acid can cyclize spontaneously to pyroglutamic acid by post-translational modification. Spontaneous cyclization of glutamic acid to pyroglutamic acid has been previously described, e.g., Chelius et al., Formation of Pyroglutamic Acid From N-terminal Glutamic Acid in Immunoglobulin Gamma Antibodies, Anal Chem. 2006;78(7):2370-2376. In some embodiments, the N-terminal of the heavy chain of the anti-HJV antibody described herein is a pyroglutamic acid. In some embodiments, the anti-HJV antibodies having N-terminal pyroglutamic acid are impurities in the population of anti-HJV antibodies (e.g., less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5%, less than 0.1%, less than 0.05%, or less than 0.01%) in the population of anti-HJV antibody. In some embodiments, the population of the anti-HJV antibodies comprises a mixture of anti-HJV antibodies having glutamic acid or pyroglutamic acid at the N-terminal of the heavy chain.

[000110] In some embodiments, the anti-HJV antibodies of the present disclosure comprises one or more of the HC CDRs (e.g., HC CDR1, HC CDR2, or HC CDR3) amino acid sequences from any one of the anti-HJV antibodies selected from Table 1. In some embodiments, the anti-HJV antibodies of the present disclosure comprise the HC CDR1, HC CDR2, and HC CDR3 as provided for any one of the antibodies elected from Table 1. In some embodiments, the anti-HJV antibodies of the present disclosure comprises one or more of the LC CDRs (e.g., LC CDR1, LC CDR2, or LC CDR3) amino acid sequences from any one of the anti-HJV antibodies selected from Table 1. In some embodiments, the anti-HJV antibodies of the present disclosure comprise the LC CDR1, LC CDR2, and LC CDR3as provided for any one of the anti-HJV antibodies selected from Table 1.

[000111] In some embodiments, the anti-HJV antibodies of the present disclosure comprises the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 as provided for any one of the anti-HJV antibodies selected from Table 1. In some embodiments, antibody heavy and light chain CDR3 domains may play a particularly important role in the binding specificity/affinity of an antibody for an antigen. Accordingly, the anti-HJV antibodies of the

disclosure may include at least the heavy and/or light chain CDR3s of any one of the anti-HJV antibodies selected from Table 1.

[000112] In some embodiments, the isolated anti-HJV antibody comprises a heavy chain variable region that comprises a heavy chain CDR1 (HC CDR1), a heavy chain CDR2 (HC CDR2), and a heavy chain CDR3 (HC CDR3).

[000113] In some embodiments, following the Kabat definition, the HC CDR1 may comprise the amino acid sequence of X_1YGMN (SEQ ID NO: 105), in which X_1 can be N or Y. Alternatively or in addition, the HC CDR2 may comprise the amino acid sequence of MIYYDSSX_2KHYADSVKG (SEQ ID NO: 106), in which X_2 can be E or D. Alternatively or in addition, the HC CDR3 may comprise the amino acid sequence of GX_3TPDX_4 (SEQ ID NO: 107), in which X_3 can be T or S, and X_4 can be Y, V, or K.

[000114] In some embodiments, following the Kabat definition, the anti-HJV antibody may comprise a light chain variable region that comprises a light chain CDR1 (LC CDR1), a light chain CDR2 (LC CDR2), and a light chain CDR3 (LC CDR3). In some embodiments, the LC CDR1 may comprise the amino acid sequence of RSSQSLX_5X_6SDGX_7TFLX_8 (SEQ ID NO: 108), in which X_5 can be A or E, X_6 can be T, S, E, or D, X_7 can be D, Y, or G, and X_8 can be E or H. Alternatively or in addition, the LC CDR2 may comprise the amino acid sequence of X_9VSX_{10}RFS (SEQ ID NO: 109), in which X_9 can be E, D or A, and X_{10} can be N, S, T, E or H. Alternatively or in addition, the LC CDR3 may comprise the amino acid sequence of X_{11}QX_{12}TX_{13}DP$X_{14}X_{15}$ (SEQ ID NO: 110), in which X_{11} can be F or M, X_{12} can be V or A, X_{13} can be H or Y, X_{14} can be M, L or V, and X_{15} can be T or S.

[000115] Also within the scope of the present disclosure are functional variants of any of the exemplary anti-HJV antibodies as disclosed herein. A functional variant may contain one or more amino acid residue variations in the V_H and/or V_L, or in one or more of the HC CDRs and/or one or more of the LC CDRs as relative to the reference antibody, while retaining substantially similar binding and biological activities (*e.g.*, substantially similar binding affinity, binding specificity, inhibitory activity, anti-inflammatory activity, or a combination thereof) as the reference antibody.

[000116] In some embodiments, any of the anti-HJV antibodies of the disclosure have one or more CDRs (e.g., HC CDR or LC CDR) sequences substantially similar to any of the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and/or LC CDR3 sequences from one of the anti-HJV antibodies selected from Table 1. In some embodiments, the position of one or more CDRs along the VH (e.g., HC CDR1, HC CDR2, or HC CDR3) and/or VL (e.g., LC CDR1, LC CDR2, or LC CDR3) region of an antibody described herein can vary by one,

two, three, four, five, or six amino acid positions so long as immunospecific binding to hemojuvelin (e.g., human hemojuvelin) is maintained (e.g., substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% of the binding of the original antibody from which it is derived). For example, in some embodiments, the position defining a CDR of any antibody described herein can vary by shifting the N-terminal and/or C-terminal boundary of the CDR by one, two, three, four, five, or six amino acids, relative to the CDR position of any one of the antibodies described herein, so long as immunospecific binding to hemojuvelin (e.g., human hemojuvelin) is maintained (e.g., substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% of the binding of the original antibody from which it is derived). In another embodiment, the length of one or more CDRs along the VH (e.g., HC CDR1, HC CDR2, or HC CDR3) and/or VL (e.g., LC CDR1, LC CDR2, or LC CDR3) region of an antibody described herein can vary (e.g., be shorter or longer) by one, two, three, four, five, or more amino acids, so long as immunospecific binding to hemojuvelin (e.g., human hemojuvelin) is maintained (e.g., substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% of the binding of the original antibody from which it is derived).

[000117] Accordingly, in some embodiments, a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and/or LC CDR3 described herein may be one, two, three, four, five or more amino acids shorter than one or more of the CDRs described herein (e.g., CDRS from any of the anti-HJV antibodies selected from Table 1) so long as immunospecific binding to hemojuvelin (e.g., human hemojuvelin) is maintained (e.g., substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and/or LC CDR3 described herein may be one, two, three, four, five or more amino acids longer than one or more of the CDRs described herein (e.g., CDRS from any of the anti-HJV antibodies selected from Table 1) so long as immunospecific binding to hemojuvelin (e.g., human hemojuvelin) is maintained (e.g., substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, the amino portion of a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and/or LC CDR3 described herein can be extended by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (e.g., CDRS from any of the anti-HJV antibodies selected from Table 1) so

long as immunospecific binding to hemojuvelin (e.g., human hemojuvelin) is maintained (e.g., substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, the carboxy portion of a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and/or LC CDR3 described herein can be extended by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (e.g., CDRS from any of the anti-HJV antibodies selected from Table 1) so long as immunospecific binding to hemojuvelin (e.g., human hemojuvelin) is maintained (e.g., substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, the amino portion of a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and/or LC CDR3 described herein can be shortened by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (e.g., CDRS from any of the anti-HJV antibodies selected from Table 1) so long as immunospecific binding to hemojuvelin (e.g., human hemojuvelin) is maintained (e.g., substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, the carboxy portion of a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and/or LC CDR3 described herein can be shortened by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (e.g., CDRS from any of the anti-HJV antibodies selected from Table 1) so long as immunospecific binding to hemojuvelin (e.g., human hemojuvelin) is maintained (e.g., substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). Any method can be used to ascertain whether immunospecific binding to hemojuvelin (e.g., human hemojuvelin) is maintained, for example, using binding assays and conditions described in the art.

[000118] In some examples, any of the anti-HJV antibodies of the disclosure have one or more CDR (e.g., HC CDR or LC CDR) sequences substantially similar to any one of the anti-HJV antibodies selected from Table 1. For example, the antibodies may include one or more CDR sequence(s) from any of the anti-HJV antibodies selected from Table 1 containing up to 5, 4, 3, 2, or 1 amino acid residue variations as compared to the corresponding CDR region in any one of the CDRs provided herein (e.g., CDRs from any of the anti-HJV antibodies selected from Table 1) so long as immunospecific binding to hemojuvelin (e.g., human hemojuvelin) is maintained (e.g., substantially maintained, for example, at least 50%, at least

60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, any of the amino acid variations in any of the CDRs provided herein may be conservative variations. Conservative variations can be introduced into the CDRs at positions where the residues are not likely to be involved in interacting with a hemojuvelin protein (e.g., a human hemojuvelin protein), for example, as determined based on a crystal structure. Some aspects of the disclosure provide anti-HJV antibodies that comprise one or more of the heavy chain variable (VH) and/or light chain variable (VL) domains provided herein. In some embodiments, any of the VH domains provided herein include one or more of the HC CDR sequences (e.g., HC CDR1, HC CDR2, and HC CDR3) provided herein, for example, any of the CDR-H sequences provided in any one of the anti-HJV selected from Table 1. In some embodiments, any of the VL domains provided herein include one or more of the CDR-L sequences (e.g., LC CDR1, LC CDR2, and LC CDR3) provided herein, for example, any of the LC CDR sequences provided in any one of the anti-HJV antibodies selected from Table 1.

[000119] In some embodiments, the anti-HJV antibodies of the disclosure include any antibody that includes a heavy chain variable domain and/or a light chain variable domain of any one of the anti-HJV antibodies selected from Table 1, and variants thereof. In some embodiments, anti-HJV antibodies of the disclosure include any antibody that includes the heavy chain variable and light chain variable pairs of any anti-HJV antibodies selected from Table 1.

[000120] Aspects of the disclosure provide anti-HJV antibodies having a heavy chain variable (VH) and/or a light chain variable (VL) domain amino acid sequence homologous to any of those described herein. In some embodiments, the anti-HJV antibody comprises a heavy chain variable sequence or a light chain variable sequence that is at least 75% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the heavy chain variable sequence and/ or any light chain variable sequence of any one of the anti-HJV antibodies selected from Table 1. In some embodiments, the homologous heavy chain variable and/or a light chain variable amino acid sequences do not vary within any of the CDR sequences provided herein. For example, in some embodiments, the degree of sequence variation (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) may occur within a heavy chain variable and/or a light chain variable sequence excluding any of the CDR sequences provided herein. In some embodiments, any of the anti-HJV antibodies provided herein comprise a heavy chain variable sequence and a light chain variable sequence that comprises a framework sequence

that is at least 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to the framework sequence of any anti-HJV antibodies selected from Table 1.

[000121] In some embodiments, the anti-HJV antibody of the present disclosure is a humanized antibody (e.g., a humanized variant containing one or more CDRs of Table 1). In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2, and a LC CDR3 that are the same as the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 shown in Table 1, and comprises a humanized heavy chain variable region and/or a humanized light chain variable region.

[000122] Humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. In some embodiments, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, the humanized antibody may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences, but are included to further refine and optimize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Antibodies may have Fc regions modified as described in WO 99/58572. Other forms of humanized antibodies have one or more CDRs (one, two, three, four, five, six) which are altered with respect to the original antibody, which are also termed one or more CDRs derived from one or more CDRs from the original antibody. Humanized antibodies may also involve affinity maturation.

[000123] In some embodiments, humanization is achieved by grafting the CDRs (e.g., as shown in Table 1) into the human variable domains (e.g., IGKV1-NL1*01 and IGHV1-3*01 human variable domain). In some embodiments, the anti-HJV antibody of the present disclosure is a humanized variant comprising one or more amino acid substitutions (e.g., in the VH framework region) as compared with any one of the VHs listed in Table 1, and/or one or more amino acid substitutions (e.g., in the VL framework region) as compared with any one of the VLs listed in Table 1.

[000124] In some embodiments, the anti-HJV antibody of the present disclosure is a humanized antibody comprising a VH containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VH of any of the anti-HJV antibodies listed in Table 1. Alternatively or in addition, the anti-HJV antibody of the present disclosure is a humanized antibody comprising a VL containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VL of any one of the anti-HJV antibodies listed in Table 1.

[000125] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, HC CDR2 and HC CDR3 of a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, LC CDR2 and LC CDR3 of a light chain variable domain having the amino acid sequence of SEQ ID NO: 8.

[000126] In some embodiments, according to the Kabat definition system, the anti-HJV antibody of the present disclosure comprises a HC CDR1 having the amino acid sequence of SEQ ID NO: 1, a HC CDR2 having the amino acid sequence of SEQ ID NO: 2, a HC CDR3 having the amino acid sequence of SEQ ID NO: 3, a LC CDR1 having the amino acid sequence of SEQ ID NO: 4, a LC CDR2 having the amino acid sequence of SEQ ID NO: 5, and a LC CDR3 having the amino acid sequence of SEQ ID NO: 6.

[000127] In some embodiments, anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 3. "Collectively," as used anywhere in the present disclosure, means that the total number of amino acid variations in all of the three heavy chain CDRs is within the defined range. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2 or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 4, LC CDR2 having the amino acid sequence of SEQ ID NO: 5, and LC CDR3 having the amino acid sequence of SEQ ID NO: 6.

[000128] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3 that collectively are at least 80% (e.g., 80%, 85%,

90%, 95%, 98%, or 99%) identical to the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the to the LC CDR1 having the amino acid sequence of SEQ ID NO: 4, LC CDR2 having the amino acid sequence of SEQ ID NO: 5, and LC CDR3 having the amino acid sequence of SEQ ID NO: 6.

[000129] In some embodiments, the anti-HJV antibody of the present disclosure comprises: a HC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1; a HC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR2 having the amino acid sequence of SEQ ID NO: 2; and/or a HC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR3 having the amino acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises: a LC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 4; a LC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR2 having the amino acid sequence of SEQ ID NO: 5; and/or a LC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR3 having the amino acid sequence of SEQ ID NO: 6.

[000130] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 8.

[000131] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VH as set forth in SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VL as set forth in SEQ ID NO: 8.

[000132] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VH as set forth in SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VL as set forth in SEQ ID NO: 8.

[000133] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, HC CDR2 and HC CDR3 of a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, LC CDR2 and LC CDR3 of a light chain variable domain having the amino acid sequence of SEQ ID NO: 30.

[000134] In some embodiments, according to the Kabat definition system, the anti-HJV antibody of the present disclosure comprises a HC CDR1 having the amino acid sequence of SEQ ID NO: 1, a HC CDR2 having the amino acid sequence of SEQ ID NO: 2, a HC CDR3 having the amino acid sequence of SEQ ID NO: 3, a LC CDR1 having the amino acid sequence of SEQ ID NO: 4, a LC CDR2 having the amino acid sequence of SEQ ID NO: 49, and a LC CDR3 having the amino acid sequence of SEQ ID NO: 24.

[000135] In some embodiments, anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 3. "Collectively," as used anywhere in the present disclosure, means that the total number of amino acid variations in all of the three heavy chain CDRs is within the defined range. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2 or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 4, LC CDR2 having the amino acid sequence of SEQ ID NO: 49, and LC CDR3 having the amino acid sequence of SEQ ID NO: 24.

[000136] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3

having the amino acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the to the LC CDR1 having the amino acid sequence of SEQ ID NO: 4, LC CDR2 having the amino acid sequence of SEQ ID NO: 49, and LC CDR3 having the amino acid sequence of SEQ ID NO: 24.

[000137] In some embodiments, the anti-HJV antibody of the present disclosure comprises: a HC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1; a HC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR2 having the amino acid sequence of SEQ ID NO: 2; and/or a HC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR3 having the amino acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises: a LC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 4; a LC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR2 having the amino acid sequence of SEQ ID NO: 49; and/or a LC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR3 having the amino acid sequence of SEQ ID NO: 24.

[000138] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 30.

[000139] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VH as set forth in SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VL as set forth in SEQ ID NO: 30.

[000140] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%,

98%, or 99%) identical to the VH as set forth in SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VL as set forth in SEQ ID NO: 30.

[000141] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, HC CDR2 and HC CDR3 of a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, LC CDR2 and LC CDR3 of a light chain variable domain having the amino acid sequence of SEQ ID NO: 31.

[000142] In some embodiments, according to the Kabat definition system, the anti-HJV antibody of the present disclosure comprises a HC CDR1 having the amino acid sequence of SEQ ID NO: 1, a HC CDR2 having the amino acid sequence of SEQ ID NO: 2, a HC CDR3 having the amino acid sequence of SEQ ID NO: 3, a LC CDR1 having the amino acid sequence of SEQ ID NO: 4, a LC CDR2 having the amino acid sequence of SEQ ID NO: 18, and a LC CDR3 having the amino acid sequence of SEQ ID NO: 25.

[000143] In some embodiments, anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 3. "Collectively," as used anywhere in the present disclosure, means that the total number of amino acid variations in all of the three heavy chain CDRs is within the defined range. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2 or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 4, LC CDR2 having the amino acid sequence of SEQ ID NO: 18, and LC CDR3 having the amino acid sequence of SEQ ID NO: 25.

[000144] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3 that

collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the to the LC CDR1 having the amino acid sequence of SEQ ID NO: 4, LC CDR2 having the amino acid sequence of SEQ ID NO: 18, and LC CDR3 having the amino acid sequence of SEQ ID NO: 25.

[000145] In some embodiments, the anti-HJV antibody of the present disclosure comprises: a HC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1; a HC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR2 having the amino acid sequence of SEQ ID NO: 2; and/or a HC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR3 having the amino acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises: a LC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 4; a LC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR2 having the amino acid sequence of SEQ ID NO: 18; and/or a LC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR3 having the amino acid sequence of SEQ ID NO: 25

[000146] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 31

[000147] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VH as set forth in SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VL as set forth in SEQ ID NO: 31

[000148] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VH as set forth in SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising an amino acid

sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VL as set forth in SEQ ID NO: 31.

[000149] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, HC CDR2 and HC CDR3 of a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, LC CDR2 and LC CDR3 of a light chain variable domain having the amino acid sequence of SEQ ID NO: 32.

[000150] In some embodiments, according to the Kabat definition system, the anti-HJV antibody of the present disclosure comprises a HC CDR1 having the amino acid sequence of SEQ ID NO: 1, a HC CDR2 having the amino acid sequence of SEQ ID NO: 2, a HC CDR3 having the amino acid sequence of SEQ ID NO: 3, a LC CDR1 having the amino acid sequence of SEQ ID NO: 14, a LC CDR2 having the amino acid sequence of SEQ ID NO: 19, and a LC CDR3 having the amino acid sequence of SEQ ID NO: 25.

[000151] In some embodiments, anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 3. "Collectively," as used anywhere in the present disclosure, means that the total number of amino acid variations in all of the three heavy chain CDRs is within the defined range. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2 or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 14, LC CDR2 having the amino acid sequence of SEQ ID NO: 19, and LC CDR3 having the amino acid sequence of SEQ ID NO: 25.

[000152] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the to the LC CDR1 having the amino acid sequence of SEQ ID NO: 14, LC CDR2 having the amino

acid sequence of SEQ ID NO: 19, and LC CDR3 having the amino acid sequence of SEQ ID NO: 25.

[000153] In some embodiments, the anti-HJV antibody of the present disclosure comprises: a HC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1; a HC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR2 having the amino acid sequence of SEQ ID NO: 2; and/or a HC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR3 having the amino acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises: a LC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 14; a LC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR2 having the amino acid sequence of SEQ ID NO: 19; and/or a LC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR3 having the amino acid sequence of SEQ ID NO: 25.

[000154] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 32.

[000155] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VH as set forth in SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VL as set forth in SEQ ID NO: 32.

[000156] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VH as set forth in SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VL as set forth in SEQ ID NO: 32.

[000157] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, HC CDR2 and HC CDR3 of a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, LC CDR2 and LC CDR3 of a light chain variable domain having the amino acid sequence of SEQ ID NO: 33.

[000158] In some embodiments, according to the Kabat definition system, the anti-HJV antibody of the present disclosure comprises a HC CDR1 having the amino acid sequence of SEQ ID NO: 1, a HC CDR2 having the amino acid sequence of SEQ ID NO: 2, a HC CDR3 having the amino acid sequence of SEQ ID NO: 3, a LC CDR1 having the amino acid sequence of SEQ ID NO: 15, a LC CDR2 having the amino acid sequence of SEQ ID NO: 20, and a LC CDR3 having the amino acid sequence of SEQ ID NO: 26.

[000159] In some embodiments, anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 3. "Collectively," as used anywhere in the present disclosure, means that the total number of amino acid variations in all of the three heavy chain CDRs is within the defined range. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2 or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 15, LC CDR2 having the amino acid sequence of SEQ ID NO: 20, and LC CDR3 having the amino acid sequence of SEQ ID NO: 26.

[000160] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the to the LC CDR1 having the amino acid sequence of SEQ ID NO: 15, LC CDR2 having the amino acid sequence of SEQ ID NO: 20, and LC CDR3 having the amino acid sequence of SEQ ID NO: 26.

[000161] In some embodiments, the anti-HJV antibody of the present disclosure comprises: a HC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1; a HC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR2 having the amino acid sequence of SEQ ID NO: 2; and/or a HC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR3 having the amino acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises: a LC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 15; a LC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR2 having the amino acid sequence of SEQ ID NO: 20; and/or a LC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR3 having the amino acid sequence of SEQ ID NO: 26.

[000162] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 33.

[000163] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VH as set forth in SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VL as set forth in SEQ ID NO: 33.

[000164] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VH as set forth in SEQ ID NO: 7. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VL as set forth in SEQ ID NO: 33.

[000165] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, HC CDR2 and HC CDR3 of a heavy chain variable domain having the amino

acid sequence of SEQ ID NO: 34. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, LC CDR2 and LC CDR3 of a light chain variable domain having the amino acid sequence of SEQ ID NO: 35.

[000166] In some embodiments, according to the Kabat definition system, the anti-HJV antibody of the present disclosure comprises a HC CDR1 having the amino acid sequence of SEQ ID NO: 9, a HC CDR2 having the amino acid sequence of SEQ ID NO: 2, a HC CDR3 having the amino acid sequence of SEQ ID NO: 3, a LC CDR1 having the amino acid sequence of SEQ ID NO: 16, a LC CDR2 having the amino acid sequence of SEQ ID NO: 21, and a LC CDR3 having the amino acid sequence of SEQ ID NO: 27.

[000167] In some embodiments, anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 9, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 3. "Collectively," as used anywhere in the present disclosure, means that the total number of amino acid variations in all of the three heavy chain CDRs is within the defined range. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2 or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 16, LC CDR2 having the amino acid sequence of SEQ ID NO: 21, and LC CDR3 having the amino acid sequence of SEQ ID NO: 27.

[000168] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the HC CDR1 having the amino acid sequence of SEQ ID NO: 9, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the to the LC CDR1 having the amino acid sequence of SEQ ID NO: 16, LC CDR2 having the amino acid sequence of SEQ ID NO: 21, and LC CDR3 having the amino acid sequence of SEQ ID NO: 27.

[000169] In some embodiments, the anti-HJV antibody of the present disclosure comprises: a HC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino

acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 9; a HC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR2 having the amino acid sequence of SEQ ID NO: 2; and/or a HC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR3 having the amino acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises: a LC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 16; a LC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR2 having the amino acid sequence of SEQ ID NO: 21; and/or a LC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR3 having the amino acid sequence of SEQ ID NO: 27.

[000170] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 34. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 35.

[000171] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VH as set forth in SEQ ID NO: 34. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VL as set forth in SEQ ID NO: 35.

[000172] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VH as set forth in SEQ ID NO: 34. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VL as set forth in SEQ ID NO: 35.

[000173] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, HC CDR2 and HC CDR3 of a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 36. Alternatively or in addition, the anti-HJV antibody of the

present disclosure comprises a LC CDR1, LC CDR2 and LC CDR3 of a light chain variable domain having the amino acid sequence of SEQ ID NO: 37.

[000174] In some embodiments, according to the Kabat definition system, the anti-HJV antibody of the present disclosure comprises a HC CDR1 having the amino acid sequence of SEQ ID NO: 1, a HC CDR2 having the amino acid sequence of SEQ ID NO: 10, a HC CDR3 having the amino acid sequence of SEQ ID NO: 11, a LC CDR1 having the amino acid sequence of SEQ ID NO: 17, a LC CDR2 having the amino acid sequence of SEQ ID NO: 18, and a LC CDR3 having the amino acid sequence of SEQ ID NO: 28.

[000175] In some embodiments, anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 10, and HC CDR3 having the amino acid sequence of SEQ ID NO: 11. "Collectively," as used anywhere in the present disclosure, means that the total number of amino acid variations in all of the three heavy chain CDRs is within the defined range. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2 or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 17, LC CDR2 having the amino acid sequence of SEQ ID NO: 18, and LC CDR3 having the amino acid sequence of SEQ ID NO: 28.

[000176] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 10, and HC CDR3 having the amino acid sequence of SEQ ID NO: 11. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the to the LC CDR1 having the amino acid sequence of SEQ ID NO: 17, LC CDR2 having the amino acid sequence of SEQ ID NO: 18, and LC CDR3 having the amino acid sequence of SEQ ID NO: 28.

[000177] In some embodiments, the anti-HJV antibody of the present disclosure comprises: a HC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID

NO: 1; a HC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR2 having the amino acid sequence of SEQ ID NO: 10; and/or a HC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR3 having the amino acid sequence of SEQ ID NO: 11. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises: a LC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 17; a LC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR2 having the amino acid sequence of SEQ ID NO: 18; and/or a LC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR3 having the amino acid sequence of SEQ ID NO: 28.

[000178] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 36. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 37.

[000179] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VH as set forth in SEQ ID NO: 36. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VL as set forth in SEQ ID NO: 37.

[000180] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VH as set forth in SEQ ID NO: 36. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VL as set forth in SEQ ID NO: 37.

[000181] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, HC CDR2 and HC CDR3 of a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 38. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, LC CDR2 and LC CDR3 of a light chain variable domain having the amino acid sequence of SEQ ID NO: 39.

[000182] In some embodiments, according to the Kabat definition system, the anti-HJV antibody of the present disclosure comprises a HC CDR1 having the amino acid sequence of SEQ ID NO: 1, a HC CDR2 having the amino acid sequence of SEQ ID NO: 2, a HC CDR3 having the amino acid sequence of SEQ ID NO: 3, a LC CDR1 having the amino acid sequence of SEQ ID NO: 17, a LC CDR2 having the amino acid sequence of SEQ ID NO: 5, and a LC CDR3 having the amino acid sequence of SEQ ID NO: 27.

[000183] In some embodiments, anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 3. "Collectively," as used anywhere in the present disclosure, means that the total number of amino acid variations in all of the three heavy chain CDRs is within the defined range. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2 or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 17, LC CDR2 having the amino acid sequence of SEQ ID NO: 5, and LC CDR3 having the amino acid sequence of SEQ ID NO: 27.

[000184] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the to the LC CDR1 having the amino acid sequence of SEQ ID NO: 17, LC CDR2 having the amino acid sequence of SEQ ID NO: 5, and LC CDR3 having the amino acid sequence of SEQ ID NO: 27.

[000185] In some embodiments, the anti-HJV antibody of the present disclosure comprises: a HC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1; a HC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR2 having the amino acid sequence of

SEQ ID NO: 2; and/or a HC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR3 having the amino acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises: a LC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 17; a LC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR2 having the amino acid sequence of SEQ ID NO: 5; and/or a LC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR3 having the amino acid sequence of SEQ ID NO: 27.

[000186] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 38. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 39.

[000187] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VH as set forth in SEQ ID NO: 38. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VL as set forth in SEQ ID NO: 39.

[000188] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VH as set forth in SEQ ID NO: 38. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VL as set forth in SEQ ID NO: 39.

[000189] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, HC CDR2 and HC CDR3 of a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 38. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, LC CDR2 and LC CDR3 of a light chain variable domain having the amino acid sequence of SEQ ID NO: 41.

[000190] In some embodiments, according to the Kabat definition system, the anti-HJV antibody of the present disclosure comprises a HC CDR1 having the amino acid sequence of

SEQ ID NO: 1, a HC CDR2 having the amino acid sequence of SEQ ID NO: 2, a HC CDR3 having the amino acid sequence of SEQ ID NO: 3, a LC CDR1 having the amino acid sequence of SEQ ID NO: 50, a LC CDR2 having the amino acid sequence of SEQ ID NO: 22, and a LC CDR3 having the amino acid sequence of SEQ ID NO: 28.

[000191] In some embodiments, anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 3. "Collectively," as used anywhere in the present disclosure, means that the total number of amino acid variations in all of the three heavy chain CDRs is within the defined range. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2 or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 50, LC CDR2 having the amino acid sequence of SEQ ID NO: 22, and LC CDR3 having the amino acid sequence of SEQ ID NO: 28.

[000192] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the to the LC CDR1 having the amino acid sequence of SEQ ID NO: 50, LC CDR2 having the amino acid sequence of SEQ ID NO: 22, and LC CDR3 having the amino acid sequence of SEQ ID NO: 28.

[000193] In some embodiments, the anti-HJV antibody of the present disclosure comprises: a HC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1; a HC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR2 having the amino acid sequence of SEQ ID NO: 2; and/or a HC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR3 having the amino

acid sequence of SEQ ID NO: 3. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises: a LC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 50; a LC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR2 having the amino acid sequence of SEQ ID NO: 22; and/or a LC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR3 having the amino acid sequence of SEQ ID NO: 28.

[000194] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 38. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 41.

[000195] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VH as set forth in SEQ ID NO: 38. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VL as set forth in SEQ ID NO: 41.

[000196] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VH as set forth in SEQ ID NO: 38. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VL as set forth in SEQ ID NO: 41.

[000197] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, HC CDR2 and HC CDR3 of a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 42. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, LC CDR2 and LC CDR3 of a light chain variable domain having the amino acid sequence of SEQ ID NO: 43.

[000198] In some embodiments, according to the Kabat definition system, the anti-HJV antibody of the present disclosure comprises a HC CDR1 having the amino acid sequence of SEQ ID NO: 1, a HC CDR2 having the amino acid sequence of SEQ ID NO: 2, a HC CDR3 having the amino acid sequence of SEQ ID NO: 12, a LC CDR1 having the amino acid

sequence of SEQ ID NO: 15, a LC CDR2 having the amino acid sequence of SEQ ID NO: 23, and a LC CDR3 having the amino acid sequence of SEQ ID NO: 27.

[000199] In some embodiments, anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 12. "Collectively," as used anywhere in the present disclosure, means that the total number of amino acid variations in all of the three heavy chain CDRs is within the defined range. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2 or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 15, LC CDR2 having the amino acid sequence of SEQ ID NO: 23, and LC CDR3 having the amino acid sequence of SEQ ID NO: 27.

[000200] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 12. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the to the LC CDR1 having the amino acid sequence of SEQ ID NO: 15, LC CDR2 having the amino acid sequence of SEQ ID NO: 23, and LC CDR3 having the amino acid sequence of SEQ ID NO: 27.

[000201] In some embodiments, the anti-HJV antibody of the present disclosure comprises: a HC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1; a HC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR2 having the amino acid sequence of SEQ ID NO: 2; and/or a HC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR3 having the amino acid sequence of SEQ ID NO: 12. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises: a LC CDR1 having no more than 3 amino acid variations (e.g.,

no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 15; a LC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR2 having the amino acid sequence of SEQ ID NO: 23; and/or a LC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR3 having the amino acid sequence of SEQ ID NO: 27.

[000202] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 42. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 43.

[000203] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VH as set forth in SEQ ID NO: 42. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VL as set forth in SEQ ID NO: 43.

[000204] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VH as set forth in SEQ ID NO: 42. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VL as set forth in SEQ ID NO: 43.

[000205] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, HC CDR2 and HC CDR3 of a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 44. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, LC CDR2 and LC CDR3 of a light chain variable domain having the amino acid sequence of SEQ ID NO: 45.

[000206] In some embodiments, according to the Kabat definition system, the anti-HJV antibody of the present disclosure comprises a HC CDR1 having the amino acid sequence of SEQ ID NO: 1, a HC CDR2 having the amino acid sequence of SEQ ID NO: 2, a HC CDR3 having the amino acid sequence of SEQ ID NO: 13, a LC CDR1 having the amino acid sequence of SEQ ID NO: 16, a LC CDR2 having the amino acid sequence of SEQ ID NO: 21, and a LC CDR3 having the amino acid sequence of SEQ ID NO: 29.

[000207] In some embodiments, anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 13. "Collectively," as used anywhere in the present disclosure, means that the total number of amino acid variations in all of the three heavy chain CDRs is within the defined range. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2 or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 16, LC CDR2 having the amino acid sequence of SEQ ID NO: 21, and LC CDR3 having the amino acid sequence of SEQ ID NO: 29.

[000208] In some embodiments, the anti-HJV antibody of the present disclosure comprises a HC CDR1, a HC CDR2, and a HC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the HC CDR1 having the amino acid sequence of SEQ ID NO: 1, HC CDR2 having the amino acid sequence of SEQ ID NO: 2, and HC CDR3 having the amino acid sequence of SEQ ID NO: 13. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a LC CDR1, a LC CDR2, and a LC CDR3 that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the to the LC CDR1 having the amino acid sequence of SEQ ID NO: 16, LC CDR2 having the amino acid sequence of SEQ ID NO: 21, and LC CDR3 having the amino acid sequence of SEQ ID NO: 29.

[000209] In some embodiments, the anti-HJV antibody of the present disclosure comprises: a HC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR1 having the amino acid sequence of SEQ ID NO: 1; a HC CDR2 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR2 having the amino acid sequence of SEQ ID NO: 2; and/or a HC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the HC CDR3 having the amino acid sequence of SEQ ID NO: 13. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises: a LC CDR1 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR1 having the amino acid sequence of SEQ ID NO: 16; a LC CDR2 having no more than 3 amino acid

variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR2 having the amino acid sequence of SEQ ID NO: 21; and/or a LC CDR3 having no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the LC CDR3 having the amino acid sequence of SEQ ID NO: 29.

[000210] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 44. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 45.

[000211] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VH as set forth in SEQ ID NO: 44. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VL as set forth in SEQ ID NO: 45.

[000212] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VH as set forth in SEQ ID NO: 44. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a VL comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the VL as set forth in SEQ ID NO: 45.

[000213] The CDRs of an antibody may have different amino acid sequences when different definition systems are used (e.g., the IMGT definition, the Kabat definition, or the Chothia definition). A definition system annotates each amino acid in a given antibody sequence (e.g., VH or VL sequence) with a number, and numbers corresponding to the heavy chain and light chain CDRs are provided in Table 2. The CDRs listed in Table 1 are defined in accordance with the Kabat definition. One skilled in the art is able to derive the CDR sequences using the different numbering systems for the anti-HJV antibodies provided in Table 1.

Table 2. CDR Definitions

	IMGT[1]	**Kabat[2]**	**Chothia[3]**
HC CDR1	27-38	31-35	26-32
HC CDR2	56-65	50-65	53-55
HC CDR3	105-116/117	95-102	96-101
LC CDR1	27-38	24-34	26-32

LC CDR2	56-65	50-56	50-52
LC CDR3	105-116/117	89-97	91-96

[1] IMGT®, the international ImMunoGeneTics information system®, imgt.org, Lefranc, M.-P. et al., Nucleic Acids Res., 27:209-212 (1999)
[2] Kabat et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242
[3] Chothia et al., J. Mol. Biol. 196:901-917 (1987))

[000214] In some embodiments, the anti-HJV antibody of the present disclosure is a chimeric antibody, which can include a heavy constant region and a light constant region from a human antibody. Chimeric antibodies refer to antibodies having a variable region or part of variable region from a first species and a constant region from a second species. Typically, in these chimeric antibodies, the variable region of both light and heavy chains mimics the variable regions of antibodies derived from one species of mammals (e.g., a non-human mammal such as mouse, rabbit, and rat), while the constant portions are homologous to the sequences in antibodies derived from another mammal such as human. In some embodiments, amino acid modifications can be made in the variable region and/or the constant region.

[000215] In some embodiments, the anti-HJV antibody described herein is a chimeric antibody, which can include a heavy constant region and a light constant region from a human antibody. Chimeric antibodies refer to antibodies having a variable region or part of variable region from a first species and a constant region from a second species. Typically, in these chimeric antibodies, the variable region of both light and heavy chains mimics the variable regions of antibodies derived from one species of mammals (*e.g.*, a non-human mammal such as mouse, rabbit, and rat), while the constant portions are homologous to the sequences in antibodies derived from another mammal such as human. In some embodiments, amino acid modifications can be made in the variable region and/or the constant region.

[000216] In some embodiments, the anti-HJV antibody of the present disclosure comprises a VL domain and/or VH domain of any one of the anti-HJV antibodies selected from Table 1, and comprises a constant region comprising the amino acid sequences of the constant regions of an IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule, any class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2), or any subclass (e.g., IgG2a and IgG2b) of immunoglobulin molecule. Non-limiting examples of human constant regions are described in the art, e.g., see Kabat E A et al., (1991) supra. An example of a human IgG1 constant region is given below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSL

TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 103)

[000217] In some embodiments, the heavy chain of any of the anti-HJV antibodies described herein comprises a mutant human IgG1 constant region. For example, the introduction of LALA mutations (a mutant derived from mAb b12 that has been mutated to replace the lower hinge residues Leu234 Leu235 with Ala234 and Ala235) in the CH2 domain of human IgG1 is known to reduce Fcg receptor binding (Bruhns, P., et al. (2009) and Xu, D. et al. (2000)). The mutant human IgG1 constant region is provided below (mutations bonded and underlined):

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 46)

[000218] In some embodiments, the heavy chain of any of the anti-HJV antibodies described herein further comprises mutations in human IgG1 constant region. For example, the introduction of T250Q and M248L substitutions. In some embodiments, such substitution may affect FcRn binding and serum half-life (WO2005047307 and WO2013063110). An exemplary IgG1 constant region comprising the LALA mutation and the QL mutation is provided below (mutations bonded and underlined):

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVF
LFPPKPKD**Q**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
LHEALHNHYTQKSLSLSPGK (SEQ ID NO: 48)

[000219] In some embodiments, during the production of the antibodies, particularly with Chinese Hamster Ovary Cells (CHO cells), it can be appreciated that the lysine at the C-terminus of the heavy chain is cleaved. Accordingly, a human IgG1 constant region within a secreted antibody can be:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 111)

[000220] In some embodiments, a mutant human IgG1 comprising the LALA mutations in a secreted antibody can be:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 112)

[000221] In some embodiments, a mutant human IgG1 comprising the LALA mutations and the QL mutations can be:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVF
LFPPKPKD**Q**LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
LHEALHNHYTQKSLSLSPG (SEQ ID NO: 113)

[000222] In some embodiments, the light chain of any of the anti-HJV antibodies described herein may further comprise a light chain constant region (CL), which can be any CL known in the art. In some examples, the CL is a kappa light chain. In other examples, the CL is a lambda light chain. In some embodiments, the CL is a kappa light chain, the sequence of which is provided below:

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK
DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 47)

[000223] Other antibody heavy and light chain constant regions are well known in the art, e.g., those provided in the IMGT database (www.imgt.org) or at www.vbase2.org/vbstat.php., both of which are incorporated by reference herein.

[000224] In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising any one of the VH as listed in Table 1 or any variants thereof and a heavy chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 112, or SEQ ID NO: 113. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising any one of the VH as listed in Table 1 or any variants thereof and a heavy chain constant region that contains no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 112, or SEQ ID NO: 113. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain

comprising any one of the VH as listed in Table 1 or any variants thereof and a heavy chain constant region as set forth in SEQ ID NO: 46. In some embodiments, the anti-HJV antibody described herein comprises heavy chain comprising any one of the VH as listed in Table 1 or any variants thereof and a heavy chain constant region as set forth in SEQ ID NO: 48. In some embodiments, the anti-HJV antibody described herein comprises heavy chain comprising any one of the VH as listed in Table 1 or any variants thereof and a heavy chain constant region as set forth in SEQ ID NO: 112. In some embodiments, the anti-HJV antibody described herein comprises heavy chain comprising any one of the VH as listed in Table 1 or any variants thereof and a heavy chain constant region as set forth in SEQ ID NO: 113.

[000225] In some embodiments, the anti-HJV antibody described herein comprises a light chain comprising any one of the VL as listed in Table 1 or any variants thereof and a light chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to SEQ ID NO: 47. In some embodiments, the anti-HJV antibody described herein comprises a light chain comprising any one of the VL as listed in Table 1 or any variants thereof and a light chain constant region contains no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with SEQ ID NO: 47. In some embodiments, the anti-HJV antibody described herein comprises a light chain comprising any one of the VL as listed in Table 1 or any variants thereof and a light chain constant region set forth in SEQ ID NO: 47.

[000226] Examples of IgG heavy chain and light chain amino acid sequences of the anti-HJV antibodies described are provided in Table 1 above.

[000227] In some embodiments, the anti-HJV antibody of the present disclosure comprises a heavy chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 51, 57, 59, 61, 63, 66, 68, 114, 115, 116, 117, 118, 119 or 120. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a light chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 52, 53, 54, 55, 56, 58, 60, 62, 65, 67 or 69. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 51, 57, 59, 61, 63,

66, 68, 114, 115, 116, 117, 118, 119 or 120. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 52, 53, 54, 55, 56, 58, 60, 62, 65, 67 or 69. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 51, 57, 59, 61, 63, 66, 68, 114, 115, 116, 117, 118, 119 or 120. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 52, 53, 54, 55, 56, 58, 60, 62, 65, 67 or 69.

[000228] In some embodiments, the anti-HJV antibody of the present disclosure comprises a heavy chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 51 or 114. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a light chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 52. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 51 or 114. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 52. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 51 or 114. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 52.

[000229] In some embodiments, the anti-HJV antibody of the present disclosure comprises a heavy chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 51 or 114. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a light chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 53. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 51 or 114.

Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 53. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 51 or 114. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 53.

[000230] In some embodiments, the anti-HJV antibody of the present disclosure comprises a heavy chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 51 or 114. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a light chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 54. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 51 or 114. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 54. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 51 or 114. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 54.

[000231] In some embodiments, the anti-HJV antibody of the present disclosure comprises a heavy chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 51 or 114. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a light chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 55. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 51 or 114. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or

99%) identical to any one of SEQ ID NOs: 55. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 51 or 114. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 55.

[000232] In some embodiments, the anti-HJV antibody of the present disclosure comprises a heavy chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 51 or 114. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a light chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 56. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 51 or 114. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 56. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 51 or 114. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 56.

[000233] In some embodiments, the anti-HJV antibody of the present disclosure comprises a heavy chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 57 or 115. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a light chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 58. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 57 or 115. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 58. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of

SEQ ID NOs: 57 or 115. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 58.

[000234] In some embodiments, the anti-HJV antibody of the present disclosure comprises a heavy chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 59 or 116. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a light chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 60. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 59 or 116. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 60. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 59 or 116. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 60.

[000235] In some embodiments, the anti-HJV antibody of the present disclosure comprises a heavy chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 61 or 117. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a light chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 62. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 61 or 117. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 62. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 61 or 117. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 62.

[000236] In some embodiments, the anti-HJV antibody of the present disclosure comprises a heavy chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 63 or 118. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a light chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 62. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 63 or 118. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 62. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 63 or 118. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 62.

[000237] In some embodiments, the anti-HJV antibody of the present disclosure comprises a heavy chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 61 or 117. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a light chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 65. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 61 or 117. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 65. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 61 or 117. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 65.

[000238] In some embodiments, the anti-HJV antibody of the present disclosure comprises a heavy chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18,

17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 66 or 119. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a light chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 67. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 66 or 119. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 67. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 66 or 119. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 67.

[000239] In some embodiments, the anti-HJV antibody of the present disclosure comprises a heavy chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 68 or 120. Alternatively or in addition, the anti-HJV antibody of the present disclosure comprises a light chain containing no more than 20 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 69. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 68 or 120. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 69. In some embodiments, the anti-HJV antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 68 or 120. Alternatively or in addition, the anti-HJV antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 69.

[000240] The anti-HJV antibodies described herein can be in any antibody form, including, but not limited to, intact (i.e., full-length) antibodies, antigen-binding fragments thereof (such as Fab, F(ab'), F(ab')2, Fv), single chain antibodies, bi-specific antibodies, or nanobodies. In some embodiments, the anti-HJV antibody described herein is a scFv. In some embodiments,

the anti-HJV antibody described herein is a scFv-Fab (e.g., scFv fused to a portion of a constant region).

[000241] In some embodiments, conservative mutations can be introduced into antibody sequences (e.g., CDRs or framework sequences) at positions where the residues are not likely to be involved in interacting with a target antigen (e.g., hemojuvelin), for example, as determined based on a crystal structure. In some embodiments, one, two or more mutations (*e.g.,* amino acid substitutions) are introduced into the Fc region of an anti-HJV antibody described herein (*e.g.,* in a CH2 domain (residues 231-340 of human IgG1) and/or CH3 domain (residues 341-447 of human IgG1) and/or the hinge region, with numbering according to the Kabat numbering system (*e.g.,* the EU index in Kabat)) to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding and/or antigen-dependent cellular cytotoxicity.

[000242] In some embodiments, one, two or more mutations (*e.g.,* amino acid substitutions) are introduced into the hinge region of the Fc region (CH1 domain) such that the number of cysteine residues in the hinge region are altered (*e.g.,* increased or decreased) as described in, e.g., U.S. Pat. No. 5,677,425. The number of cysteine residues in the hinge region of the CH1 domain can be altered to, *e.g.,* facilitate assembly of the light and heavy chains, or to alter (*e.g.,* increase or decrease) the stability of the antibody or to facilitate linker conjugation.

[000243] In some embodiments, one, two or more mutations (*e.g.,* amino acid substitutions) are introduced into the Fc region of a muscle-targeting antibody described herein (e.g., in a CH2 domain (residues 231-340 of human IgG1) and/or CH3 domain (residues 341-447 of human IgG1) and/or the hinge region, with numbering according to the Kabat numbering system (*e.g.,* the EU index in Kabat)) to increase or decrease the affinity of the antibody for an Fc receptor (*e.g.*, an activated Fc receptor) on the surface of an effector cell. Mutations in the Fc region of an antibody that decrease or increase the affinity of an antibody for an Fc receptor and techniques for introducing such mutations into the Fc receptor or fragment thereof are known to one of skill in the art. Examples of mutations in the Fc receptor of an antibody that can be made to alter the affinity of the antibody for an Fc receptor are described in, e.g., Smith P et al., (2012) PNAS 109: 6181-6186, U.S. Pat. No. 6,737,056, and International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631, which are incorporated herein by reference.

[000244] In some embodiments, one, two or more amino acid mutations (*i.e.,* substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to alter (*e.g.,* decrease or

increase) half-life of the antibody *in vivo*. See, e.g., International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631; and U.S. Pat. Nos. 5,869,046, 6,121,022, 6,277,375 and 6,165,745 for examples of mutations that will alter (*e.g.,* decrease or increase) the half-life of an antibody *in vivo*.

[000245] In some embodiments, one, two or more amino acid mutations (*i.e.,* substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to decrease the half-life of the anti-HJV antibody *in vivo*. In some embodiments, one, two or more amino acid mutations (*i.e.,* substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to increase the half-life of the antibody *in vivo*. In some embodiments, the antibodies can have one or more amino acid mutations (*e.g.,* substitutions) in the second constant (CH2) domain (residues 231-340 of human IgG1) and/or the third constant (CH3) domain (residues 341-447 of human IgG1), with numbering according to the EU index in Kabat (Kabat E A et al., (1991) supra). In some embodiments, the constant region of the IgG1 of an antibody described herein comprises a methionine (M) to tyrosine (Y) substitution in position 252, a serine (S) to threonine (T) substitution in position 254, and a threonine (T) to glutamic acid (E) substitution in position 256, numbered according to the EU index as in Kabat. See U.S. Pat. No. 7,658,921, which is incorporated herein by reference. This type of mutant IgG, referred to as "YTE mutant" has been shown to display fourfold increased half-life as compared to wild-type versions of the same antibody (see Dall'Acqua W F et al., (2006) J Biol Chem 281: 23514-24). In some embodiments, an antibody comprises an IgG constant domain comprising one, two, three or more amino acid substitutions of amino acid residues at positions 251-257, 285-290, 308-314, 385-389, and 428-436, numbered according to the EU index as in Kabat.

[000246] In some embodiments, one, two or more amino acid substitutions are introduced into an IgG constant domain Fc region to alter the effector function(s) of the anti-HJV antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Pat. Nos. 5,624,821 and 5,648,260. In some embodiments, the deletion or inactivation (through point mutations or other means) of a constant region domain can reduce Fc receptor binding of the circulating antibody thereby increasing tumor localization. See, e.g., U.S. Pat. Nos. 5,585,097 and 8,591,886 for a description of mutations that delete or inactivate the constant domain and thereby increase tumor localization. In some embodiments, one or more amino

acid substitutions may be introduced into the Fc region of an antibody described herein to remove potential glycosylation sites on Fc region, which may reduce Fc receptor binding (see, *e.g.,* Shields R L et al., (2001) J Biol Chem 276: 6591-604).

[000247] In some embodiments, one or more amino in the constant region of an anti-HJV antibody described herein can be replaced with a different amino acid residue such that the antibody has altered Clq binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Pat. No. 6,194,551 (Idusogie et al). In some embodiments, one or more amino acid residues in the N-terminal region of the CH2 domain of an antibody described herein are altered to thereby alter the ability of the antibody to fix complement. This approach is described further in International Publication No. WO 94/29351. In some embodiments, the Fc region of an antibody described herein is modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to increase the affinity of the antibody for an Fcγ receptor. This approach is described further in International Publication No. WO 00/42072.

[000248] In some embodiments, the heavy and/or light chain variable domain(s) sequence(s) of the antibodies provided herein can be used to generate, for example, CDR-grafted, chimeric, humanized, or composite human antibodies or antigen-binding fragments, as described elsewhere herein. As understood by one of ordinary skill in the art, any variant, CDR-grafted, chimeric, humanized, or composite antibodies derived from any of the antibodies provided herein may be useful in the compositions and methods described herein and will maintain the ability to specifically bind hemojuvelin, such that the variant, CDR-grafted, chimeric, humanized, or composite antibody has at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% or more binding to hemojuvelin relative to the original antibody from which it is derived.

[000249] In some embodiments, the antibodies provided herein comprise mutations that confer desirable properties to the antibodies. For example, to avoid potential complications due to Fab-arm exchange, which is known to occur with native IgG4 mAbs, the antibodies provided herein may comprise a stabilizing 'Adair' mutation (Angal S., et al., "A single amino acid substitution abolishes the heterogeneity of chimeric mouse/human (IgG4) antibody," Mol Immunol 30, 105-108; 1993), where serine 228 (EU numbering; residue 241 Kabat numbering) is converted to proline resulting in an IgG1-like hinge sequence. Accordingly, any of the antibodies may include a stabilizing 'Adair' mutation.

[000250] In some embodiments, an antibody is modified, e.g., modified via glycosylation, phosphorylation, sumoylation, and/or methylation. In some embodiments, an antibody is a

glycosylated antibody, which is conjugated to one or more sugar or carbohydrate molecules. In some embodiments, the one or more sugar or carbohydrate molecule are conjugated to the antibody via N-glycosylation, O-glycosylation, C-glycosylation, glypiation (GPI anchor attachment), and/or phosphoglycosylation. In some embodiments, the one or more sugar or carbohydrate molecules are monosaccharides, disaccharides, oligosaccharides, or glycans. In some embodiments, the one or more sugar or carbohydrate molecule is a branched oligosaccharide or a branched glycan. In some embodiments, the one or more sugar or carbohydrate molecule includes a mannose unit, a glucose unit, an N-acetylglucosamine unit, an N-acetylgalactosamine unit, a galactose unit, a fucose unit, or a phospholipid unit. In some embodiments, there are about 1-10, about 1-5, about 5-10, about 1-4, about 1-3, or about 2 sugar molecules. In some embodiments, a glycosylated antibody is fully or partially glycosylated. In some embodiments, an antibody is glycosylated by chemical reactions or by enzymatic means. In some embodiments, an antibody is glycosylated in vitro or inside a cell, which may optionally be deficient in an enzyme in the N- or O- glycosylation pathway, e.g. a glycosyltransferase. In some embodiments, an antibody is functionalized with sugar or carbohydrate molecules as described in International Patent Application Publication WO2014065661, published on May 1, 2014, entitled, "*Modified antibody, antibody-conjugate and process for the preparation thereof*".

[000251] In some embodiments, any one of the anti-HJV antibodies described herein may comprise a signal peptide in the heavy and/or light chain sequence (e.g., a N-terminal signal peptide). In some embodiments, the anti-HJV antibody described herein comprises any one of the VH and VL sequences, any one of the IgG heavy chain and light chain sequences, or any one of the F(ab') heavy chain and light chain sequences described herein, and further comprises a signal peptide (e.g., a N-terminal signal peptide). In some embodiments, the signal peptide comprises the amino acid sequence of MEFGLSWLFLVAILKGVQC (SEQ ID NO: 104).

III. Preparation of the Anti-HJV Antibodies

[000252] Antibodies capable of binding hemojuvelin as described herein can be made by any method known in the art. See, for example, Harlow and Lane, (1998) Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York.

[000253] In some embodiments, antibodies specific to a target antigen (e.g., HJV) can be made by the conventional hybridoma technology. The full-length target antigen or a fragment thereof, optionally coupled to a carrier protein such as KLH, can be used to immunize a host

animal for generating antibodies binding to that antigen. The route and schedule of immunization of the host animal are generally in keeping with established and conventional techniques for antibody stimulation and production, as further described herein. General techniques for production of mouse, humanized, and human antibodies are known in the art and are described herein. It is contemplated that any mammalian subject including humans or antibody producing cells therefrom can be manipulated to serve as the basis for production of mammalian, including human hybridoma cell lines. Typically, the host animal is inoculated intraperitoneally, intramuscularly, orally, subcutaneously, intraplantar, and/or intradermally with an amount of immunogen, including as described herein.

[000254] If desired, an antibody (monoclonal or polyclonal) of interest (e.g., produced by a hybridoma) may be sequenced and the polynucleotide sequence may then be cloned into a vector for expression or propagation. The sequence encoding the antibody of interest may be maintained in vector in a host cell and the host cell can then be expanded and frozen for future use. In an alternative, the polynucleotide sequence may be used for genetic manipulation to "humanize" the antibody or to improve the affinity (affinity maturation), or other characteristics of the antibody. For example, the constant region may be engineered to more resemble human constant regions to avoid immune response if the antibody is used in clinical trials and treatments in humans. It may be desirable to genetically manipulate the antibody sequence to obtain greater affinity to the target antigen and greater efficacy. It will be apparent to one of skill in the art that one or more polynucleotide changes can be made to the antibody and still maintain its binding specificity to the target antigen.

[000255] In other embodiments, fully human antibodies can be obtained by using commercially available mice that have been engineered to express specific human immunoglobulin proteins. Transgenic animals that are designed to produce a more desirable (e.g., fully human antibodies) or more robust immune response may also be used for generation of humanized or human antibodies. Examples of such technology are XenomouseRTM from Amgen, Inc. (Fremont, CA) and HuMAb-MouseRTM and TC MouseTM from Medarex, Inc. (Princeton, NJ) or H2L2 mice from Harbour Antibodies BV (Holland). In another alternative, antibodies may be made recombinantly by phage display or yeast technology. See, for example, U.S. Pat. Nos. 5,565,332; 5,580,717; 5,733,743; and 6,265,150; and Winter et al., (1994) Annu. Rev. Immunol. 12:433-455. Alternatively, the phage display technology (McCafferty et al., (1990) Nature 348:552-553) can be used to produce human antibodies and antibody fragments in vitro, from immunoglobulin variable (V) domain gene repertoires from unimmunized donors.

[000256] Antigen-binding fragments of an intact antibody (full-length antibody) can be prepared via routine methods. For example, F(ab')2 fragments can be produced by pepsin digestion of an antibody molecule, and Fab fragments that can be generated by reducing the disulfide bridges of F(ab')2 fragments. Genetically engineered antibodies, such as humanized antibodies, chimeric antibodies, single-chain antibodies, and bi-specific antibodies, can be produced via, e.g., conventional recombinant technology. In one example, DNA encoding a monoclonal antibodies specific to a target antigen can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into one or more expression vectors, which are then transfected into host cells such as E. coli cells, simian COS cells, Chinese hamster ovary (CHO) cells, human HEK293 cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. See, e.g., PCT Publication No. WO 87/04462. The DNA can then be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences, Morrison et al., (1984) Proc. Nat. Acad. Sci. 81:6851, or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. In that manner, genetically engineered antibodies, such as "chimeric" or "hybrid" antibodies; can be prepared that have the binding specificity of a target antigen.

[000257] A single-chain antibody can be prepared via recombinant technology by linking a nucleotide sequence coding for a heavy chain variable region and a nucleotide sequence coding for a light chain variable region. Preferably, a flexible linker is incorporated between the two variable regions.

[000258] Alternatively, techniques described for the production of single chain antibodies (U.S. Patent Nos. 4,946,778 and 4,704,692) can be adapted to produce a phage or yeast scFv library and scFv clones specific to HJV can be identified from the library following routine procedures. Positive clones can be subjected to further screening to identify those that has high HJV binding affinity.

[000259] Antibodies obtained following a method known in the art and described herein can be characterized using methods well known in the art. For example, one method is to identify the epitope to which the antigen binds, or "epitope mapping." There are many methods known in the art for mapping and characterizing the location of epitopes on proteins,

including solving the crystal structure of an antibody-antigen complex, competition assays, gene fragment expression assays, and synthetic peptide-based assays, as described, for example, in Chapter 11 of Harlow and Lane, Using Antibodies, a Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1999. In one example, epitope mapping can be accomplished use H/D-Ex (hydrogen deuterium exchange) coupled with proteolysis and mass spectrometry. In an additional example, epitope mapping can be used to determine the sequence to which an antibody binds. The epitope can be a linear epitope, i.e., contained in a single stretch of amino acids, or a conformational epitope formed by a three-dimensional interaction of amino acids that may not necessarily be contained in a single stretch (primary structure linear sequence). Peptides of varying lengths (e.g., at least 4-6 amino acids long) can be isolated or synthesized (e.g., recombinantly) and used for binding assays with an antibody. In another example, the epitope to which the antibody binds can be determined in a systematic screening by using overlapping peptides derived from the target antigen sequence and determining binding by the antibody. According to the gene fragment expression assays, the open reading frame encoding the target antigen is fragmented either randomly or by specific genetic constructions and the reactivity of the expressed fragments of the antigen with the antibody to be tested is determined. The gene fragments may, for example, be produced by PCR and then transcribed and translated into protein in vitro, in the presence of radioactive amino acids. The binding of the antibody to the radioactively labeled antigen fragments is then determined by immunoprecipitation and gel electrophoresis. Certain epitopes can also be identified by using large libraries of random peptide sequences displayed on the surface of phage particles (phage libraries). Alternatively, a defined library of overlapping peptide fragments can be tested for binding to the test antibody in simple binding assays. In an additional example, mutagenesis of an antigen binding domain, domain swapping experiments and alanine scanning mutagenesis can be performed to identify residues required, sufficient, and/or necessary for epitope binding. Alternatively, competition assays can be performed using other antibodies known to bind to the same antigen to determine whether an antibody binds to the same epitope as the other antibodies. Competition assays are well known to those of skill in the art.

[000260] In some examples, an anti-HJV antibody is prepared by recombinant technology as exemplified below. Nucleic acids encoding the heavy and light chain of an anti-HJV antibody as described herein can be cloned into one expression vector, each nucleotide sequence being in operable linkage to a suitable promoter. In one example, each of the nucleotide sequences encoding the heavy chain and light chain is in operable linkage to a distinct promoter.

Alternatively, the nucleotide sequences encoding the heavy chain and the light chain can be in operable linkage with a single promoter, such that both heavy and light chains are expressed from the same promoter. When necessary, an internal ribosomal entry site (IRES) can be inserted between the heavy chain and light chain encoding sequences.

[000261] In some examples, the nucleotide sequences encoding the two chains of the antibody are cloned into two vectors, which can be introduced into the same or different cells. When the two chains are expressed in different cells, each of them can be isolated from the host cells expressing such and the isolated heavy chains and light chains can be mixed and incubated under suitable conditions allowing for the formation of the antibody.

[000262] Generally, a nucleic acid sequence encoding one or all chains of an antibody can be cloned into a suitable expression vector in operable linkage with a suitable promoter using methods known in the art. For example, the nucleotide sequence and vector can be contacted, under suitable conditions, with a restriction enzyme to create complementary ends on each molecule that can pair with each other and be joined together with a ligase. Alternatively, synthetic nucleic acid linkers can be ligated to the termini of a gene. These synthetic linkers contain nucleic acid sequences that correspond to a particular restriction site in the vector. The selection of expression vectors/promoter would depend on the type of host cells for use in producing the antibodies.

[000263] A variety of promoters can be used for expression of the antibodies described herein, including, but not limited to, cytomegalovirus (CMV) intermediate early promoter, a viral LTR such as the Rous sarcoma virus LTR, HIV-LTR, HTLV-1 LTR, the simian virus 40 (SV40) early promoter, E. coli lac UV promoter, and the herpes simplex tk virus promoter.

[000264] Regulatable promoters can also be used. Such regulatable promoters include those using the lac repressor from E. coli as a transcription modulator to regulate transcription from lac operator bearing mammalian cell promoters [Brown, M. et al., Cell, 49:603-612 (1987)], those using the tetracycline repressor (tetR) [Gossen, M., and Bujard, H., Proc. Natl. Acad. Sci. USA 89:5547-555115 (1992); Yao, F. et al., Human Gene Therapy, 9:1939-1950 (1998); Shockelt, P., et al., Proc. Natl. Acad. Sci. USA, 92:6522-6526 (1995)]. Other systems include FK506 dimer, VP16 or p65 using astradiol, RU486, diphenol murislerone, or rapamycin. Inducible systems are available from Invitrogen, Clontech and Ariad, among others.

[000265] Regulatable promoters that include a repressor with the operon can be used. In one embodiment, the lac repressor from E. coli can function as a transcriptional modulator to regulate transcription from lac operator-bearing mammalian cell promoters [M. Brown et al.,

Cell, 49:603-612 (1987)]; Gossen and Bujard (1992); [M. Gossen et al., Natl. Acad. Sci. USA, 89:5547-5551(1992)] combined the tetracycline repressor (tetR) with the transcription activator (VP 16) to create a tetR-mammalian cell transcription activator fusion protein, tTa (tetR-VP 16), with the tetO bearing minimal promoter derived from the human cytomegalovirus (hCMV) promoter to create a tetR-tet operator system to control gene expression in mammalian cells. In one embodiment, a tetracycline inducible switch is used. The tetracycline repressor (tetR) alone, rather than the tetR-mammalian cell transcription factor fusion derivatives can function as potent trans-modulator to regulate gene expression in mammalian cells when the tetracycline operator is properly positioned downstream for the TATA element of the CMVIE promoter (Yao et al., Human Gene Therapy). One particular advantage of this tetracycline inducible switch is that it does not require the use of a tetracycline repressor-mammalian cells transactivator or repressor fusion protein, which in some instances can be toxic to cells (Gossen 5 et al., Natl. Acad. Sci. USA, 89:5547-5551 (1992); Shockett et al., Proc. Natl. Acad. Sci. USA, 92:6522-6526 (1995)), to achieve its regulatable effects.

[000266] Additionally, the vector can contain, for example, some or all of the following: a selectable marker gene, such as the neomycin gene for selection of stable or transient transfectants in mammalian cells; enhancer/promoter sequences from the immediate early gene of human CMV for high levels of transcription; transcription termination and RNA processing signals from SV40 for mRNA stability; SV40 polyoma origins of replication and ColE1 for proper episomal replication; internal ribosome binding sites (IRESes), versatile multiple cloning sites; and T7 and SP6 RNA promoters for in vitro transcription of sense and antisense RNA. Suitable vectors and methods for producing vectors containing transgenes are well known and available in the art. Examples of polyadenylation signals useful to practice the methods described herein include, but are not limited to, human collagen I polyadenylation signal, human collagen II polyadenylation signal, and SV40 polyadenylation signal.

[000267] One or more vectors (e.g., expression vectors) comprising nucleic acids encoding any of the antibodies (e.g., the nucleic acid coding sequence listed in Table 3) may be introduced into suitable host cells for producing the antibodies. Non-limiting examples of the host cells include Chinese hamster ovary (CHO) cells, dhfr- CHO cell, human embryonic kidney (HEK)-293 cells, verda reno (VERO) cells, nonsecreting null (NS0) cells, human embryonic retinal (PER.C6) cells, Sp2/0 cells, baby hamster kidney (BHK) cells, Madin-Darby Canine Kidney (MDCK) cells, Madin-Darby Bovine Kidney (MDBK) cells, and

monkey kidney CV1 line transformed by SV40 (COS) cells. In some embodiments, the host cell expressing the anti-HJV antibodies are CHO cells. The host cells can be cultured under suitable conditions for expression of the antibody or any polypeptide chain thereof. Such antibodies or polypeptide chains thereof can be recovered by the cultured cells (e.g., from the cells or the culture supernatant) via a conventional method, e.g., affinity purification. If necessary, polypeptide chains of the antibody can be incubated under suitable conditions for a suitable period of time allowing for production of the antibody. In some embodiments, the host cell comprises the nucleic acid encoding the heavy chain of the anti-HJV antibody. In some embodiments, the host cell comprises the nucleic acid encoding the light chain of the anti-HJV antibody. In some embodiments, the host cell comprises the nucleic acid encoding the heavy chain and the nucleic acid encoding the light chain.

[000268] In some embodiments, methods for preparing an antibody described herein involve a recombinant expression vector that encodes both the heavy chain and the light chain of an anti-HJV antibody, as also described herein. The recombinant expression vector can be introduced into a suitable host cell (e.g., a dhfr- CHO cell) by a conventional method, e.g., calcium phosphate mediated transfection. Positive transformant host cells can be selected and cultured under suitable conditions allowing for the expression of the two polypeptide chains that form the antibody, which can be recovered from the cells or from the culture medium. When necessary, the two chains recovered from the host cells can be incubated under suitable conditions allowing for the formation of the antibody.

[000269] In one example, two recombinant expression vectors are provided, one encoding the heavy chain of the anti-HJV antibody and the other encoding the light chain of the anti-HJV antibody. Both of the two recombinant expression vectors can be introduced into a suitable host cell (e.g., dhfr- CHO cell) by a conventional method, e.g., calcium phosphate-mediated transfection.

[000270] Alternatively, each of the expression vectors can be introduced into a suitable host cells. Positive transformants can be selected and cultured under suitable conditions allowing for the expression of the polypeptide chains of the antibody. When the two expression vectors are introduced into the same host cells, the antibody produced therein can be recovered from the host cells or from the culture medium. If necessary, the polypeptide chains can be recovered from the host cells or from the culture medium and then incubated under suitable conditions allowing for formation of the antibody. When the two expression vectors are introduced into different host cells, each of them can be recovered from the corresponding

host cells or from the corresponding culture media. The two polypeptide chains can then be incubated under suitable conditions for formation of the antibody.

[000271] Standard molecular biology techniques are used to prepare the recombinant expression vector, transfect the host cells, select for transformants, culture the host cells and recovery of the antibodies from the culture medium. For example, some antibodies can be isolated by affinity chromatography with a Protein A or Protein G coupled matrix.

[000272] Any of the nucleic acids encoding the heavy chain, the light chain, or both of an anti-HJV antibody as described herein (e.g., as provided in Table 3), vectors (e.g., expression vectors) containing such; and host cells comprising the vectors are within the scope of the present disclosure.

[000273] Table 3: Nucleic acids Sequences encoding the VH/VL of anti-HJV antibodies listed in Table 1

humanized HA Antibody		Nucleic Acid Sequences	SEQ ID NO
hHA-001	VH	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAATTGGATTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGAATG ATATACTACGATAGCTCAGAAAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGAACA ACACCAGATTATTGGGGTCAAGGAACAATGGTAACCGTGTCAAGC	70
	VL	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGACGAGCGACG GAGACACTTTTCTTGAGTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGAGGTATCAACGAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTTCAAGTCACCCACGACCCC ATGACGTTCGGACAAGGAACTAAGCTCGAAATCAAA	72
	Heavy Chain	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAATTGGATTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGAATG ATATACTACGATAGCTCAGAAAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGAACA ACACCAGATTATTGGGGTCAAGGAACAATGGTAACCGTGTCAAGCGCGTC GACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCT CTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA CCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACAC CTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG TGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGG GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTG GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC CCATCCCGCGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGT CAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC	71

		AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA	
	Light Chain	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGACGAGCGACG GAGACACTTTTCTTGAGTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGAGGTATCAACGAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTTCAAGTCACCCACGACCCC ATGACGTTCGGACAAGGAACTAAGCTCGAAATCAAAAGAACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCC TGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGG AGAGTGTTGA	73
hHA-002	VH	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAATTGGATTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGAATG ATATACTACGATAGCTCAGAAAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGAACA ACACCAGATTATTGGGGTCAAGGAACAATGGTAACCGTGTCAAGC	70
	VL	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGACGAGCGACG GAGACACTTTTCTTGAGTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGAGGTATCAAGCAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTATGCAAGTCACCCACGACCCC CTGACCTTCGGACAAGGAACTAAGCTCGAAATCAAA	74
	Heavy Chain	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAATTGGATTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGAATG ATATACTACGATAGCTCAGAAAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGAACA ACACCAGATTATTGGGGTCAAGGAACAATGGTAACCGTGTCAAGCGCGTC GACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCT CTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA CCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACAC CTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG TGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGG GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTG GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC CCATCCCGCGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGT CAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA	71

	Light Chain	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGACGAGCGACG GAGACACTTTTCTTGAGTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGAGGTATCAAGCAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTATGCAAGTCACCCACGACCCC CTGACCTTCGGACAAGGAACTAAGCTCGAAATCAAAAGAACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCC TGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGG AGAGTGTTGA	75
hHA-003	VH	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAATTGGATTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGAATG ATATACTACGATAGCTCAGAAAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGAACA ACACCAGATTATTGGGGTCAAGGAACAATGGTAACCGTGTCAAGC	70
	VL	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGACCAGCGACG GAGATACTTTTCTTGAGTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGAGGTATCAAACAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGTCACCCACGACCCC GTCACGTTCGGACAAGGAACTAAGCTCGAAATCAAA	76
	Heavy Chain	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAATTGGATTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGAATG ATATACTACGATAGCTCAGAAAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGAACA ACACCAGATTATTGGGGTCAAGGAACAATGGTAACCGTGTCAAGCGCGTC GACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCT CTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA CCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACAC CTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG TGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGG GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTG GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC CCATCCCGCGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGT CAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA	71
	Light Chain	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGACCAGCGACG GAGATACTTTTCTTGAGTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGAGGTATCAAACAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGTCACCCACGACCCC	77

		GTCACGTTCGGACAAGGAACTAAGCTCGAAATCAAAAGAACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCC TGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGG AGAGTGTTGA	
hHA-004	VH	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAATTGGATTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGAATG ATATACTACGATAGCTCAGAAAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGAACA ACACCAGATTATTGGGGTCAAGGAACAATGGTAACCGTGTCAAGC	70
	VL	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGTCCAGCGACG GAGACACTTTTCTTGAGTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGATGTATCAACTAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTTCAAGTCACCCATGACCCC GTGACCTTCGGACAAGGAACTAAGCTCGAAATCAAA	78
	Heavy Chain	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAATTGGATTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGAATG ATATACTACGATAGCTCAGAAAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGAACA ACACCAGATTATTGGGGTCAAGGAACAATGGTAACCGTGTCAAGCGCGTC GACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCT CTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA CCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACAC CTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG TGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGG GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTG GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC CCATCCCGCGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGT CAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA	71
	Light Chain	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGTCCAGCGACG GAGACACTTTTCTTGAGTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGATGTATCAACTAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTTCAAGTCACCCATGACCCC GTGACCTTCGGACAAGGAACTAAGCTCGAAATCAAAAGAACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCC TGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA	79

		GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGG AGAGTGTTGA	
hHA-005	VH	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAATTGGATTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGAATG ATATACTACGATAGCTCAGAAAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGAACA ACACCAGATTATTGGGGTCAAGGAACAATGGTAACCGTGTCAAGC	70
	VL	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGGAAAGCGACG GATACACTTTTCTTGAATGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGATGTATCAGAAAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGCGACCTACGACCCC CTCACCTTCGGACAAGGAACTAAGCTCGAAATCAAA	80
	Heavy Chain	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAATTGGATTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGAATG ATATACTACGATAGCTCAGAAAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGAACA ACACCAGATTATTGGGGTCAAGGAACAATGGTAACCGTGTCAAGCGCGTC GACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCT CTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA CCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACAC CTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG TGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGG GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTG GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC CCATCCCGCGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGT CAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA	71
	Light Chain	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGGAAAGCGACG GATACACTTTTCTTGAATGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGATGTATCAGAAAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGCGACCTACGACCCC CTCACCTTCGGACAAGGAACTAAGCTCGAAATCAAAAGAACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCC TGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGG AGAGTGTTGA	81
hHA-006	VH	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTTACTATGGAA TGAACTGGATTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGCATG ATATACTACGACAGCTCGGAGAAACATTATGCCGACTCAGTTAAAGGAAG	82

		ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGGACG ACGCCCGATTACTGGGGTCAAGGAACAATGGTAACCGTGTCAAGC	
	VL	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGGACAGCGACG GAGGAACTTTTCTTGAGTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGACGTATCAAGCAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTTCAAGCGACCCACGACCCC CTGACGTTCGGACAAGGAACTAAGCTCGAAATCAAA	83
	Heavy Chain	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTTACTATGGAA TGAACTGGATTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGCATG ATATACTACGACAGCTCGGAGAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGGACG ACGCCCGATTACTGGGGTCAAGGAACAATGGTAACCGTGTCAAGCGCGTC GACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCT CTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA CCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACAC CTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG TGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGG GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTG GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC CCATCCCGCGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGT CAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA	84
	Light Chain	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGGACAGCGACG GAGGAACTTTTCTTGAGTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGACGTATCAAGCAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTTCAAGCGACCCACGACCCC CTGACGTTCGGACAAGGAACTAAGCTCGAAATCAAAAGAACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCC TGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGG AGAGTGTTGA	85
hHA-007	VH	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAACTGGATAAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGCATG ATATACTACGACAGCTCGGACAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGGACG ACGCCGGATGTATGGGGTCAAGGAACAATGGTAACCGTGTCAAGC	86
	VL	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAAGAGAGCGACG GATACACTTTTCTTCATTGGTTCCAACAAAGACCCGGACAAAGCCCACGC	87

		CTGCTTATTTACGAGGTATCAAACAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGCCACCCACGACCCC GTGACGTTCGGACAAGGAACTAAGCTCGAAATCAAA	
	Heavy Chain	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAACTGGATAAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGCATG ATATACTACGACAGCTCGGACAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGGACG ACGCCGGATGTATGGGGTCAAGGAACAATGGTAACCGTGTCAAGCGCGTC GACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCT CTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA CCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACAC CTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG TGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGG GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTG GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC CCATCCCGCGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGT CAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA	88
	Light Chain	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAAGAGAGCGACG GATACACTTTTCTTCATTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGAGGTATCAAACAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGCCACCCACGACCCC GTGACGTTCGGACAAGGAACTAAGCTCGAAATCAAAAGAACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCC TGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGG AGAGTGTTGA	89
hHA-008	VH	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAACCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAACTGGGTTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGCATG ATATATTACGACAGCTCGGAGAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGGACC ACCCCCGATTACTGGGGTCAAGGAACAATGGTAACCGTGTCAAGC	90
	VL	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAAGAAAGCGACG GATACACTTTTCTTCACTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGAGGTATCAACCAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGCCACCCACGACCCC CTGACCTTCGGACAAGGAACTAAGCTCGAAATCAAA	91

	Heavy Chain	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAACCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAACTGGGTTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGCATG ATATATTACGACAGCTCGGAGAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGGACC ACCCCCGATTACTGGGGTCAAGGAACAATGGTAACCGTGTCAAGCGCGTC GACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCT CTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA CCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACAC CTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG TGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGG GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTG GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC CCATCCCGCGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGT CAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA	92
	Light Chain	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAAGAAAGCGACG GATACACTTTTCTTCACTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGAGGTATCAACCAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGCCACCCACGACCCC CTGACCTTCGGACAAGGAACTAAGCTCGAAATCAAAAGAACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCC TGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGG AGAGTGTTGA	93
hHA-008-QL	VH	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAACCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAACTGGGTTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGCATG ATATATTACGACAGCTCGGAGAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGGACC ACCCCCGATTACTGGGGTCAAGGAACAATGGTAACCGTGTCAAGC	90
	VL	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAAGAAAGCGACG GATACACTTTTCTTCACTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGAGGTATCAACCAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGCCACCCACGACCCC CTGACCTTCGGACAAGGAACTAAGCTCGAAATCAAA	91
	Heavy Chain	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAACCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAACTGGGTTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGCATG ATATATTACGACAGCTCGGAGAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGGACC	94

		ACCCCCGATTACTGGGGTCAAGGAACAATGGTAACCGTGTCAAGCGCGTC GACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCT CTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA CCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACAC CTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG TGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGG GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACCAACTCATG ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTG GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC CCATCCCGCGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGT CAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCCGTGCTGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA	
	Light Chain	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAAGAAAGCGACG GATACACTTTTCTTCACTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGAGGTATCAACCAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGCCACCCACGACCCC CTGACCTTCGGACAAGGAACTAAGCTCGAAATCAAAAGAACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCC TGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGG AGAGTGTTGA	93
hHA-009	VH	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAACCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAACTGGGTTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGCATG ATATATTACGACAGCTCGGAGAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGGACC ACCCCCGATTACTGGGGTCAAGGAACAATGGTAACCGTGTCAAGC	90
	VL	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGCGGACAGCGACG GAGATACTTTTCTTCACTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGCGGTATCACACAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGCCACCCATGACCCC GTCACGTTCGGACAAGGAACTAAGCTCGAAATCAAA	95
	Heavy Chain	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAACCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAACTGGGTTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGCATG ATATATTACGACAGCTCGGAGAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGGACC ACCCCCGATTACTGGGGTCAAGGAACAATGGTAACCGTGTCAAGCGCGTC GACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCT CTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA CCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACAC CTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG TGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG	92

		AATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGG GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTG GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC CCATCCCGCGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGT CAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA	
	Light Chain	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGCGGACAGCGACG GAGATACTTTTCTTCACTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGCGGTATCACACAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGCCACCCATGACCCC GTCACGTTCGGACAAGGAACTAAGCTCGAAATCAAAAGAACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCC TGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGG AGAGTGTTGA	96
hHA-010	VH	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAACTGGGTTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGCATG ATATACTACGACAGCTCCGAGAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGCACG ACGCCCGATAAATGGGGTCAAGGAACAATGGTAACCGTGTCAAGC	97
	VL	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGGAGAGCGACG GATACACTTTTCTTGAGTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGAGGTATCACATAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGCGACCCACGACCCC CTGACGTTCGGACAAGGAACTAAGCTCGAAATCAAA	98
	Heavy Chain	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAACTGGGTTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGCATG ATATACTACGACAGCTCCGAGAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGCACG ACGCCCGATAAATGGGGTCAAGGAACAATGGTAACCGTGTCAAGCGCGTC GACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCT CTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA CCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACAC CTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG TGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGG GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTG	99

		GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC CCATCCCGCGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGT CAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA	
	Light Chain	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGGAGAGCGACG GATACACTTTTCTTGAGTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGAGGTATCACATAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGCGACCCACGACCCC CTGACGTTCGGACAAGGAACTAAGCTCGAAATCAAAAGAACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCC TGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGG AGAGTGTTGA	100
hHA-011	VH	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAACTGGGTTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGAATG ATATACTACGACAGCTCCGAGAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGCTCG ACCCCCGATTACTGGGGTCAAGGAACAATGGTAACCGTGTCAAGC	101
	VL	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGGACAGCGACG GAGGCACTTTTCTTGAGTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGACGTATCAAGCAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGCCACCCACGACCCC CTCAGCTTCGGACAAGGAACTAAGCTCGAAATCAAA	102
	Heavy Chain	GAAGTACAGTTGGTAGAAAGCGGCGGAGGACTTGTGCAGCCAGGTGGATC TCTCAGACTTTCATGTGCCGCAAGCGGTTTTACTTTTAGTAACTATGGAA TGAACTGGGTTAGACAAGCGCCCGGAAAAGGATTGGAATGGATAGGAATG ATATACTACGACAGCTCCGAGAAACATTATGCCGACTCAGTTAAAGGAAG ATTTACAATATCAAGAGACAATAGCAAAAACACACTTTATCTTCAAATGA ATTCACTGCGAGCCGAGGATACAGCAGTCTATTATTGCGCAAAAGGCTCG ACCCCCGATTACTGGGGTCAAGGAACAATGGTAACCGTGTCAAGCGCGTC GACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCT CTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA CCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACAC CTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG TGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGG GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTG GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC CCATCCCGCGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGT CAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC	40

		TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA	
	Light Chain	GACGTAGTACTGACCCAAAGCCCCCTTTCTCTCCCAGTAACCCTCGGACA ACCAGCCTCAATTTCATGCAGATCATCACAATCACTTGAGGACAGCGACG GAGGCACTTTTCTTGAGTGGTTCCAACAAAGACCCGGACAAAGCCCACGC CTGCTTATTTACGACGTATCAAGCAGATTCTCAGGAGTTCCAGACAGATT TTCAGGCAGCGGATCCGGCACAGACTTCACCCTTAAAATTAGCAGAGTAG AAGCAGAAGATGTAGGAGTGTATTATTGTTTCCAAGCCACCCACGACCCC CTCAGCTTCGGACAAGGAACTAAGCTCGAAATCAAAAGAACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCC TGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGG AGAGTGTTGA	64

[000274] In some embodiments, the anti-HJV described herein is produced by expressing (i) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 71, and/or (ii) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 73.

[000275] In some embodiments, the anti-HJV described herein is produced by expressing (i) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 71, and/or (ii) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 75.

[000276] In some embodiments, the anti-HJV described herein is produced by expressing (i) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 71, and/or (ii) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 77.

[000277] In some embodiments, the anti-HJV described herein is produced by expressing (i) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 71, and/or (ii) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 79.

[000278] In some embodiments, the anti-HJV described herein is produced by expressing (i) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 71, and/or (ii) a nucleic

acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 81.

[000279] In some embodiments, the anti-HJV described herein is produced by expressing (i) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 84, and/or (ii) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 85.

[000280] In some embodiments, the anti-HJV described herein is produced by expressing (i) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 88, and/or (ii) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 89.

[000281] In some embodiments, the anti-HJV described herein is produced by expressing (i) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 92, and/or (ii) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 93.

[000282] In some embodiments, the anti-HJV described herein is produced by expressing (i) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 94, and/or (ii) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 93.

[000283] In some embodiments, the anti-HJV described herein is produced by expressing (i) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 92, and/or (ii) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 96.

[000284] In some embodiments, the anti-HJV described herein is produced by expressing (i) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 99, and/or (ii) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 100.

[000285] In some embodiments, the anti-HJV described herein is produced by expressing (i) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%,

94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 40, and/or (ii) a nucleic acid at least 60% (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO: 64.

[000286] In some embodiments, the anti-HJV antibodies described herein can be used for delivering a molecular payload to a target cell or a target tissue (e.g., a cell or tissue that expresses HJV). Accordingly, the anti-HJV antibody described herein can be linked to a molecular payload. The complexes described herein may be used in various applications, e.g., diagnostic or therapeutic applications.

[000287] In some embodiments, the complex described herein is used to modulate the activity or function of at least one gene, protein, and/or nucleic acid. In some embodiments, the molecular payload is responsible for the modulation of a gene, protein, and/or nucleic acids. A molecular payload may be a small molecule, protein, nucleic acid, oligonucleotide, or any molecular entity capable of modulating the activity or function of a gene, protein, and/or nucleic acid in a cell. In some embodiments, a molecular payload is an oligonucleotide that targets a disease-associated repeat in muscle cells.

IV. Pharmaceutical Composition

[000288] The antibodies, as well as the encoding nucleic acids or nucleic acid sets, vectors comprising such, or host cells comprising the vectors, as described herein can be mixed with a pharmaceutically acceptable carrier (excipient) to form a pharmaceutical composition for use in treating a target disease. "Acceptable" means that the carrier must be compatible with the active ingredient of the composition (and preferably, capable of stabilizing the active ingredient) and not deleterious to the subject to be treated. Pharmaceutically acceptable excipients (carriers) including buffers, which are well known in the art. See, e.g., Remington: The Science and Practice of Pharmacy 20th Ed. (2000) Lippincott Williams and Wilkins, Ed. K. E. Hoover.

[000289] The anti-HJV antibody containing pharmaceutical composition disclosed herein may further comprise a suitable buffer agent. A buffer agent is a weak acid or base used to maintain the pH of a solution near a chosen value after the addition of another acid or base. In some examples, the buffer agent disclosed herein can be a buffer agent capable of maintaining physiological pH despite changes in carbon dioxide concentration (produced by cellular respiration). Exemplary buffer agents include, but are not limited to a HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) buffer, Dulbecco's phosphate-buffered saline (DPBS) buffer, or Phosphate-buffered Saline (PBS) buffer. Such buffers may comprise

disodium hydrogen phosphate and sodium chloride, or potassium dihydrogen phosphate and potassium chloride.

[000290] In some embodiments, the buffer agent in the pharmaceutical composition described herein may maintain a pH value of about 5-8. For example, the pH of the pharmaceutical composition can be about 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, or 8.0. In other examples, the pharmaceutical composition may have a pH value lower than 7, for example, about 7, 6.8, 6.5, 6.3, 6, 5.8, 5.5, 5.3, or 5.

[000291] The pharmaceutical composition described herein comprises one or more suitable salts. A salt is an ionic compound that can be formed by the neutralization reaction of an acid and a base. (Skoog, D.A; West, D.M.; Holler, J.F.; Crouch, S.R. (2004). "chapters 14–16". Fundamentals of Analytical Chemistry (8th ed.)). Salts are composed of related numbers of cations (positively charged ions) and anions (negative ions) so that the product is electrically neutral (without a net charge).

[000292] In some embodiments, the pharmaceutical compositions can comprise pharmaceutically acceptable carriers, excipients, or stabilizers in the form of lyophilized formulations or aqueous solutions. (Remington: The Science and Practice of Pharmacy 20th Ed. (2000) Lippincott Williams and Wilkins, Ed. K. E. Hoover). In some embodiments, the pharmaceutical composition can be formulated for intravenous injection. In some embodiments, the pharmaceutical composition can be formulated for subcutaneous injection.

[000293] The pharmaceutical compositions to be used for in vivo administration must be sterile. This is readily accomplished by, for example, filtration through sterile filtration membranes. Therapeutic antibody compositions are generally placed into a container having a sterile access port, for example, an intravenous or subcutaneous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

V. Methods of Use

[000294] Aspects of the disclosure relate to compositions and methods for treating myelofibrosis and/or one or more conditions arising as a result of myelofibrosis in a subject.

[000295] FIG. 12 depicts the hepcidin stimulatory pathway and the physiological regulation of iron homeostasis by hepcidin. As generically shown, Hepcidin operates by binding to the iron exporter Ferroportin in iron-releasing target cells (e.g., hepatocytes, duodenal enterocytes, tissue macrophages, and other cell types). The binding of hepcidin blocks iron efflux and triggers ubiquitination, internalization, and lysosomal degradation of ferroportin. This leads to intracellular iron retention and eventually decreased systemic iron levels.

[000296] The HAMP gene encodes hepcidin precursor protein, which is primarily expressed by hepatocytes in the liver, and at lower levels by other cells in extrahepatic tissues. The precursor protein is subsequently cleaved to yield bioactive hepcidin. In some embodiments, a hepcidin antagonist of the present disclosure is a HAMP antagonist, which antagonizes hepcidin function by binding HAMP or a transcription or translation product thereof, or by inhibiting a transcriptional or translational regulator of HAMP to reduce HAMP expression. Examples of transcriptional regulators of HAMP include, without limitation, SMAD1/5/8 (e.g., BMP-SMAD signaling pathway) and STAT3 (e.g., JAK-STAT signaling pathway). Accordingly, in some embodiments, the HAMP antagonist is a BMP-SMAD signaling pathway inhibitor or a JAK-STAT signaling pathway inhibitor.

[000297] Increases in serum or tissue iron trigger transcriptional induction of hepcidin via the BMP-SMAD signaling pathway. The mechanism involves secretion of bone morphogenetic protein 6 (BMP6) from liver sinusoidal endothelial cells, which binds to a BMP receptor (BMPR) on hepatocytes and thereby activates the SMAD signaling cascade. Examples of BMP receptors include type I (e.g., ALK2, ALK3, ALK6) and type II (e.g., ActRIIA, BMPRII) BMP receptors. A central regulator of the BMP-SMAD signaling pathway for hepcidin stimulation is the BMP co-receptor, hemojuvelin (HJV). Accordingly, in some aspects, the disclosure relates to hemojuvelin antagonists (e.g., anti-HJV antibodies and compositions thereof) for targeting hepcidin, e.g., for modulating iron homeostasis for the treatment of myelofibrosis and/or one or more conditions arising as a result of myelofibrosis. In some embodiments, the disclosure provides methods for modulating iron homeostasis for the treatment of myelofibrosis that involve direct inhibition of binding of hepcidin to the iron exporter ferroportin. In some embodiments, the hepcidin antagonist is an anti-HJV antibody.

[000298] Myelofibrosis (MF) is a myeloproliferative disorder characterized by proliferation of abnormal blood stem cells leading to bone marrow fibrosis. Production of healthy blood cells (megakaryocytes responsible for platelet production and erythrocytes) is impaired. MF can be categorized as primary MF (PMF) and secondary MF (SMF). PMF and SMF have similar clinical profiles which include anemia, fatigue, and splenomegaly are common presenting symptoms. Primary myelofibrosis (PMF) is characterized as MF that occurs on its own. In some embodiments, PMF may be associated with increased level of proinflammatory cytokines (e.g., IL-6) in the subject (see, e.g., Čokić et al. Proinflammatory Cytokine IL-6 and JAK-STAT Signaling Pathway in Myeloproliferative Neoplasms, Mediators Inflamm. 2015; 2015: 453020). Secondary myelofibrosis (SMF) occurs as the result of a separate disease, e.g. scar tissue in the bone marrow as a complication of an autoimmune disease. In

some embodiments, a subject described herein is has or is suspected of having PMF. In some embodiments, a subject described herein is has or is suspected of having SMF.

[000299] In some embodiments, a subject having or suspect of having myelofibrosis (e.g., PMF and/or SMF) comprises one or more mutations in one or more genes (e.g., a JAK2 gene, a Thrombopoietin Receptor (MPL) gene, a calreticulin (CALR) gene, a Lymphocyte-Specific Adapter Protein Lnk (LNK) gene, a ASXL Transcriptional Regulator 1 (ASXL1) gene, a Serine And Arginine Rich Splicing Factor 2 (SRSF2) gene, a Protein Phosphatase, $Mg2^{+}/Mn2^{+}$ Dependent 1D (PPM1D) gene, Isocitrate Dehydrogenase ($NADP^{(+)}$) 1/ Isocitrate Dehydrogenase ($NADP^{(+)}$) 2 (IDH1/2) genes, a Tet Methylcytosine Dioxygenase 2 (TET2) gene, a Enhancer Of Zeste 2 Polycomb Repressive Complex 2 Subunit (EZH2) gene, a U2 Small Nuclear RNA Auxiliary Factor 1 (U2AF1) gene, a Nuclear Factor, Erythroid 2 (NFE2) gene, a SH2B Adaptor Protein 3 (SH2B3) gene, a Splicing Factor 3b Subunit 1 (SF3B1) gene, a Cbl Proto-Oncogene (CBL) gene or a combination thereof.

[000300] In some embodiments, the subject has one or more mutations in the JAK2 gene. JAK2 plays an integral role in transducing signals from receptors involved in myeloid cell lineage proliferation by EPO, TPO, and/or G-CSF (see, e.g., Alshemmari et al., *Molecular Pathogenesis and Clinical Significance of Driver Mutations in Primary Myelofibrosis*: A Review, Med Princ Pract, 2016;25(6):501-509). In some embodiments, the subject contains a human JAK2 gene having initiating mutations in an exon 12 or exon 14. In some embodiments, the initiating mutation in the JAK2 gene is in exon 14 and results in a V617F substitution. In some embodiments, the V617F mutation leads or over-activation of JAK2 and its associated signaling pathways. In some embodiments, the over-activation of JAK2 leads to myelofibrosis (e.g., PMF, and/or SMF).

[000301] In some embodiments, a subject has one or more mutations in the Thrombopoietin Receptor (MPL) gene. MPL is the cognate receptor of thrombopoietin (TPO), and mutations that result in gain of function of the MPL gene lead to impairment in megakaryocytes production. In some embodiments, the subject comprises a W515L/K mutation of MPL. In some embodiments, the some embodiments, a subject having one or more mutations in MPL gene has a greater chance (e.g., more than 10%, more than 20%, more than 30%, more than 40%, more than 50%, more than 60%, more than 70%, more than 80%, more than 90%, more than 2-fold, more than 3-fold, more than 4-fold, more than 5-fold, more than 6-fold, more than 7-fold, more than 8-fold, more than 9-fold, or more than 10-fold) of developing anemia

compared to the overall subjects having MF (Guglielmelli P et al., Anaemia characterises patients with myelofibrosis harboring Mpl mutation. Br J Haematol 2007; 137: 244–247).

[000302] In some embodiments, a subject has one or more mutations in the calreticulin (CALR) gene. The CALR gene encodes the calreticulin protein, which is a multifactorial protein that regulates calcium homeostasis, cell signaling, gene expression, cell adhesion, autoimmunity and apoptosis. About 140 CALR mutations have been identified with 19 variant to be associated with MF. In some embodiments, the subject has or is suspect of having MF has an Exon 9 mutation in the CALR gene.

[000303] Additional mutations in other gene that are associated with MF have been identified. Non-limiting examples of genes associated with MF include, e.g., JAK2, MPL, CLAR, LNK, ASXL1, SRSF2, PPM1D, IDH1/2, TET2, EZH2, U2AF1, NFE2, SH2B3, SF3B1 or CBL. In some embodiments, a subject has or is suspect of having MF comprises one or more mutations in one or more of the genes described herein.

[000304] In some embodiments, the subject has one or more mutations in genes involved in epigenetic regulation or splicing. In some embodiments the one or more mutations in genes involved in epigenetic regulation or splicing is ASXL1, DNMT3A, TET2, SRSF2, U2AF1, EZH2 or SF3B1. In some embodiments, the subject has mutations in IDH1/2 associated with risk of progression to MBN-BP.

[000305] In some aspects, the disclosure relates to compositions (e.g., anti-HJV antibodies and compositions thereof) and methods for treating myelofibrosis in a subject. In some embodiments, a subject to be treated in accordance with the disclosure may be identified based on an appropriate diagnostic or prognostic methodology. For example, the Dynamic International Prognostic Scoring System (DIPSS) and age-adjusted DIPSS provide models of patient outcome based on several patient-specific variables, including age, hemoglobin level, white blood cell count, peripheral blood blasts, and constitutional symptoms (see, e.g., Passamonti, F., et al. Blood. 2010 Mar 4;115(9):1703-8, which is incorporated herein by reference). The DIPSS model calculates a DIPSS score which allows for allocating a patient into a risk category for prognosis purposes. A DIPSS score of 0 identifies a “low risk” patient, a DIPSS score of 1-2 identifies an “intermediate-1 risk” patient, a DIPSS score of 3-4 identifies an “intermediate-2 risk” patient, and a DIPSS score of 5-6 identifies a “high risk” patient. Accordingly, in some embodiments, a subject in need of treatment in accordance with the application may have a DIPSS score of at least 1. In some embodiments, the subject

has a DIPSS score of 1-4 (e.g., 1, 2, 3, or 4). In some embodiments, the subject has a DIPSS score of 5 or 6 (e.g., 5 or 6).

[000306] In some embodiments, a subject to be treated in accordance with the disclosure may be assessed by an appropriate diagnostic or prognostic methodology. For example, the Myeloproliferative Neoplasm-Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) provides a 10-item instrument designed to assess the most representative and clinically relevant symptoms among patients with MPNs. The tool records the patient's assessment of the incidence and severity of these disease-related symptoms. It can be used to track symptoms over time and guide subsequent management decisions (see e.g., Emanuel RM, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs, J Clin Oncol. 2012;30(33):4098-4103, which is incorporated herein by reference). The MPN-SAF TSS includes symptoms such as fatigue, early satiety, inactivity, concentration problems, abdominal discomfort, night sweats, bone pain, itching, unintentional weight loss, and fever. Each symptom is rated by a Symptom severity on a 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) scale. The MPN-SAF TSS has a possible range of 0 to 100, with 100 representing the highest level of symptom severity. In some embodiments, a Myelofibrosis Symptom Assessment Form (MFSAF) is derived from MPN-SAF TSS. MFSAF is an instrument that measures the symptoms reported by >10% of MF patients, and includes a measure of quality of life (QoL). MFSAF includes a comprehensive evaluation of fatigue, an assessment of splenomegaly and associated mechanical symptoms, and an evaluation of other symptoms such as night sweats, itching (pruritus), bone pain, fever, unintentional weight loss and overall quality of life (see e.g., Mesa et al., The Myelofibrosis Symptom Assessment Form (MFSAF): An Evidence-based Brief Inventory to Measure Quality of Life and Symptomatic Response to Treatment in Myelofibrosis, Leuk Res. 2009 Sep; 33(9): 1199–1203, which is incorporated herein by reference). MFSAF can be used to track symptoms over time and guide subsequent management decisions. In some embodiments, a patient has a MPN-SAF TSS of 0-100 (e.g., any score number between 0 and 100), 10-100 (e.g., any score number between 10 and 100), 20-100 (e.g., any score number between 20 and 100), 30-100 (e.g., any score number between 30 and 100), 40-100 (e.g., any score number between 40 and 100), 50-100 (e.g., any score number between 50 and 100), 60-100 (e.g., any score number between 60 and 100), 70-100 (e.g., any score number between 70 and 100), 80-100 (e.g., any score number between 80 and 100), or 90-100 (e.g., any score number between 00 and 100).

[000307] In some aspects, a subject having MF (e.g., PMF or SMF) develops anemia. Anemia in MF is the result of a multifactorial process.

[000308] In some embodiments, anemia in MF may be therapy related. In some embodiments, MF patients have been previously treated with JAK inhibitors (e.g., Ruxolitinib or Fedratinib). In some embodiments, patients receiving JAK inhibitors (e.g., Ruxolitinib or Fedratinib) exhibits higher chance of developing MF-related anemia. Inhibition of JAK-STAT signaling pathway leads to inhibition of erythropoietin-mediated JAK2 signaling, which is essential for erythropoiesis. In some embodiments, new-onset anemia has been identified as a major adverse event associated JAK inhibitor (e.g., ruxolitinib) treatment (see, e.g., Verstovsek S, Kantarjian H, Mesa RA, et al. S*afety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis*. N Engl J Med. 2010;363(12):1117-1127; Verstovsek S, Mesa RA, Gotlib J, et al. *A doubleblind, placebo-controlled trial of ruxolitinib for myelofibrosis*. N Engl J Med. 2012;366(9):799-807; Parganas E, Wang D, Stravopodis D, et al. *Jak2 is essential for signaling through a variety of cytokine receptors*. Cell. 1998;93(3):385-395; Neubauer H, Cumano A, M¨ uller M, Wu H, Huffstadt U, Pfeffer K. *Jak2 deficiency defines an essential developmental checkpoint in definitive hematopoiesis*. Cell. 1998;93(3):397-409, the entire contents of each of which are incorporated herein by reference).

[000309] In some embodiments, the subject has or is at risk of having constitutional or microvascular symptoms associated with Myeloproliferative neoplasms (MPN). In some embodiments, the subject has or is at risk of having thromboembolic or hemorrhagic complications. In some embodiments, the subject has or is at risk of having MPN-blast phase acute myeloid leukemia (AML). In some embodiments, the subject exhibits ribosomopathy in megakaryocytes. In some embodiments, the subject exhibits reduced GATA1 expression, particularly in megakaryocytes. In some embodiments, the subject exhibits defects in megakaryocytic function or maturation. In some embodiments, the subject does not have a nutritional iron deficiency. In some embodiments, the subject presents with thrombocytopenia, anemia, and/or neutropenia.

[000310] In some embodiments, myelofibrosis-associated anemia is caused by ineffective erythropoiesis due to bone marrow suppression and deficiencies in iron metabolism, increased destruction of red blood cell due to splenomegaly, increased plasma volume, abnormal pro-inflammatory environment in the bone marrow, or a combination thereof.

[000311] In some embodiments, the myelofibrosis-associated anemia is associated with abnormal iron metabolism. In some embodiments, the abnormal iron metabolism in MF

patients is functional iron deficiency (FID). FID represents a state of iron-restricted erythropoiesis characterized by an imbalance between iron demand and serum iron that is readily available for effective erythropoiesis. In FID, even when the body has adequate or increased systemic iron stores, iron is sequestered and not available for erythropoiesis. In some embodiments, FID is caused by an increase of hepcidin relative to the iron store levels. In some embodiments, increased hepcidin expression is caused by upregulation of pro-inflammatory cytokines. For example, IL-6 was reported to be higher in anemic MF patients (Birgegard et al., Inflammatory Functional Iron Deficiency Common in Myelofibrosis, Contributes to Anaemia and Impairs Quality of Life. From the Nordic MPN Study Group, Eur J Haematol. 2019 Mar;102(3):235-240).

[000312] In some embodiments, the myelofibrosis-associated anemia is characterized by high serum pro-inflammatory cytokine levels.

[000313] In myelofibrosis (e.g., PMF), pro-inflammatory cytokines that induce hepcidin synthesis, such as IL-6 and oncostatin-M, are typically increased and associated with iron sequestration, macrophage iron loading, as well as myeloid proliferation and macrophage activation. These increased hepcidin levels may lead to anemia.

[000314] In some embodiments, the pro-inflammatory cytokine is IL-6. Normal range of IL-6 (e.g., in subjects without disease) is equal or less than 1.8 pg/ml. In some embodiments, the subject has a higher-than-normal serum IL-6 levels, e.g., greater than 1.8 pg/ml.

[000315] In some embodiments, the present disclosure provides a method of treating a subject having myelofibrosis. In some embodiments, the subject has anemia resulting from hepcidin synthesis that is induced by pro-inflammatory cytokines. In some embodiments, the pro-inflammatory cytokine that increases hepcidin synthesis is IL-6. In some embodiments, administration of the anti-HJV antibody to the subject reduces hepcidin synthesis induced by pro-inflammatory cytokines (e.g., IL-6). In some embodiments, the administration of the anti-HJV antibody ameliorates FID associated with increased hepcidin synthesis induced by proinflammatory cytokines (e.g., IL-6).

[000316] Determination of whether an amount of the antibody (e.g., anti-HJV antibody) achieved the therapeutic effect would be evident to one of skill in the art based on the teachings provided herein. Effective amounts vary, as recognized by those skilled in the art, depending on the particular condition being treated, the severity of the condition, the individual patient parameters including age, physical condition, size, gender and weight, the duration of the treatment, the nature of concurrent therapy (if any), the specific route of administration and like factors within the knowledge and expertise of the health practitioner.

These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. The particular dosage regimen, *i.e.*, dose, timing and repetition, used in the method described herein will depend on the particular subject and that subject's medical history, as discussed herein.

[000317] Empirical considerations, such as time to maximum effect, the half-life, and/or time above a specific concentration generally will contribute to the determination of the dosage. For example, antibodies that are compatible with the human immune system, such as humanized antibodies or fully human antibodies, may be used to prolong half-life of the antibody and to prevent the antibody being attacked by the host's immune system. Other reasons for dose-adjusting include differences in pharmacokinetics or pharmacodynamic response driven by sex, age, individual response, polymorphisms on the antibody target and/or receptors involved in antibody clearance. Frequency of administration may be determined and adjusted over the course of therapy, and is generally, but not necessarily, based on treatment and/or suppression and/or amelioration and/or delay of a target disease/disorder. Alternatively, sustained continuous release formulations of an antibody may be appropriate. Various formulations and devices for achieving sustained release are known in the art.

[000318] In some embodiments, dosages for an antibody as described herein may be determined empirically in individuals who have been given one or more administration(s) of the antibody. Individuals are given incremental dosages of the antagonist. To assess efficacy of the antagonist, an indicator of the disease/disorder can be followed.

[000319] Dosing frequencies may vary in accordance with the claimed methods. In some embodiments, a composition may be administered once. In some embodiments, a composition will be administered on multiple occasions. In some embodiments, dosing frequency is every week, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, every 8 weeks, every 9 weeks, or every 10 weeks; or once every month, every 2 months, or every 3 months, or longer. In some embodiments, a composition will be administered daily, biweekly, weekly, bimonthly, monthly, or at any time interval that provide suitable (e.g., maximal) efficacy while minimizing safety risks to the subject. Generally, the efficacy and the treatment and safety risks may be monitored throughout the course of treatment.

[000320] In some embodiments, administration of anti-HJV antibody results in a decrease in circulating hepcidin-25 concentration and/or increase serum TSAT% (see, e.g., FIGs. 7D-7E), and in some embodiments, these effects persist for a period of time (e.g., one month or more).

Accordingly, in some embodiments, timing and frequency of administration of anti-HJV antibody can be determined by monitoring one or more biomarkers, e.g., criteria to assess iron availability or flag possible iron overload. For example, in some embodiments, anti-HJV antibody is administered intermittently or in accordance with the level of a particular biomarker such as circulating hepcidin-25 levels, circulating transferrin level, or transferrin saturation percentage (TSAT%). In some embodiments, a biomarker level can be used to determine whether a subject is a candidate for treatment. However, in some embodiments, a biomarker may be used to determine whether to continue treatment or to resume a treatment or to halt a treatment, e.g., halt treatment with an anti-HJV antibody.

[000321] For example, in some embodiments, a subject may be considered as not being a candidate for treatment if TSAT% of the subject is at or above 70%, at or above 75%, at or above 80%, at or above 85%, at or above 90%, or at or above 95%. In some cases, if TSAT% of the subject is at or above 70%, at or above 75%, at or above 80%, at or above 85%, at or above 90%, or at or above 95%, an ongoing treatment with an anti-HJV antibody may be stopped or temporarily stopped, e.g., to prevent iron overload. In other embodiments, administration of an anti-HJV antibody may be performed when a TSAT% of a subject is at or below 95%, at or below 90%, at or below 80%, at or below 70 %, at or below 65%, at or below 60%, at or below 55%, at or below 50%, at or below 45%, at or below 40%, at or below 35%, or at or below 30%. Thus, in some embodiments, TSAT% of a subject can be monitored, e.g., continuously or periodically, while a patient is receiving a treatment or under care of a treating physician, e.g., for anemia, to prevent iron overload or otherwise to assess whether further treatments are appropriate. It should be appreciated, however, that other suitable markers may be monitored to determine dosage and dosage frequency (including, for example, ferritin levels, serum iron levels, creatinine levels, etc.) in accordance with the methods provided herein.

[000322] In some embodiments, a subject may be administered a composition provided herein (e.g., an anti-HJV antibody) at one or more intervals during a set period of time. In some cases, periods of time during which a subject is administered a composition at one or more intervals may be separated by periods of time in which the subject is not administered the composition. In some embodiments, the relative durations of respective periods of time may depend on the subject's response to treatment or severity of disease or both and/or may be determined based on the judgment of a treating physician. For example, in some embodiments, during the course of a year a subject may be administered a composition weekly, biweekly or monthly for two months and then the administration is stopped for ten

months. In some embodiments, during the course of a year a subject may be administered a composition weekly, biweekly or monthly for three months and then the administration is stopped for nine months. In some embodiments, during the course of a year a subject may be administered a composition weekly, biweekly or monthly for four months and then the administration is stopped for eight months. In some embodiments, during the course of a year a subject may be administered a composition weekly, biweekly or monthly for five months and then the administration is stopped for seven months. In some embodiments, during the course of a year a subject may be administered a composition weekly, biweekly or monthly for six months and then the administration is stopped for six months. In some embodiments, during the course of a year a subject may be administered a composition weekly, biweekly or monthly for seven months and then the administration is stopped for five months. In some embodiments, during the course of a year a subject may be administered a composition weekly, biweekly or monthly for eight months and then the administration is stopped for four months. In some embodiments, during the course of a year a subject may be administered a composition weekly, biweekly or monthly for nine months and then the administration is stopped for three months. In some embodiments, during the course of a year a subject may be administered a composition weekly, biweekly or monthly for ten months and then the administration is stopped for two months. In some embodiments, during the course of a year a subject may be administered a composition weekly, biweekly or monthly for two months on, two months off; or for three months on, three months off; or for four months on, four months off.

[000323] Generally, for administration of any of the antibodies described herein, a dose may be about 0.01 mg/kg, 0.05 mg/kg. 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 0.6 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 20 mg/kg, 30 mg/kg, 40 mg/kg, 50 mg/kg, 60 mg/kg, 70 mg/kg, 80 mg/kg, 90 mg/kg or 100 mg/kg.

[000324] In some embodiments, the dosage the anti-HJV antibody is up to 0.01 mg/kg, up to 0.05 mg/kg. up to 0.1 mg/kg, up to 0.2 mg/kg, up to 0.3 mg/kg, up to 0.4 mg/kg, up to 0.5 mg/kg, up to 0.6 mg/kg, up to 1 mg/kg, mg/kg, up to 2 mg/kg, up to 3 mg/kg, up to 4 mg/kg, up to 5 g/kg, up to 6 mg/kg, up to 7 mg/kg, up to 8 mg/kg, up to 9 mg/kg, up to 10 mg/kg, up to 20 mg/kg, up to 30 mg/kg, up to 40 mg/kg, up to 50 mg/kg, up to 60 mg/kg, up to 70 mg/kg, 80 mg/kg, up to 90 mg/kg, up to 100 mg/kg or more.

[000325] However, in some embodiments, the dose of the anti-HJV antibody can be in a range of 0.01 mg/kg to 100 mg/kg, 0.01 mg/kg to 10 mg/kg, 0.5 mg/kg to 15 mg/kg, 1 mg/kg

to 15 mg/kg, 5 mg/kg to 25 mg/kg, 10 mg/kg to 30 mg/kg, 20 mg/kg to 40 mg/kg, 30 mg/kg to 50 mg/kg, 40 mg/kg to 60 mg/kg, 50 mg/kg to 75 mg/kg, or 50 mg/kg to 100 mg/kg

[000326] In some embodiments, the antibodies described herein are administered to a subject in need of the treatment at an amount sufficient to inhibit the activity of the target antigen (e.g., an amount sufficient to inhibit HJV-induced BMP signaling) by at least 20% (e.g., 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater) in vivo. In other embodiments, the antibody is administered in an amount effective in reducing the activity level of a target antigen by at least 20% (e.g., 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater).

[000327] In some embodiments, an antibody can be administered parenterally. For example, a parenterally administered composition may be administered by subcutaneous, intracutaneous, intravenous, intraperitoneal, intratumor, intramuscular, intraarticular, intraarterial, or infusion techniques. In addition, it can be administered to the subject via injectable depot routes of administration such as using 1-, 3-, or 6-month depot injectable or biodegradable materials and methods.

[000328] In some embodiments, an antibody (e.g., an anti-HJV antibody) is administered intravenously. In some embodiments, an antibody (e.g., an anti-HJV antibody) is administered subcutaneously. In some embodiments, subcutaneous administration of an ani-HJV antibody results in similar bioavailability compared to intravenous administration of the same antibody at the same dose.

[000329] In some embodiments, subcutaneous administration of the anti-HJV antibody yields the comparable pharmacodynamics effects (e.g., decreased circulating hepcidin-25 levels, increased TSAT%, and/or increased serum iron levels) at lower maximum concentrations (C_{max}) of the anti-HJV antibody compared to intravenous administration of the same antibody. C_{max} is the maximum (or peak) serum concentration that a drug (e.g., an anti-HJV antibody) after the drug has been administered and before the administration of a second dose. In some embodiments, achieving a low C_{max} within a short period of time (e.g., within 12 hours, within 24 hours) after administration of an anti-HJV antibody minimizes undesirable increases in serum iron response, and/or minimizes chances of off-target effects of the antibody (e.g., binding to RGMa). In some embodiments, blunting C_{max} by subcutaneous administration of an anti-HJV antibody avoids an undesirably sharp increase in serum iron response. In some embodiments, blunting C_{max} by subcutaneous administration of an anti-HJV antibody reduces the off-target effects of the antibody. In some embodiments, the C_{max} reached by subcutaneous administration is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at

least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% lower than the C_{max} reached by intravenous administration of an anti-HJV antibody.

[000330] For intravenous injection, water soluble antibodies can be administered by the drip method, whereby a pharmaceutical formulation containing the antibody and a physiologically acceptable excipient is infused. Physiologically acceptable excipients may include, for example, 5% dextrose, 0.9% saline. Ringer's solution or other suitable excipients. Other injectable compositions may contain various carriers such as vegetable oils, dimethylactamide, dimethyformamide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, and polyols (glycerol, propylene glycol, liquid polyethylene glycol, and the like). In some cases, preparations, e.g., a sterile formulation of a suitable soluble salt form of the antibody, can be dissolved and administered in a pharmaceutical excipient such as Water-for-Injection, 0.9% saline, or 5% glucose solution.

[000331] In one embodiment, an antibody is administered via site-specific or targeted local delivery techniques. Examples of site-specific or targeted local delivery techniques include various implantable depot sources of the antibody or local delivery catheters, such as infusion catheters, an indwelling catheter, or a needle catheter, synthetic grafts, adventitial wraps, shunts and stents or other implantable devices, site specific carriers, direct injection, or direct application. See, *e.g.*, PCT Publication No. WO 00/53211 and U.S. Pat. No. 5,981,568.

[000332] In some embodiments, more than one antibody, or a combination of an antibody and another suitable therapeutic agent, may be administered to a subject in need of the treatment. The antibody can also be used in conjunction with other agents that serve to enhance and/or complement the effectiveness of the agents. Treatment efficacy for a target disease/disorder can be assessed by methods well-known in the art.

[000333] The anti-HJV antibody and treatment methods involving such as described in the present disclosure may be utilized in combination with other types of therapy for the target disease or disorder disclosed herein. In this context, an antibody composition and a therapeutic agent may be given either simultaneously or sequentially. Examples include chemotherapy, immune therapy (e.g. therapies involving other hepcidin antagonists), surgery, radiation, gene therapy, and so forth, or anti-infection therapy. Such therapies can be administered simultaneously or sequentially (in any order) with the treatment according to the present disclosure.

[000334] For example, the combination therapy can include the anti-HJV antibody and pharmaceutical composition described herein, co-formulated with and/or co-administered

with, at least one additional therapeutic agent. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus preventing possible toxicities or complications associated with the various monotherapies. Moreover, the additional therapeutic agents disclosed herein may act on pathways in addition to or distinct from the hepcidin/BMP pathway, and thus may enhance and/or synergize with the effects of the anti-HJV antibodies.

[000335] In some aspects, the disclosure relates to compositions (e.g., anti-HJV antibodies and compositions thereof) and methods for treating myelofibrosis-associated anemia. The myelofibrosis-associated anemia may be characterized as a mild to moderate anemia or a severe anemia in accordance with appropriate diagnostic threshold parameters. For example, in some embodiments, the myelofibrosis-associated anemia is characterized based on a level of hemoglobin (Hgb), wherein the severity of the anemia increases with decreasing levels of Hgb. In some embodiments, mild to moderate anemia is associated with Hgb levels of at least 8 g/dL and less than the lower limit of normal (e.g., between about 8 and about 14 g/dL, between about 8 and about 12 g/dL, between about 8 and about 10 g/dL, between about 10 and about 14 g/dL, or between about 10 and about 12 g/dL). In some embodiments, severe anemia is associated with Hgb levels of about 8 g/dL or lower (e.g., between about 2 and about 8 g/dL, between about 4 and about 8 g/dL, or between about 6 and about 8 g/dL). In some embodiments, severe anemia is associated with erythrocyte-transfusion dependence. In some embodiments, severe anemia is associated with erythrocyte-transfusion independence resulting from a therapeutic intervention (e.g., therapeutic reversal of a transfusion dependent state), where a subject is dependent upon ongoing therapeutic treatment to maintain transfusion independence.

[000336] In some aspects, the disclosure provides compositions and methods for treating a subject that is known to have, or is suspected of having, a hematologic disorder characterized by low systemic iron levels. In some embodiments, the subject has myelofibrosis and/or one or more conditions arising as a result of myelofibrosis, as described elsewhere herein. In some embodiments, the subject is erythrocyte-transfusion dependent. In some embodiments, the subject is erythrocyte-transfusion independent.

[000337] Accordingly, in some embodiments, a subject in need of treatment in accordance with the disclosure has previously received therapeutic intervention for a hematologic disorder. In some embodiments, the subject has previously undergone a surgical procedure for treating one or more hematologic disorders. In some embodiments, the subject has

previously undergone a splenectomy. In some embodiments, the subject has previously received a therapeutic agent for treating one or more hematologic disorders.

[000338] In some embodiments, a subject has previously received an erythropoietin stimulating agent. In some embodiments, the erythropoietin stimulating agent is selected from the group consisting of danazol, prednisone, thalidomide, lenalidomide, and pomalidomide.

[000339] In some embodiments, a subject has previously received a JAK-STAT pathway inhibitor. In some embodiments, the JAK-STAT pathway inhibitor is a JAK inhibitor or a STAT inhibitor. In some embodiments, the JAK inhibitor is selective for one or both of subtypes JAK1 and JAK2 (e.g., a JAK1/2 inhibitor). In some embodiments, the STAT inhibitor is a STAT3 inhibitor. In some embodiments, the JAK1/2 or STAT3 inhibitor is selected from the group consisting of ruxolitinib, fedratinib, momelotinib, pacritinib, INCB039110, AG490, and PpYLKTK.

[000340] In some embodiments, a subject has previously received a growth factor ligand trap. In some embodiments, the growth factor ligand trap is a transforming growth factor beta (TGF-β) ligand trap. In some embodiments, the TGF-β ligand trap is sotatercept or luspatercept. In some embodiments, a subject has previously received an anti-fibrotic agent. In some embodiments, the anti-fibrotic agent is PRM-151.

[000341] In some embodiments, a subject in need of treatment in accordance with the disclosure continues to receive a therapeutic treatment for a hematologic disorder. The disclosure therefore provides, in some aspects, compositions and methods for treating myelofibrosis and/or one or more conditions arising as a result of myelofibrosis by administering to a subject in need thereof a hepcidin antagonist (e.g., anti-HJV antibodies and compositions thereof) in combination with one or more therapeutic treatments for a hematologic disorder.

[000342] In some embodiments, a subject is administered a hemojuvelin antagonist (e.g., anti-HJV antibodies and compositions thereof) in combination with an erythropoietin stimulating agent. In some embodiments, the erythropoietin stimulating agent is selected from the group consisting of danazol, prednisone, thalidomide, lenalidomide, and pomalidomide.

[000343] In some embodiments, a subject is administered a hemojuvelin antagonist (e.g., anti-HJV antibodies and compositions thereof) in combination with a JAK-STAT pathway inhibitor. In some embodiments, the JAK-STAT pathway inhibitor is a JAK inhibitor or a STAT inhibitor. In some embodiments, the JAK inhibitor is selective for one or both of

subtypes JAK1 and JAK2 (e.g., a JAK1/2 inhibitor). In some embodiments, the STAT inhibitor is a STAT3 inhibitor. In some embodiments, the JAK1/2 or STAT3 inhibitor is selected from the group consisting of ruxolitinib, fedratinib, momelotinib, pacritinib, INCB039110, AG490, and PpYLKTK. In some embodiments, a subject is administered a hemojuvelin antagonist (e.g., anti-HJV antibodies and compositions thereof) in combination with ruxolitinib.

[000344] In some embodiments, the hemojuvelin antagonist (e.g., anti-HJV antibodies and compositions thereof) reduces the extent to which a subject exhibits an anemic response to the JAK-STAT pathway inhibitor. For example, in some embodiments, a subject treated with a JAK-STAT pathway inhibitor as a monotherapy may be characterized as having a deficiency in the ability of blood to transport oxygen as compared to the subject's pretreatment state, a deficiency in red blood cells as compared to the subject's pretreatment state, a deficiency in hemoglobin as compared to the subject's pretreatment state, an/or a deficiency in total blood volume as compared to the subject's pretreatment state. Accordingly, in some embodiments, the hemojuvelin antagonist (e.g., anti-HJV antibodies and compositions thereof) reduces the extent to which a subject exhibits an anemic response to a JAK-STAT pathway inhibitor selected from the group consisting of ruxolitinib, fedratinib, momelotinib, pacritinib, INCB039110, AG490, and PpYLKTK. In some embodiments, the hemojuvelin antagonist (e.g., anti-HJV antibodies and compositions thereof) reduces the extent to which a subject exhibits an anemic response to ruxolitinib administration.

[000345] In some embodiments, a subject is administered a hemojuvelin antagonist (e.g., anti-HJV antibodies and compositions thereof) in combination with a growth factor ligand trap. In some embodiments, the growth factor ligand trap is a transforming growth factor beta (TGF-β) ligand trap. In some embodiments, the TGF-β ligand trap is sotatercept or luspatercept. In some embodiments, a subject is administered a hemojuvelin antagonist (e.g., anti-HJV antibodies and compositions thereof) in combination with an anti-fibrotic agent. In some embodiments, the anti-fibrotic agent is PRM-151.

[000346] Successful treatment of a subject in accordance with the disclosure may be determined by methods known in the art or by a skilled practitioner. In some embodiments, HJV antagonist (e.g., anti-HJV antibodies and compositions thereof) treatment is evaluated based on hepcidin levels (e.g., circulating hepcidin-25 levels) in a subject. For example, in some embodiments, baseline hepcidin levels (e.g., circulating hepcidin-25 levels) in a subject are determined (e.g., before treatment with anti-HJV antibody or otherwise in absence of anti-

HJV antibody treatment at the time of determining) and compared to post-treatment hepcidin levels (e.g., circulating hepcidin-25 levels) in the subject. In some embodiments, a subject is successfully treated where an anti-HJV antibody decreases hepcidin levels (e.g., circulating hepcidin-25 levels) in the subject by between about 1 ng/mL and about 300 ng/mL. In some embodiments, the anti-HJV antibody decreases hepcidin levels (e.g., circulating hepcidin-25 levels) in a subject by between about 1 ng/mL and about 200 ng/mL, between about 1 ng/mL and about 100 ng/mL, between about 1 ng/mL and about 50 ng/mL, between about 1 ng/mL and about 10 ng/mL, between about 10 ng/mL and about 100 ng/mL, or between about 10 ng/mL and about 50 ng/mL. In some embodiments, the present disclosure provides a method for reducing hepcidin (e.g., circulating hepcidin-25 levels) in a subject having myelofibrosis. In some embodiments, 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. In some embodiments, the administration reduces hepcidin (e.g., circulating hepcidin-25 levels) by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% of hepcidin (e.g., circulating hepcidin-25 levels) compared to the hepcidin (e.g., circulating hepcidin-25 levels) level in the subject prior to administration.

[000347] In some embodiments, anti-HJV antibody treatment is evaluated based on serum ferritin levels in a subject. For example, in some embodiments, baseline serum ferritin levels in a subject are determined (e.g., before treatment with an anti-HJV antibody or otherwise in absence of anti-HJV antibody treatment at the time of determining) and compared to post-treatment serum ferritin levels in the subject. In some embodiments, a subject is successfully treated where an anti-HJV antibody decreases serum ferritin levels in the subject by between about 1 ng/mL and about 200 ng/mL. In some embodiments, the anti-HJV antibody decreases serum ferritin levels in a subject by between about 1 ng/mL and about 100 ng/mL, between about 1 ng/mL and about 50 ng/mL, between about 1 ng/mL and about 25 ng/mL, between about 1 ng/mL and about 10 ng/mL, between about 10 ng/mL and about 100 ng/mL, or between about 10 ng/mL and about 50 ng/mL.

[000348] In some embodiments, anti-HJV antibody treatment is evaluated based on serum hemoglobin levels in a subject. For example, in some embodiments, baseline serum hemoglobin levels in a subject are determined (e.g., before treatment with an anti-HJV antibody or otherwise in absence of anti-HJV antibody treatment at the time of determining) and compared to post-treatment serum hemoglobin levels in the subject. In some

embodiments, a subject is successfully treated where an anti-HJV antibody decreases serum hemoglobin levels in the subject by between about 0.01 g/dL and about 5 g/dL. In some embodiments, the anti-HJV antibody decreases serum ferritin levels in a subject by between about 0.01 g/dL and about 1 g/dL, between about 0.1 g/dL and about 5 g/dL, between about 1 g/dL and about 5 g/dL, between about 0.01 g/dL and about 0.1 g/dL, between about 0.5 g/dL and about 2.5 g/dL, or between about 0.1 g/dL and about 1 g/dL.

[000349] In some aspects, other hepcidin antagonist can be a hepcidin inhibitor. In some embodiments, the hepcidin inhibitor is a molecule that specifically binds hepcidin (e.g., an antibody, an anticalin, or an aptamer). Examples of molecules that specifically bind hepcidin include, without limitation, PRS-080, LY2787106, NOX-H94 (Lexaptepid Pegol), 12B9m, LS-B4534, lipocalin mutein, and hNGAL mutein (see also U.S. Patent Nos. 8,629,250; 9,315,577; 9,051,382; 9,657,098; 9,610,356; 8,530,619; and U.S. Patent Publication Nos. US 2015/0291675, US 2018/0057812, and US 2017/0247448, which are incorporated herein by reference).

[000350] In some embodiments, other hepcidin antagonist can be a molecule that specifically binds ferroportin (e.g., an antibody, an anticalin, or an aptamer). In some embodiments, the molecule that specifically binds ferroportin is LY2928057. Molecules that bind ferroportin to inhibit hepcidin binding without affecting ferroportin activity have been described (see also U.S. Patent No. 8,183,346, which is incorporated herein by reference). In some embodiments, the hepcidin inhibitor is a chemical modifier compound that modifies hepcidin or ferroportin to inhibit the hepcidin-ferroportin binding interaction. For example, in some embodiments, the hepcidin inhibitor is fursultiamine (see, e.g., Fung and Nemeth. Haematologica. 2013 Nov; 98(11):1667-76).

[000351] In yet other aspects, other hepcidin antagonist can be of the disclosure is a HAMP antagonist that binds HAMP or a transcription or translation product thereof. Examples of such HAMP antagonists include, without limitation, antisense oligonucleotides, small molecule inhibitor compounds, and antibodies, anticalins, or aptamers specific for a HAMP transcription or translation product. An antisense oligonucleotide may be single-stranded or double-stranded. As a set of non-limiting examples, an antisense oligonucleotide may be, but is not limited to, a small interfering RNA (siRNA), microRNA (miRNA), short hairpin RNA (shRNA), dicer substrate interfering RNA (dsiRNA), short siRNA, or single-stranded siRNA. In some embodiments, a double-stranded antisense oligonucleotide is an RNAi oligonucleotide. Specific examples of HAMP antisense oligonucleotides include, without

limitation, siHepcidin and XEN701 (see also U.S. Patent Publication Nos. US 2016/0186172 and US 2012/0115930, which are incorporated herein by reference).

[000352] In some embodiments, the HAMP antagonist binds to or otherwise downregulates a molecule involved in the BMP-SMAD and/or JAK-STAT signaling pathways. In some embodiments, the HAMP antagonist is an antisense oligonucleotide, a small molecule compound, an antibody, an anticalin, or an aptamer. Examples of molecules targeted by HAMP antagonists of the disclosure include, without limitation, HFE, BMP6, BMP receptors, transferrin, transferrin receptors, SMAD1/5/8 and SMAD4, IL-6, IL-6 receptors, JAK1/2, and STAT3. In some embodiments, hepcidin antagonists of the disclosure are antagonists (e.g., inhibitors) of any one or more of these molecules.

[000353] In some embodiments, other hepcidin antagonist can be of the present disclosure is a BMP6 antagonist, which reduces hepcidin function by binding BMP6 and/or a BMP receptor to inhibit activation of the BMP-SMAD signaling pathway. In some embodiments, the BMP6 antagonist is an ALK2 inhibitor, such as, for example, LDN-212854, LDN-193189, LDN-214117, BLU-782, and others as disclosed in Hudson, L. et al., *Novel Quinazolinone Inhibitors of ALK2 Flip between Alternate Binding Modes: Structure–Activity Relationship, Structural Characterization, Kinase Profiling, and Cellular Proof of Concept.* Med. Chem.2018, 61, 16, 7261-7272 and Carvalho D, et al., *ALK2 inhibitors display beneficial effects in preclinical models of ACVR1 mutant diffuse intrinsic pontine glioma.* Communications Biologyvolume 2, Article number: 156 (2019), the relevant contents of each of which are incorporated herein by reference. In some embodiments, the BMP6 antagonist is a soluble HJV polypeptide, including fragments and/or fusion molecules thereof (e.g., HJV-Fc), for example as described in U.S. Patent No. 7,534,764; U.S. Publication No. US 2012/064076; and International Publication Nos. WO 2008/124768 and WO 2012/150973, which are incorporated herein by reference. Additional examples of BMP6 antagonists include, without limitation, TP-0184, FKBP12, a twisted gastrulation protein, dorsomorphin, noggin, chordin, ventroptin, follistatin, follistatin-related gene (FLRG), heparin, sulphated glycosaminoglycan, and Sclerostin domain-containing 1 protein (SOSTDC1). Additional examples of BMP6 antagonists that may be useful in certain methods provided herein are provided, for example, in U.S. Patent Nos. 8,318,167; 9,556,251; 9,862,764; 10,202,356; 9,682,983; 8,507,501; 9,738,636; and 8,795,665; U.S. Publication Nos. US 2010/0093760; US 2014/0199314; US 2014/0086919; US 2016/0263117; US2016/0115167; US2017/0197968; US2017/0190705; US2017/0305883; US 2018/0021340; and US 2018/0118835; and PCT Publication Nos. WO 2017/216724; WO 2018/136634; WO

2018/053234; WO 2018/185341; WO 2016/146651; and WO 2018/200855; which are incorporated herein by reference.

[000354] Efficient iron signaling via the BMP-SMAD signaling pathway involves auxiliary factors, such as the diferric transferrin (Tf) sensor transferrin receptor 2 (TfR) to stimulate hepcidin expression (FIG. 12). In some embodiments, a hepcidin antagonist of the present disclosure is a transferrin antagonist, which antagonizes hepcidin function by binding transferrin and/or transferrin receptor 2 to inhibit activation of the BMP-SMAD signaling pathway. In some embodiments, the transferrin antagonist is an antisense oligonucleotide targeting Tf and/or TfR, such as siTfR2 (see, e.g., U.S. Patent No. US 9,228,188, which is incorporated herein by reference).

[000355] As detailed in the above, STAT3 is a transcriptional regulator of HAMP expression. Accordingly, in some embodiments, the HAMP antagonist is a JAK-STAT signaling pathway inhibitor. In some embodiments, the JAK-STAT signaling pathway inhibitor is a JAK inhibitor or a STAT inhibitor. In some embodiments, the JAK inhibitor is selective for one or both of subtypes JAK1 and JAK2 (e.g., a JAK1/2 inhibitor). In some embodiments, the STAT inhibitor is a STAT3 inhibitor. Examples of JAK1/2 and STAT3 inhibitors include, without limitation, ruxolitinib, fedratinib, momelotinib, pacritinib, INCB039110, AG490, and PpYLKTK.

[000356] The JAK-STAT3 signaling pathway is activated by the inflammatory cytokine IL-6. The binding of IL-6 to an IL-6 receptor (IL-6R) triggers receptor dimerization on hepatocytes, which leads to activation of the JAK-STAT3 signaling pathway (FIG. 12). Accordingly, in some embodiments, the JAK-STAT signaling pathway inhibitor is an IL-6 antagonist, which antagonizes hepcidin function by binding IL-6 and/or an IL-6 receptor to inhibit activation of the JAK-STAT3 signaling pathway. In some embodiments, the IL-6 antagonist is selected from the group consisting of Infliximab, Curcumin, 3,3′-Diindolylmethane, Tocilizumab, and Siltuximab. Additional examples of IL-6 and IL-6R inhibitors that may be useful in certain methods provided herein are provided, for example, in U.S. Patent Publication No. US 2017/0029499, which is incorporated herein by reference.

[000357] Any of the anti-HJV antibodies disclosed herein can also be used for detecting presence of HJV (e.g., soluble HJV) in vitro or in vivo. Results obtained from such detection methods can be used for diagnostic purposes (e.g., diagnosing diseases associated with HJV) or for scientific research purposes (e.g., identifying new HJV secreting cell types, studying bioactivity and/or regulation of secreted HJV). For assay uses such as diagnostic uses, an anti-HJV antibody as described herein may be conjugated with a detectable label (e.g., an

imaging agent such as a contrast agent) for detecting presence of HJV (e.g., soluble HJV), either in vivo or in vitro. As used herein, "conjugated" or "attached" means two entities are associated, preferably with sufficient affinity that the therapeutic/diagnostic benefit of the association between the two entities is realized. The association between the two entities can be either direct or via a linker, such as a polymer linker.

[000358] Conjugated or attached can include covalent or noncovalent bonding as well as other forms of association, such as entrapment, e.g., of one entity on or within the other, or of either or both entities on or within a third entity, such as a micelle.

[000359] In other embodiments, an anti-HJV antibody as described herein can be attached to a detectable label, which is a compound that is capable of releasing a detectable signal, either directly or indirectly, such that the aptamer can be detected, measured, and/or qualified, in vitro or in vivo. Examples of such "detectable labels" are intended to include, but are not limited to, fluorescent labels, chemiluminescent labels, colorimetric labels, enzymatic markers, radioactive isotopes, and affinity tags such as biotin. Such labels can be conjugated to the aptamer, directly or indirectly, by conventional methods.

[000360] In some embodiments, the detectable label is an agent suitable for detecting HJV expressing cells in vitro, which can be a radioactive molecule, a radiopharmaceutical, or an iron oxide particle. Radioactive molecules suitable for in vivo imaging include, but are not limited to, ^{122}I, ^{123}I,^{124}I, ^{125}I, ^{131}I, ^{18}F, ^{75}Br, ^{76}Br, ^{77}Br, ^{211}At, ^{225}Ac, ^{177}Lu, ^{153}Sm, ^{186}Re, ^{188}Re, ^{67}Cu, ^{213}Bi, ^{212}Bi, ^{212}Pb, and ^{67}Ga. Exemplary radiopharmaceuticals suitable for in vivo imaging include ^{111}In Oxyquinoline, ^{131}I Sodium iodide, ^{99}mTc Mebrofenin, and ^{99}mTc Red Blood Cells, ^{123}I Sodium iodide, ^{99}mTc Exametazime, ^{99}mTc Macroaggregate Albumin, ^{99}mTc Medronate, ^{99}mTc Mertiatide, ^{99}mTc Oxidronate, ^{99}mTc Pentetate, ^{99}mTc Pertechnetate, ^{99}mTc Sestamibi, ^{99}mTc Sulfur Colloid, ^{99}mTc Tetrofosmin, Thallium-201, or Xenon-133.

[000361] The reporting agent can also be a dye, e.g., a fluorophore, which is useful in detecting a disease mediated by HJV expressing cells in tissue samples.

[000362] To perform a diagnostic assay in vitro, an anti-HJV antibody can be brought in contact with a sample suspected of containing HJV, e.g., HJV expressing cells or soluble HJV in disease microenvironment. The antibody and the sample may be incubated under suitable conditions for a suitable period to allow for binding of the antibody to the HJV antigen. Such an interaction can then be detected via routine methods, e.g., ELISA, histological staining or FACS.

[000363] To perform a diagnostic assay in vivo, a suitable amount of anti-HJV antibodies,

conjugated with a label (e.g., an imaging agent or a contrast agent), can be administered to a subject in need of the examination. Presence of the labeled antibody can be detected based on the signal released from the label by routine methods.

[000364] To perform scientific research assays, an anti-HJV antibody can be used to study bioactivity of HJV, detect the presence of HJV intracellularly, and or regulating the effect of HJV. For example, a suitable amount of anti-HJV can be brought in contact with a sample (e.g. a new cell type that is not previously identified as HJV producing cells) suspected of producing HJV. The cells are permeabilized prior to contacting the anti-HJV antibody. The antibody and the sample may be incubated under suitable conditions for a suitable period to allow for binding of the antibody to the HJV antigen. Such an interaction can then be detected via routine methods, e.g., ELISA, histological staining or FACS.

VI. Kits for Therapeutic and Diagnostic Applications

[000365] The present disclosure also provides kits for the therapeutic or diagnostic applications as disclosed herein. Such kits can include one or more containers comprising an anti-HJV antibody, e.g., any of those described herein.

[000366] In some embodiments, the kit can comprise instructions for use in accordance with any of the methods described herein. The included instructions can comprise a description of administration of the anti-HJV antibody to treat, delay the onset, or alleviate a target disease as those described herein. The kit may further comprise a description of selecting an individual suitable for treatment based on identifying whether that individual has the target disease. In still other embodiments, the instructions comprise a description of administering an antibody to an individual at risk of the target disease.

[000367] The instructions relating to the use of an anti-HJV antibody generally include information as to dosage, dosing schedule, and route of administration for the intended treatment. The containers may be unit doses, bulk packages (e.g., multi-dose packages) or sub-unit doses. Instructions supplied in the kits of the invention are typically written instructions on a label or package insert (e.g., a paper sheet included in the kit), but machine-readable instructions (e.g., instructions carried on a magnetic or optical storage disk) are also acceptable.

[000368] The label or package insert indicates that the composition is used for treating, delaying the onset and/or alleviating a disease or disorder. Instructions may be provided for practicing any of the methods described herein.

[000369] The kits of this invention are in suitable packaging. Suitable packaging includes,

but is not limited to, vials, bottles, jars, flexible packaging (e.g., sealed Mylar or plastic bags), and the like.

[000370] Also contemplated are packages for use in combination with a specific device, such as an infusion device, such as a minipump. A kit may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The container may also have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an anti-HJV antibody as those described herein.

[000371] Kits may optionally provide additional components such as buffers and interpretive information. Normally, the kit comprises a container and a label or package insert(s) on or associated with the container. In some embodiments, the invention provides articles of manufacture comprising contents of the kits described above.

[000372] Also provided herein are kits for use in detecting hemojuvelin in a sample. Such a kit may comprise any of the anti-HJV antibodies described herein. In some instances, the anti-HJV antibody can be conjugated with a detectable label as those described herein. As used herein, "conjugated" or "attached" means two entities are associated, preferably with sufficient affinity that the therapeutic/diagnostic benefit of the association between the two entities is realized. The association between the two entities can be either direct or via a linker, such as a polymer linker. Conjugated or attached can include covalent or noncovalent bonding as well as other forms of association, such as entrapment, e.g., of one entity on or within the other, or of either or both entities on or within a third entity, such as a micelle.

[000373] Alternatively or in addition, the kit may comprise a secondary antibody capable of binding to anti-HJV antibody. The kit may further comprise instructions for using the anti-HJV antibody for detecting hemojuvelin.

EXAMPLES

Example 1: Anti-HJV antibodies generation and characterization

[000374] From rats immunized with human hemojuvelin, hybridoma clones capable of binding to human hemojuvelin were identified. The anti-hemojuvelin monoclonal antibodies (mAb with rat IgG1/κ) were humanized by CDR grafting (hHA antibodies with hIgG1 constant region carrying the L234A, L235A mutations). Affinity matured anti-HJV (e.g., HA-001 to HA-011) *in vitro* yeast display assay. A general process for generation of humanized

affinity matured anti-HJV antibodies is illustrated in FIG. 1A.

[000375] Binding affinities of the anti-HJV antibodies to soluble human RGMa, Rat RGMa and human RGMc were measured by BIAcore analysis. Table 4 shows the affinity of the anti-hemojuvelin antibodies to human RGMa. Table 5 shows the affinity of the anti-hemojuvelin antibodies to rat RGMa. Table 6 shows the affinity of the anti-hemojuvelin antibodies to human RGMc.

Table 4: Binding Affinity (by BIAcore) of anti-HJV antibodies to Human RGMa

Ab Name	K_a (1/MS)	K_d (1/s)	KD (M)
hHA-001	1.8E+06	6.7E-05	3.8E-11
hHA-002	1.4E+06	5.0E-05	3.7E-11
hHA-003	1.1E+06	1.4E-04	1.2E-10
hHA-004	1.4E+06	2.2E-05	1.5E-11
hHA-005	1.9E+06	2.5E-04	1.3E-10
hHA-006	1.2E+06	1.4E-04	1.2E-10
hHA-007	5.9E+05	8.9E-05	1.5E-10
hHA-008	8.7E+05	2.7E-05	3.1E-11
hHA-009	8.6E+05	4.0E-04	4.7E-10
hHA-010	8.5E+05	1.0E-04	1.2E-10
hHA-011	9.3E+05	9.9E-05	1.1E-10
hHA	6.0E+06	2.2E-03	3.7E-09
HA	1.2E+06	2.9E-03	2.4E-09

Table 5: Binding Affinity (by BIAcore) of anti-HJV antibodies to rat RGMa

Ab Name	K_a (1/MS)	K_d (1/s)	KD (M)
hHA-001	1.2E+06	3.6E-05	3.1E-11

hHA-002	1.0E+06	5.5E-05	5.3E-11
hHA-003	8.7E+05	3.1E-05	3.6E-11
hHA-004	1.1E+06	<1e-6	<9.4e-13
hHA-005	1.4E+06	2.1E-04	1.5E-10
hHA-006	9.4E+05	3.0E-05	3.2E-11
hHA-007	5.1E+05	<1e-6	<2.0e-12
hHA-008	6.6E+05	<1e-6	<1.5e-12
hHA-009	6.8E+05	2.1E-04	3.1E-10
hHA-010	6.6E+05	2.6E-05	3.9E-11
hHA-011	7.0E+05	5.2E-05	7.4E-11
hHA	8.3E+05	1.7E-03	2.1E-09
HA	8.3E+05	2.5E-03	3.0E-09

Table 6: Binding Affinity (by BIAcore) of anti-HJV antibodies to Human RGMc

Ab Name	***K_a (1/MS)***	***K_d (1/s)***	**KD (M)**
hHA-001	1.08E+07	1.65E-03	1.6E-10
hHA-002	7.65E+06	1.70E-03	2.25E-10
hHA-003	8.10E+06	2.40E-03	3E-10
hHA-004	7.85E+06	1.04E-03	1.3E-10
hHA-005	4.15E+07	1.36E-02	3.2E-10
hHA-006	6.65E+06	2.55E-03	3.85E-10
hHA-007	5.05E+06	2.15E-03	4.25E-10
hHA-008	3.95E+06	3.90E-04	1.05E-10

hHA-009	1.55E+07	1.07E-02	7.1E-10
hHA-010	9.90E+06	4.40E-03	4.45E-10
hHA-011	5.05E+06	1.40E-03	2.85E-10
hHA	8.3E+05		2.1E-08

[000376] Within these antibodies, at lease hHA-004, hHA-008, hHA-009 and hHA-011 showed strong binding to human RGMc, and were selected for further testing. Sensorgrams by BIAcore analysis of antibodies HA, hHA-004, hHA-008, hHA-009 and hHA-011 are shown in FIGs. 1B-1G. hHA-008 was further tested for its binding affinity to human RGMa, Cyno RGMa, Rat RGMa, human RGMc, Cyno RGMc, Rat RGMc, and human RGMb, and the respective binding affinity is shown in Table 7. hHA-008 showed high affinity binding to human RGMa and RGMc with strong cross-reactivity to cyno and rodent species.

Table 7: Binding affinities of hHA-008 to human RGMa, Cyno RGMa, Rat RGMa, human RGMc, Cyno RGMc, Rat RGMc, and Human RGMb.

RGM antigen in solution	hHA-008			hHA		
	ka (1/Ms)	kd (1/s)	KD (M)	ka (1/Ms)	kd (1/s)	KD (M)
Human RGMa	4.9E+05	3.6E-05	7.4E-11	2.7E+05	2.3E-03	8.3E-09
Cyno RGMa	5.5E+05	3.5E-04	6.4E-10	2.1E+05	6.6E-04	3.1E-09
Rat RGMa	3.1E+05	3.6E-05	1.2E-10	2.3E+05	2.1E-03	9.1E-09
Human RGMc	2.5E+06	2.9E-04	1.2E-10	1.4E+06	n/a	4.0E-08*
cyno RGMc	2.6E+06	3.1E-04	1.2E-10	1.8E+06	n/a	3.2E-08*
Rat RGMc	1.4E+06	3.2E-04	2.3E-10			6.6E-08**
Human RGMb	no significant binding			no significant binding		

* Data for the hHA with human and cyno RGMc was fitted to a two-state model. k_{a1} represents the Ab Ag association in a two-state binding model

** Data for the hHA with Rat RGMc was fitted to a steady state affinity model

[000377] The RGMc (HJV) BMP reporter gene assay was used for screening and characterization potency of anti-HJV antibodies in blocking membrane-bound RGMc induced BMP/Smad1/5/8 signaling. The assay is directly related to the mechanism of action of the anti-HJV mAbs in inhibiting RGMc/BMP/Smad1/5/8 signaling pathway that is responsible for induction of iron hormone hepcidin gene expression. The principle of HJV BMP reporter assay is illustrated in FIG. 2A.

[000378] The BRE-Luc reporter gene vector initially described by Korchynskyi and Dijke (J. Biol. Chem. 2002; 277:4883c) was used to transiently transfect porcine kidney epithelial cell line LLC-PK1 with or without co-transfection of an RGMa expression vector by Babbit et al (J. Biol. Chem. 2005; 280:29820) to determine if RGMa expression modulates BMP signaling. In BRE-Luc transiently transfected cells, RGMa was demonstrated to enhance BMP signaling through the Smad1/5/8 signaling pathway, consistent with a role for RGMa as a BMP co-receptor. All RGM members (RGMa, RGMb, and RGMc) act as BMP co-receptor and enhance BMP signaling. The BRE-Luc reporter vector was constructed and established the RGM BMP reporter gene assay in HEK293 cells. Human RGMc expression vector used in the assay was pcDNA-hRGMc.

[000379] HEK293 cells were cultured in growth media (base media DMEM (Invitrogen catalog #11965-092) containing 10% fetal bovine serum (Gibco #10438-026) and 1% sodium pyruvate (Invitrogen, catalog # 11360-070)). To prepare cells for transfection, 9 x 10^6 cells HEK293 cells were plated in 10 cm dishes and incubated at 37°C, 5% CO_2 for 6 hours. The cells were then transfected using PolyJet (µL): DNA (µg) ratio of 2:1, specifically 20 µl PolyJet (SignaGen, cat # SL100688) with 5 µg pGL[*luc2P*/BRE/Hygro] DNA (Abbvie) and 5 µg pcDNA-hRGMc (Abbvie) for 16 hours at 37°C, 5% CO_2. The media was replaced with fresh HEK293 growth media for 6 hours. The cells were then trypsinized with TrpLE (ThermoFisher, cat # 12605010), counted, and plated in 96-well white assay plates (Thermo Scientific Nunclon delta F96, cat #136102) at 1 x 10^5 cells per well. The cells were treated with anti-RGMc mAb, anti-BMP2/4 mAb (R&D Systems, cat # MAB3552) (as a positive control), or an isotype control mAb for 16 hours at 37°C, 5% CO_2. Luciferase activity was detected using the One-Glo Luciferase kit (Promega, cat # E6120) and measurement on a TopCount luminescence counter. The results showed that anti-HJV antibodies dose-dependently inhibit RGMc potentiated BMP signaling (FIG. 2B). The IC50 (nM) of each of the antibodies tested in inhibiting RGMc signaling in BMP reporter assay are shown in Table 8.

Table 8: IC50 of the anti-HJV antibodies in BMP reporter assay for RGMc.

	HA	hHA	hHA-004	hHA-008	hHA-009	hHA-011
IC50 (nM)	5.713	17.08	0.3124	0.3772	1.362	0.0554

[000380] Further, the anti-HJV antibodies were tested for their ability to inhibit RGMa signaling in BMP reporter assays. The hHA-004 and hHA-011 showed potent inhibition on membrane-bound human RGMa in RGMa BMP reporter gene assay, whereas hHA-008 and hHA-009 showed no to minimal inhibition on RGMa activity. The hHA antibody showed no inhibition to membrane bound RGMa. The rat mAb HA showed inhibition on RGMa but to much less extent as compared to hHA-004 and hHA-011. FIG. 2C. The IC50 (nM) of each of the antibodies tested in inhibiting RGMa signaling in BMP reporter assay are shown in Table 9.

Table 9: IC50 of the anti-HJV antibodies in BMP reporter assay for RGMa

	HA	hHA-004	hHA-008	hHA-009	hHA-011
IC50 (nM)	47.63	2.014	~56.54	1.566E-008	1.657

[000381] The above data showed that the potency of the anti-HJV antibodies in neutralizing membrane RGMc in BMP reporter assay correlates with binding affinity on soluble RGMc. A summary of the anti-HJV antibody binding affinity to soluble human RGMc, and their capability to inhibit membrane bound RGMc and RGMa signaling are shown in Table 10.

Table 10: Anti-HJV antibody binding affinity to soluble human RGMc, and their capability to inhibit membrane bound RGMc and RGMa signaling.

IgG	**Binding Affinity (BIAcore) on soluble hRGMc**			**Potency on membrane hRGMc (RGMc/BMP reporter assay) IC_{50} (nM)**	**Potency on membrane hRGMa (RGMa/BMP reporter assay) IC_{50} (nM)**
	Ka (1/MS)	***Kd (1/s)***	**K_D (M)**		
hHA-004	7.85E+06	1.04E-03	1.30E-10	0.31	2
hHA-008	3.95E+06	3.90E-04	1.05E-10	0.37	Minimal inhibition
hHA-009	1.55E+07	1.07E-02	7.10E-10	1.36	No inhibition

hHA-011	5.05E+06	1.40E-03	2.85E-10	0.52	1.7
hHA	8.3E+05 (k_{a1})*	n/a	2.9E-08	17	No inhibition
HA	3.40E+06	5.00E-03	1.60E-10	5.7	48

[000382] The antibodies, including hHA, hHA-004, hHA-008, hHA-008-QL, hHA-009, and hHA-011 were tested for non-specific cell binding to HEK293 cells by FACS analysis. The data showed hHA and its hHA-008, hHA-008-QL and hHA-011 showed no to minimal non-specific cell binding on HEK293 cells at conc. up to 100 ug/ml. hHA-004 and hHA-009 showed some non-specific cell binding at higher concentrations, but to a much less extent compared to positive control IgGs (FIG. 3)

Example 2: Generation of Generation of hHA-008-QL

[000383] hHA-008-QL was developed to prolong IgG serum half-line ($t_{1/2}$). Previous studies have shown that neonatal Fc receptor (FcRn) protects IgG from catabolism, thereby increasing IgG serum half-life. Accordingly, the Fc portion of hHA-008-QL was engineered to have T250Q and M428L mutations (QL mutations) such that it has enhanced binding to FcRn. FIGs. 4A and 4B illustrates the structure of hHA-008 and hHA-008-QL respectively. A further illustration of hHA-008 and hHA-008-QL is shown in FIG. 4C.

[000384] First, hHA-008-QL was tested for its RGMa and RGMc binding capabilities, and the data showed that hHA-008-QL had binding affinities to RGMa and RGMc comparable to that of hHA-008 (Table 11)

Table 11: hHA-008-QL and hHA-008 binding affinities to RGMa and RGMc

IgG	**huRGMa**			**huRGMc**		
	ka (1/Ms)	**kd (1/s)**	**KD (M)**	**ka (1/Ms)**	**kd (1/s)**	**KD (M)**
hHA-008-QL (hIgG1mut(LALA)/QL/k)	4.3E+05	3.3E-05	7.7E-11	2.7E+06	3.3E-04	1.2E-10
hHA-008 (hIgG1mut(LALA)/k	5.4E+05	4.2E-05	7.8E-11	3.0E+06	3.2E-04	1.1E-10

Example 3: Immunogenicity studies of hHA-008 and hHA-008-QL

[000385] hHA-008 and hHA-008-QL were tested for their immunogenicity using peripheral blood mononuclear cells (PBMCs) from 50 donors (representing all major HLA0DR and HLA-DQ haplotypes) challenged with hHA-008 or hHA-008-QL in a CD4+ T cell response assay. The results showed only 4% of the 50 donors (2/50) showed a T cell response suggesting that both antibodies have low risk of immunogenicity. In this assay, Herceptin were used as negative control, to which 8% of the donors had a T cell response. Bydureon and keyhole limpet haemocyanin (KLH) were used as positive control. 32% of the donors showed T cell response to Bydureon and 100% donor had a T cell response to KLH. FIG. 5 showed T cell response in 50 donors for hHA-008 and hHA-008-QL.

[000386] Further, FcγR binding was tested for hHA-008 and hHA-008-QL as another parameter for immunogenicity. The control group, wild-type irrelevant IgG1 had significant binding to both the high and low affinity Fc gamma receptors. As expected, the binding of the wild-type irrelevant IgG4 is significantly lower than that of wild-type irrelevant IgG1. Binding to the high affinity and low affinity receptors is significantly reduced for both hHA-008 and hHA-008-QL compared to wild-type IgG1, suggesting low immunogenicity for both antibodies.

Example 4: Pharmacokinetics/Pharmacodynamics (PK/PD) Modeling of hHA-008 and hHA-008-QL

[000387] In an initial study for PK/PD of hHA-008, male rats were treated with a single dose of hHA-008 at 5 mg per kilogram of body weight (mpk) by intravenous injection. Transferrin saturation (TSAT%; determined as the percentage of serum iron over serum total iron binding capacity) were tested over time. The data showed that maximal effect of increased TSAT occurred between 4-8 days post treatment (FIG. 6A).

[000388] Further, a similar study was conducted in non-human primate Cynomolgus macaque (cyno). Both female (n=2) and male (n=2) cynos received a single dose of hHA-008 at 5 mg per kilogram of body weight (mpk) by intravenous injection. Transferrin saturation (TSAT%) were tested over time. Both female cynos showed maximum effect of increased TSAT% about 1-4 days after injection (FIG. 6B). One of the males showed the same effect, while the other one didn't respond to hHA-008 treatment (FIG. 6C). It was subsequently determined by examining the hematological profile of this male, that the lack of response was the result of this cyno having plasma Hepcidin-25 level that was below the limit of detection (below 2 ng/mL). Further, before the injection, this male cyno had a lower baseline TSAT%

and serum iron level than other cynos in the group: two days before the injection, it had a baseline TSAT% level at 18% and a serum iron level at 77 μg/dL; one day before the injection, it had a baseline TSAT% level at 14% and a serum iron level at 61 μg/dL. The low baseline TSAT% and serum iron levels, in combination with the low Hepcidin-25 levels, was indicative that this male cyno had absolute iron deficiency instead of functional iron deficiency.

[000389] Further studies examining the effects of hHA-008 administration in more than 70 cynos revealed that animals having normal baseline serum iron levels (e.g., in the range of 80 μg/dL to 180 μg/dL) and hepcidin-25 levels greater than 2 ng/mL were responsive to hHA-008 treatment in that they exhibited pronounced increase in TSAT% levels shortly after injection (e.g., within 1-2 days post treatment) in response to reduced hepcidin-25 expression.

[000390] Additional experiments were conducted in cynos. Single dose of 6 mpk of hHA-008 were administered to three cynos via intravenous injection, and TSAT% (determined as serum iron over total iron binding capacity), plasma hepcidin-25 concentration, and plasma hHA-008 concentrations were tested for each animal and time point. Similarly, the data showed that the maximum effect of increased TSAT% occurred 1-4 days after injection (T_{max}=1-4 days), which was consistent with the increase of hHA-008 concentrations. One of the animals had a drastic decline of TSAT% around day 34 (FIG. 7A) , which was consistent with the declining of plasma hHA-008 concentration around that time. Plasma hepcidin-25 concentration correlated inversely with the concentrations of hHA-008, in that hepcidin-25 was undetectable after antibody injection, and for the animal which had the drastic decline of TSAT%, hepcidin level increased around the same time (FIG. 7B). In this cyno, hHA-008 had a plasma $t_{1/2}$ of about 5 days. The animal showed decline of TSAT% and increased hepcidin-25 levels at approximately day 34, which correlated well with the decrease of hHA-008 from plasma (FIG. 7C). $T_{1/2}$ of ~ 7 days in Cyno supports ≥ one/month dosing frequency in human.

[000391] Moreover, hHA-008 had showed robust PK/PD correlation of PK (plasma antibody concentration) to TSAT% and plasma hepcidin-25 concentrations. The results of each tested Cyno are shown in FIG. 7D (Cyno 1), FIG. 7E (Cyno 2), and FIG. 7F (Cyno 3). hHA-008 showed a $t_{1/2}$ of 10.3 days in Cyno 1, $t_{1/2}$ of 8.8 days in Cyno 2, and $t_{1/2}$ of 5.1 days in Cyno 3. Hepcidin level drops to undetectable (< 2ng/ml) after hHA-008 treatment. Interestingly, return of hepcidin level to circulation was well correlated with the $t_{1/2}$ of hHA-008 in Cyno 3 (FIG. 7F).

[000392] hHA-008 antibody modulates TSAT% in a dose-dependent manner. Multiple dose studies were conducted in Cynos. The cynos (n=4 per dose level with 2 males and 2 females)

were treated with either 0 (vehicle control), 0.6 mpk hHA-008, 3 mpk hHA-008, or 60 mpk hHA-008. The resulting concentrations of hHA-008 and the corresponding TSAT% response are presented in FIG. 8A, FIG. 8B and FIG. 8C for the 0.6, 3 and 60 mpk treatments respectively, all plotted vs the vehicle control. Cynos were dosed every 14 days. Dotted lines represent dose day. TSAT% increased after dosing, and the percent modulation was consistent with the dose levels: at 0.6 mpk, TSAT reached ~60%, and at 3 mpk and 60 mpk, TSAT% was saturated, indicating that hHA-008 modulates TSAT% in a dose dependent manner. Further, after the first dose at 0.6 mpk, TSAT% levels were maintained at ~60%, while at higher dose levels, TSAT% reached 100%, suggesting that TSAT can be modulated by selection of appropriate dose-level/regimen (FIGs. 8A-8C).

Example 5: hHA-008-QL confers longer serum half-life and takes longer time to reach maximal effect compared to hHA-008

[000393] This study was designed to administer hHA-008 or hHA-008-QL at 6 mpk intravenously to Cynos (n=3). Samples were collected from each animal at 48 and 24 hr prior to treatment, and at 0, 0.04, 0.08, 0.167, 0.333, 0.5, 1, 2, 4, 8, 14, 21, 28, 35 and 42 days after treatment. TSAT% and plasma hepcidin-25 level were measured in each sample. The data showed that hHA-008 took shorter time to reach maximal effect (T_{max}) of increased TSAT% as compared to hHA-008-QL (FIG. 9A). Note that there was a non-responder in animals treated with hHA-008-QL. As discussed above, the non-responder had low hepcidin levels and low serum iron at base line prior to antibody treatment. On the other hand, hHA-008-QL had longer serum half-life (T ½=12.1 days) compared to hHA-008 (T ½= 6.76 days) (FIG. 9B). Plasma concentrations of both antibodies were measured over time, as shown in FIG. 9C. Peak plasma concentrations were determined. A summary of the data between hHA-008 and hHA-008-QL are shown in Table 12.

Table 12: hHA-008 v. hHA-008-QL

Parameter	**Units**	**hHA-008**	**hHA-008-QL**
C_{max}	µg/mL	211.15	168.4
T_{max}	days	0.083	2
T ½	days	6.76	12.1

[000394] To investigate whether the longer serum life for hHA-008-QL was attributed to

higher affinity to FcRn, both antibodies were analyzed for binding to FcRn at pH 6.0 and pH 7.4 using BIAcore. Non-specific IgG1 and IgG4 were used as controls. The dissociation constant (KD) of each of the antibody and the controls to FcRn at pH 6.0 and 7.4 were shown in Table 13, and the response curve were shown in FIGs. 10A-10B. No binding was observed of neither antibodies at pH 7.4 (FIG. 10B).

Table 13: KD for FcRn at pH 6.0 and pH 7.4

	KD (M) at pH 6.0	KD (M) at pH 7.4
IgG1	1.64E-06	no binding
IgG4	3.64E-06	no binding
hHA-008	2.95E-06	no binding
hHA-008	2.96E-06	no binding
hHA-008-QL	9.00E-07	no binding
hHA-008-QL	8.82E-07	no binding

[000395] The mutations L247A and L248A (Kabat) (L234A and L235A, EU Numbering) do not appear to significantly affect FcRn binding. The overall affinity and response (RMax) for binding of FcRn at pH 6.0 is increased for hHA-008-QL compared to hHA-008, suggesting that the QL mutation confers the longer t ½ via the binding to the receptor.

Example 6: hHA-008 Decreases IL-6 Induced Hepcidin Expression in Non-human Primates

[000396] As depict in FIG. 11, in myelofibrosis, pro-inflammatory cytokines that induce hepcidin synthesis, such as IL-6 and oncostatin-M, are typically increased and associated with iron sequestration, macrophage iron loading, as well as myeloid proliferation and macrophage activation. To test whether IL-6 indeed increases hepcidin expression and whether anti-HJV antibody is capable of inhibiting hepcidin expression induced by IL-6 in non-human primates, cynos were challenged with IL-6 on day 1, and divided into three groups. On day 4, cynos in Group 1 received vehicle control, cynos in Group 2 received hHA-008 antibody at 0.6 mg/kg, and cynos in Group 3 received hHA-008 antibody at 6.0 mg/kg. On day 11, cynos in all three groups were challenged with IL-6 again, and plasma hepcidin-25 in all cynos was measured. As shown in FIG. 13, IL-6 challenge increased plasma hepcidin-25 concentrations on Day 1, compared to pre-challenge baseline (BL) in all

three groups of cynos. After the second IL-6 challenge on Day 11, cynos in group 1 showed an increase in plasma hepcidin-25 similar to that observed on Day 1. However, for cynos in groups 2 (0.6 mg/kg hHA-008) and 3 (6 mg/kg hHA-008), the presence hHA-008 prevented the IL-6 induced increase in plasma hepcidin-25 on Day 11 in a dose-dependent manner. That is, hHA-008 was effective in preventing inflammation-induced (IL 6) hepcidin increase in a dose-dependent manner in cynos. These results suggest that anti-HJV antibody are capable of inhibiting hepcidin expression induced by the IL-6 signaling pathway.

Example 7: Epitope Mapping

[000397] Epitope mapping was performed **on** hHA-008 and hHA-008-QL, using 3720-RG-050 (Hemojuvelin (HJV) fragment, SEQ ID NO: 123).

[000398] Before epitope mapping, High-Mass MALDI mass spectrometry and chemical cross-linking was used to confirm no non-covalent aggregates of hHA-008 and hHA-008-QL and multimers of the 3720-RG-050 were detected in sample preparation.

[000399] In order to determine the epitopes of hHA-008 and hHA-008-QL on 3720-RG-050 with high resolution, 3720-RG-050/ hHA-008 and 3720-RG-050/ hHA-008-QL complexes were incubated with deuterated cross-linkers and subjected to multi-enzymatic cleavage. After enrichment of the cross-linked peptides, the samples were analyzed by high resolution mass spectrometry (nLC-LTQ-Orbitrap MS) and the data generated were analyzed using XQuest and Stavrox software.

3720-RG-050/ hHA-008 (HJV fragment/hHA-008)

[000400] After Trypsin, Chymotrypsin, ASP-N, Elastase and Thermolysin proteolysis of the protein complex 3720-RG-050/ hHA-008 with deuterated d0d12, the nLC-orbitrap MS/MS analysis detected 8 cross-linked peptides between 3720-RG-050 and hHA008.

[000401] The sequences and positions of cross-links are presented in Table 14 below.

Table 14: Cross-linked peptides detected between 3720-RG-050 and hHA-008.

hHA-008 – Chymotrypsin and Thermolysin results in interlink between hHA-008 complementarity determining regions and 3720-RG-050							
Enzyme	hHA-008 HC/hHA-008 LC	3720-RG-050	Amino Acid Residues of hHA-008 HC/hHA-008 LC	Amino acid Residues of 3720-RG-050	nAA 1	nAA2	Identified on StavroX
Chymotrypsin	hHA-008_HC (SEQ ID NO: 38)	SEQ ID NO: 123	48-53	166-189	52	170	YES

Chymotrypsin	hHA-008_LC (SEQ ID NO: 39)	SEQ ID NO: 123	95-101	165-185	97	170	YES
Chymotrypsin	hHA-008_LC (SEQ ID NO: 39)	SEQ ID NO: 123	95-101	165-185	98	171	YES
Chymotrypsin	hHA-008_LC (SEQ ID NO: 39)	SEQ ID NO: 123	95-101	165-185	98	180	YES
Chymotrypsin	hHA-008_LC (SEQ ID NO: 39)	SEQ ID NO: 123	95-101	165-185	98	182	YES
Thermolysin	hHA-008_HC (SEQ ID NO: 38)	SEQ ID NO: 123	50-60	177-184	53	182	YES
Chymotrypsin	hHA-008_LC (SEQ ID NO: 39)	SEQ ID NO: 123	95-101	165-185	98	183	YES
Thermolysin	hHA-008_HC (SEQ ID NO: 38)	SEQ ID NO: 123	51-63	181-186	58	183	YES

[000402] Using chemical cross-linking, High-Mass MALDI mass spectrometry and nLC-Orbitrap mass spectrometry, molecular interface between 3720-RG-050 and hHA-008 was characterized. FIG. 14 shows hHA-008 interacts with amino acids 170-183 (SSPMALGANATATR (SEQ ID NO: 121)) on 3720-RG-050. The interaction happens on amino acids 170, 171, 180, 182, 183 on 3720-RG-050. FIG. 15 shows the interaction of 3720-RG-050 and hHA-008. A 3720-RG-050 PDB structure was generated by homology using Swiss Model software. 3720-RG-050 amino acids 170-183 (SSPMALGANATATR (SEQ ID NO: 121)) of 3720-RG-050 sequence are shown in FIG. 15: ribbon/surface representation of front view (A); back view (B), side view 1 (C), side view 2 (D) and top view (E). F, G, H, I, J: ribbon representation of front view (F); back view (G), side view 1 (H), side view 2 (I) and top view (J).

3720-RG-050/ hHA-008-QL(HJV fragment/hHA-008-QL)

[000403] After Trypsin, Chymotrypsin, ASP-N, Elastase and Thermolysin proteolysis of the protein complex 3720-RG-050/ hHA-008-QL with deuterated d0d12, the nLC-orbitrap MS/MS analysis detected 16 cross-linked peptides between 3720-RG-050 and hHA-008-QL.

[000404] The sequences and positions of cross-links are presented in Table 15 below.

Table 15: Cross-linked peptides detected between 3720-RG-050 and HA-008-QL.

hHA-008-QL- Trypsin, Chymotrypsin, AspN, Elastase and Thermolysin results Interlink between hHA-008-QLcomplementarity determining regions and 3720-RG-050

Enzyme	hHA-008-QL HC/ hHA-008-QL LC	3720-RG-050	Amino Acid Residues of hHA-008-QL HC/hHA-008-QL LC	Amino acid Residues of 3720-RG-050	nAA1	nAA2	Identified on StavroX
Chymotrypsin	hHA-008-QL_LC (SEQ ID NO: 39)	SEQ ID NO: 123	95-101	165-185	97	169	YES
Chymotrypsin	hHA-008-QL _LC (SEQ ID NO: 39)	SEQ ID NO: 123	95-101	165-185	98	169	YES
Chymotrypsin	hHA-008-QL _LC (SEQ ID NO: 39)	SEQ ID NO: 123	95-101	165-185	98	171	YES
Chymotrypsin	hHA-008-QL _LC (SEQ ID NO: 39)	SEQ ID NO: 123	95-101	165-185	98	180	YES
Chymotrypsin	hHA-008-QL _LC (SEQ ID NO: 39)	SEQ ID NO: 123	53-67	176-185	59	180	YES
Chymotrypsin	hHA-008-QL _LC (SEQ ID NO: 39)	SEQ ID NO: 123	53-67	176-185	61	180	YES
Chymotrypsin	hHA-008-QL _LC (SEQ ID NO: 39)	SEQ ID NO: 123	95-101	165-185	98	182	YES
Chymotrypsin	hHA-008-QL _HC (SEQ ID NO: 38)	SEQ ID NO: 123	96-104	280-292	100	289	YES
Thermolysin	hHA-008-QL _HC (SEQ ID NO: 38)	SEQ ID NO: 123	29-44	283-302	32	293	YES
Elastase	hHA-008-QL _HC (SEQ ID NO: 38)	SEQ ID NO: 123	31-42	290-295	32	294	YES
Thermolysin	hHA-008-QL _HC (SEQ ID NO: 38)	SEQ ID NO: 123	29-44	283-302	32	295	YES
Trypsin	hHA-008-QL _HC (SEQ ID NO: 38)	SEQ ID NO: 123	39-58	292-299	52	295	YES
Trypsin	hHA-008-QL HC (SEQ ID NO: 38)	SEQ ID NO: 123	20-43	295-300	32	297	YES
Thermolysin	hHA-008-QL _HC (SEQ ID NO: 38)	SEQ ID NO: 123	29-44	283-302	30	300	YES
Elastase	hHA-008-QL _HC (SEQ ID NO: 38)	SEQ ID NO: 123	31-42	294-302	32	300	YES
Elastase	hHA-008-QL _HC (SEQ ID NO: 38)	SEQ ID NO: 123	31-42	294-302	38	300	YES

[000405] Using chemical cross-linking, High-Mass MALDI mass spectrometry and nLC-Orbitrap mass spectrometry, molecular interface between 3720-RG-050 and hHA-008-QL was characterized. FIG. 16 shows hHA-008-QL interacts with amino acids 169-182 (TSSPMALGANATAT (SEQ ID NO: 122)) and 289-300 (SQRLSRSERNRR (SEQ ID NO: 127)) of 3720-RG-050. The interaction happens on amino acids 169, 171, 180, 182; 289, 293, 294, 295, 297, 300 on 3720-RG-050. FIG. 17 shows the interaction 3720-RG-050/hHA-008-QL. A 3720-RG-050 PDB structure was generated by homology using Swiss Model software. 3720-RG-050 amino acids 169-182 (TSSPMALGANATAT (SEQ ID NO: 122) and 289-291 (SQR) are shown as FIG. 17: ribbon/surface representation of front view (A); back view (B), side view 1 (C), side view 2 (D) and top view (E). F, G, H, I, J: ribbon representation of front view (F); back view (G), side view 1 (H), side view 2 (I) and top view (J).

Example 8: hHA-008-QL Decreases Circulating Transferrin Level

[000406] Circulating transferrin level can be used as an indicator of the iron level in the body along with other markers (e.g., total iron binding capacity, serum ferritin level, etc.). Circulating transferrin is an iron-transport protein that reflects both protein and iron status. Transferrin increases with iron deficiency and decreases when iron status improves (see, e.g., Litchford et al., NUTRITIONAL ISSUES IN THE PATIENT WITH DIABETES AND FOOT ULCERS, Levin and O'Neal's The Diabetic Foot (Seventh Edition), 2008; Ogun et al., Biochemistry, Transferrin, Treasure Island (FL): StatPearls Publishing; 2021 Jan).

[000407] To test whether circulating transferrin level decreases after hHA-008-QL treatment, baseline transferrin level was established for each health Cynomolgus macaque (cynos) in the experiment 11 days before hHA-008-QL dosing on Day 1. Cynos were dosed with 0 mg/kg, 3 mg/kg, 30 mg/kg or 160 mg/kg of hHA-008-QL on day 1, day 15 and day 29 (n=5 in each group). Blood from each cyno was collected 96 hours, 192 hours, and 336 hours after the dosing on day 1; 48 hours, 96 hours, 192 hours, and 336 hours after the dosing on day 15; and 48 hours after the dosing on day 29. Note that blood for the 336-hour timepoint after day 1 dosing was collected 2 hours before the day 15 dosing, and blood for the 336-hour time point after day 15 dosing was collect 2 hours before the day 29 dosing. Transferrin levels were measured in all samples for each cyno, and was compared to its own baseline to calculate the percent change at each time point. The data in Table 16 show that treatment of hHA-008-QL reduced circulating transferrin levels compared to the baseline level.

Table 16: Circulating transferrin levels and the change over baseline in cynos treated with hHA-008-QL

	Males				Females			
Day(s) Relative to Start Date	**0 mg/kg/ dose**	**3 mg/kg/ dose**	**30 mg/kg/ dose**	**160 mg/kg/ dose**	**0 mg/kg/ dose**	**3 mg/kg/ dose**	**30 mg/kg/ dose**	**160 mg/kg/ dose**
Transferrin Day -11 (mg/dL; Baseline)	241.96± 14.74	227.82± 22.69	239.14± 18.75	227.58± 10.21	241.96± 14.74	227.82± 22.69	239.14± 18.75	227.58± 10.21
Transferrin	259.28±	223.74±	226.74±	217.74±	259.28±	223.74±	226.74±	217.74±

Day 1, 96 h (mg/dL)	10.46	20.49 **	13.64 **	9.88 **	10.46	20.49 **	13.64 **	9.88 **
Day 1, 96 h tCtrl	-	0.86	0.87	0.84	-	0.86	0.87	0.84
Transferrin Day 1, 192 h (mg/dL)	263.06± 19.77	224.92± 21.07 **	226.62± 11.34 **	221.64± 10.96 **	263.06± 19.77	224.92± 21.70 **	226.62± 11.34 **	221.64± 10.96 **
Day 1, 192 h tCtrl	-	0.86	0.86	0.84	-	0.86	0.86	0.84
Transferrin Day 1, 336 h (mg/dL)	260.68± 20.70	223.36± 24.75 *	228.82± 8.80	225.72± 8.08 *	260.68± 20.70	223.36± 24.75 *	228.82± 8.80	225.72± 8.08 *
Day 1, 336 h tCtrl	-	0.86	0.88	0.87	-	0.86	0.88	0.87
Transferrin Day 15, 48 h (mg/dL)	259.76± 18.52	218.06± 28.28 *	225.86± 10.73	221.78± 9.85 *	259.76± 18.52	218.06± 28.28 *	225.86± 10.73	221.78± 9.85 *
Day 15, 48 h tCtrl	-	0.84	0.87	0.85	-	0.84	0.87	0.85
Transferrin Day 15, 96 h (mg/dL)	253.88± 19.14	211.48± 22.48 **	219.52± 11.17 *	209.26± 10.27 **	253.88± 19.14	211.48± 22.48 **	219.52± 11.17 *	209.26± 10.27 **
Day 15, 96 h tCtrl	-	0.83	0.86	0.82	-	0.83	0.86	0.82
Transferrin Day 15, 192 h (mg/dL)	254.78± 24.23	215.88± 27.37	219.92± 10.13	211.30± 8.73 *	254.78± 24.23	215.88± 27.37	219.92± 10.13	211.30± 8.73 *
Day 15, 192 h tCtrl	-	0.85	0.86	0.83	-	0.85	0.86	0.83
Transferrin Day 15, 336 h (mg/dL)	268.04± 24.56	222.58± 26.20 **	235.52± 16.40	231.42± 11.07 *	268.04± 24.56	222.58± 26.20 **	235.52±1 6.40	231.42± 11.07 *
Day 15, 336 h tCtrl	-	0.83	0.88	0.86	-	0.83	0.88	0.86

Transferrin Day 29, 48 h (mg/dL)	236.04± 14.11	198.48± 19.87 **	209.30± 14.41 *	198.12±10.25 **	236.04±14.11	198.48±19.87 **	209.30±14.41 *	198.12±10.25 **
Day 29, 48 h tCtrl	-	0.84	0.89	0.84	-	0.84	0.89	0.84
Transferrin Day 29, 96 h (mg/dL)	252.24± 12.39	209.24± 24.21 **	225.80± 225.80	209.90± 8.04 **	252.24± 12.39	209.24± 24.21 **	225.80± 15.43	209.90± 8.04 **
Day 29, 96 h tCtrl	-	0.83	0.90	0.83	-	0.83	0.90	0.83
Anova & Dunnett: * = p ≤ 0.05; ** = p ≤ 0.01								

Example 9: hHA-008 Prevents Inflammation-induced (IL-6) Iron Suppression in Cynomolgus macaque

[000408] Prevention of iron suppression by hHA-008 following IL-6 challenge was investigated in this study. On Day 0, three groups of cynos (N=3/group) were challenged with 6×10^4 international units (IU) IL-6/kg subcutaneously. On Day 3 each group of 3 animals received 0 (vehicle), 0.6 or 6 mg/kg of hHA-008 intravenously, respectively. On Day 10 all groups received a second challenge of 6×10^4 IU IL-6/kg subcutaneously. Blood was collected from all cynos to evaluate serum iron level at 48 hours and 24 hours prior to each IL-6 challenge, and 2, 4, 8 and 24 hours after each IL-6 dose. The average baseline value of the samples taken 48 and 24 hours prior to each IL-6 dose were used as D0 value. The results showed that hHA-008 was effective in preventing IL-6-induced serum iron suppression in a dose-dependent manner in cynomolgus monkeys (FIG. 18).

Example 10: Subcutaneous Injection of hHA-008 in Sprague-Dawley Rats

[000409] Sprague-Dawley Rats (6 females and 6 males) were injected with hHA-008 subcutaneously at 6 mg/kg (mpk). pharmacokinetics (SC PK) and pharmacodynamics (SC PD) were evaluated 35 days after dosing. Serum mean pharmacokinetics parameters (e.g., Cmax, Tmax, t1/2, and $AUC_{0\text{-}inf}$) were shown in Table 17:

Table 17: Serum Mean Pharmacokinetic (PK) Parameters of hHA-008 Following a Single SC Administration in Sprague-Dawley Rats

Dose (mg/kg)	C_{MAX} (µg/ml) (mean±SD)	T_{MAX} (DAYS) (mean±SD)	$T_{1/2}$ (DAYS) (mean±SD)	AUC_{0-INF} (HR*MG/ML) (mean±SD)
6	37.6±6.02	3.8±0.6	4.3±1.4	13,357±1,437.4

[000410] Bioavailability of hHA-008 after subcutaneous administration was similar to bioavailability of hHA-008 after intravenous administration at 6 mg/kg, as evidenced by that subcutaneous injection bioavailability (SC bioavailability) of hHA-008 was about 84.7% of intravenous injection bioavailability of hHA-008 (IV bioavailability) (SC bioavailability = SC DN_AUC_{0-inf} / IV DN_AUC_{0-inf} x 100; DN: Dose normalized). Further, the time to reach maximum concentration (C_{max}) was 3.6 – 4 days after SC administration with a much lower Cmax as compared to the Cmax after IV administration.

[000411] At similar dose level, the PD response between the IV or SC was indistinguishable: serum hHA-008 concentration became saturated 1-2 days after dosing, remained elevated through at least 21 days and the decline in PD response (e.g., Hepcidin-25 concentration and TSAT%) was consistent with the decrease of hHA-008 serum concentration (FIG .19).

Example 11. Subcutaneous Dose Administration in Cynomolgus Monkeys

[000412] PK/PD of subcutaneous hHA-008 treatment were also evaluated in Cynomolgus (cynos). Cynos were injected with hHA-008 subcutaneously at 0.3 mpk, 0.6 mpk, 1 mpk and 6 mpk.

[000413] In the 6 mpk dosing group, 2 male and 1 female cynos received a single subcutaneous injection of hHA-008, and blood samples were collected for 61 days. Cynos received IV injection of hHA-008 at 6 mpk were used for comparison.

[000414] In the 0.3 mpk, 0.6 mpk, and 1.0 mpk groups, each group included 3 male cynos that received a single subcutaneous injection of hHA-008. Blood samples were collected for 27 days. Cynos received the same dose of hHA-008 by IV were used for comparison for each group.

[000415] After SC administration of hHA-008 in cynomolgus monkeys, bioavailability was high and increased with dose levels (55.0% at 0.3 mpk, 81.9% at 0.6 mpk, 89.5% at 1 mpk and 100% at 6 mg/kg), when compared to animals injected at the same doses via IV. Tmax was reached rapidly after dosing in a dose dependent manner (1.33 to 2.67 days). Table 18 shows serum mean Pharmacokinetic (PK) parameters of hHA-008 following a single SC administration in cynos. hHA-008 serum concentration-time profiles became indistinguishable between SC injection and IV injection 4 days after administration (FIG.

20A).

Table 18: Serum Mean Pharmacokinetic (PK) Parameters of hHA-008 Following a Single SC Administration in Cynos

Dose (mg/kg)	C_{max} (µg/mL) (mean±SD)	T_{max} (day) (mean±SD)	$t_{1/2}$ (day) (mean±SD)	$AUC_{0\text{-}inf}$* (hr*µg/mL) (mean±SD)	Bioavailability compared to IV
0.3	3.21±0.72	1.33±0.58	1.69±0.18	496.5±81.29	55%
0.6	7.2± 0.48	1.33±0.58	2.82±0.2	1417±234	81.9%
1	10.5±1.76	2±0	3.3±1.43	2942±300	89.5%
6	102±15.4	2.67±1.15	7.95±1.68	34439±2,528	100%

* extrapolation from $AUC_{0\text{-}last}$ was less than 3%.

[000416] The PD response after SC dose was variable between animals, relatively proportional to the dose-level, and similar to the PD response observed after IV dosing at 0.1 mpk, 0.6 mpk, and 1.0 mpk. For all animals, the PD response was functionally maximal (TSAT >80% and hepcidin-25 <LOQ) between 1 -2 days after dosing. The return of the PD markers (e.g., serum iron) to baseline levels was consistent with the decline in hHA-008 serum concentrations (FIGs. 20B-20D). At 6 mpk, serum iron concentrations in both SC injected group and IV injected group were too saturated to reflect the change (data not shown).

OTHER EMBODIMENTS

[000417] All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

[000418] From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also set forth as follows.

[000419] 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 X_1YGMN (SEQ ID NO: 105), in which X_1 can be N or Y; a heavy chain complementary determining region 2 (HC CDR2) set forth as MIYYDSSX_2KHYADSVKG (SEQ ID NO: 106), in which X_2 can be E or D; a heavy chain

complementary determining region 3 (HC CDR3) set forth as GX_3TPDX_4 (SEQ ID NO: 107), in which X_3 can be T or S, and X_4 can be Y, V, or K; and/or a light chain complementary determining region 1 (LC CDR1) set forth as $RSSQSLX_5X_6SDGX_7TFLX_8$ (SEQ ID NO: 108), in which X_5 can be A or E, X_6 can be T, S, E, or D, X_7 can be D, Y, or G, and X_8 can be E or H, a light chain complementary determining region 2 (LC CDR2) set forth as $X_9VSX_{10}RFS$ (SEQ ID NO: 109), in which X_9 can be E, D or A, and X_{10} can be N, S, T, E or H, a light chain complementary determining region 3 (LC CDR3) set forth as $X_{11}QX_{12}TX_{13}DPX_{14}X_{15}$ (SEQ ID NO: 110), in which X_{11} can be F or M, X_{12} can be V or A, X_{13} can be H or Y, X_{14} can be M, L or V, and X_{15} can be T or S.

[000420] 2. The method of embodiment 1, wherein the antibody comprises a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 38, and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 39.

[000421] 3. The method of embodiment 2, wherein the antibody comprises a VH comprising an amino acid sequence of SEQ ID NO: 38, and a VL comprising an amino acid sequence of SEQ ID NO: 39.

[000422] 4. The method of any one of embodiments 1-3, wherein the antibody is a humanized antibody.

[000423] 5. The method of embodiment 4, wherein the humanized antibody comprises a humanized VH and/or a humanized VL.

[000424] 6. The method of any one of embodiments 1-5, 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.

[000425] 7. The method of embodiment 6, wherein the antibody is a full-length IgG.

[000426] 8. The method of embodiment 9, wherein the antibody comprises a heavy chain constant region of the isotype IgG1, IgG2, IgG3, or IgG4.

[000427] 9. The method of embodiment 8, wherein the antibody further comprises a heavy chain constant region set forth in SEQ ID NO: 46 or SEQ ID NO: 48.

[000428] 10. The method of embodiment 9, wherein the antibody further comprises a light chain constant region set forth in SEQ ID NO: 47.

[000429] 11. The method of any one of embodiments 1-10, wherein the antibody comprises: (i) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 61, and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 62; or (ii) a heavy chain comprising an amino acid sequence at least 85% identical to

SEQ ID NO: 63, and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 62.

[000430] 12. The method of embodiment 11, wherein the antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 61, and a light chain comprising an amino acid sequence of SEQ ID NO: 62.

[000431] 13. The method of embodiment 11 wherein the antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 63, and a light chain comprising an amino acid sequence of SEQ ID NO: 62.

[000432] 14. The method of any one of embodiments 1-13, wherein the subject has myelofibrosis initiating mutations in JAK2, MPL, ASXL1, TET2, NFE2, SH2B3, SF3B1, or CALR.

[000433] 15. The method of any one of embodiments 1-14, wherein the myelofibrosis is associated with increased levels of pro-inflammatory cytokines (e.g., IL-6, oncostatin-M) in the subject.

[000434] 16. The method of any one of embodiments 1-15, wherein the subject presents with a serum hemoglobin level of less than 10 g/dL.

[000435] 17. The method of any one of embodiments 1-16, wherein the subject presents with a serum hemoglobin level of less than 8 g/dL.

[000436] 18. The method of any one of embodiments 1-17, wherein the subject is erythrocyte-transfusion dependent.

[000437] 19. The method of embodiment 18, wherein the subject is anemic.

[000438] 20. The method of any one of embodiments 1-19, wherein the subject has previously received an erythropoietin stimulating agent, a JAK-STAT inhibitor, a growth factor ligand trap, or an anti-fibrotic agent.

[000439] 21. The method of any one of embodiments 1-19, further comprising 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.

[000440] 22. The method of embodiment 20 or embodiment 21, wherein the erythropoietin stimulating agent is selected from the group consisting of danazol, prednisone, thalidomide, lenalidomide, and pomalidomide.

[000441] 23. The method of embodiment 20 or embodiment 21, wherein the JAK-STAT inhibitor is selected from the group consisting of ruxolitinib, momelotinib, pacritinib, INCB039110, AG490, and PpYLKTK.

[000442] 24. The method of embodiment 20 or embodiment 21, wherein the growth factor ligand trap is sotatercept or luspatercept.

[000443] 25. The method of embodiment 20 or embodiment 21, wherein the anti-fibrotic agent is PRM-151.

[000444] 26. An isolated antibody that binds to human hemojuvelin (HJV), wherein the antibody comprises a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 38, and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 39.

[000445] 27. The isolated antibody of embodiment 26, wherein the antibody comprises a VH comprising an amino acid sequence of SEQ ID NO: 38, and a VL comprising an amino acid sequence of SEQ ID NO: 39.

[000446] 28. The isolated antibody of embodiment 26 or embodiment 27, wherein the antibody is a humanized antibody.

[000447] 28. The isolated antibody of embodiment 28, wherein the humanized antibody comprises a humanized VH and/or a humanized VL.

[000448] 29. The isolated antibody of any one of embodiments 26-28, 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.

[000449] 30. The isolated antibody of embodiment 29, wherein the antibody is a full-length IgG.

[000450] 31. The isolated antibody of embodiment 30, wherein the antibody comprises a heavy chain constant region of the isotype IgG1, IgG2, IgG3, or IgG4.

[000451] 32. The isolated antibody of embodiment 31, wherein the antibody further comprises a heavy chain constant region set forth in SEQ ID NOs: 46, 48, 112 or 113.

[000452] 33. The isolated antibody of embodiment 32, wherein the antibody further comprises a light chain constant region set forth in SEQ ID NO: 47.

[000453] 34. The isolated antibody of any one of embodiments 26-33, wherein the antibody comprises: (i) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 61 or 117, and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 62; or (ii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 63 or 118, and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 62.

[000454] 35. The isolated antibody of embodiment 34, wherein the antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NOs: 61 or 117, and a light chain comprising an amino acid sequence of SEQ ID NO: 62.

[000455] 36. The isolated antibody of embodiment 34, wherein the antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NOs: 63 or 118, and a light chain comprising an amino acid sequence of SEQ ID NO: 62.

[000456] 37. An isolated antibody that binds to human hemojuvelin (HJV) produced by expressing in a host cell: (i) a nucleic acid sequence encoding a heavy chain, wherein the nucleic acid sequence is at least 90% identical to SEQ ID NO: 92; and/or (ii) a nucleic acid sequence encoding a light chain, wherein the nucleic acid sequence is at least 90% identical to SEQ ID NO: 93.

[000457] 38. An isolated antibody that binds to human hemojuvelin (HJV) produced by expressing in a host cell: (i) a nucleic acid sequence encoding a heavy chain, wherein the nucleic acid sequence is at least 90% identical to SEQ ID NO: 94; and/or (ii) a nucleic acid sequence encoding a light chain, wherein the nucleic acid sequence is at least 90% identical to SEQ ID NO: 93.

[000458] 39. The isolated antibody of embodiments 37 or 38, wherein the host cell is Chinese hamster ovary (CHO) cells, dhfr- CHO cell, human embryonic kidney (HEK)-293 cells, verda reno (VERO) cells, nonsecreting null (NS0) cells, human embryonic retinal (PER.C6) cells, Sp2/0 cells, baby hamster kidney (BHK) cells, Madin-Darby Canine Kidney (MDCK) cells, Madin-Darby Bovine Kidney (MDBK) cells, or monkey kidney CV1 line transformed by SV40 (COS) cells.

EQUIVALENTS AND SCOPE

[000459] In the claims, articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention

includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[000460] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, e.g., in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth in haec verba herein.

[000461] The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with "and/or" should be construed in the same fashion, i.e., "one or more" of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to "A and/or B", when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

[000462] As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of" or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e. "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or

"exactly one of." "Consisting essentially of," when used in the claims, shall have its ordinary meaning as used in the field of patent law.

[000463] As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

[000464] It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited.

[000465] In the claims, as well as in the specification above, all transitional phrases such as "comprising," "including," "carrying," "having," "containing," "involving," "holding," "composed of," and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases "consisting of" and "consisting essentially of" shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03. It should be appreciated that embodiments described in this document using an open-ended transitional phrase (e.g., "comprising") are also contemplated, in alternative embodiments, as "consisting of" and "consisting essentially of" the feature described by the open-ended transitional phrase. For example, if the application describes "a composition comprising A and B," the

application also contemplates the alternative embodiments "a composition consisting of A and B" and "a composition consisting essentially of A and B."

[000466] Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[000467] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[000468] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

[000469] The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof. The recitation of an embodiment herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

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 X_1YGMN (SEQ ID NO: 105), in which X_1 can be N or Y;

a heavy chain complementary determining region 2 (HC CDR2) set forth as MIYYDSSX_2KHYADSVKG (SEQ ID NO: 106), in which X_2 can be E or D;

a heavy chain complementary determining region 3 (HC CDR3) set forth as GX_3TPDX_4 (SEQ ID NO: 107), in which X_3 can be T or S, and X_4 can be Y, V, or K; and/or

a light chain complementary determining region 1 (LC CDR1) set forth as RSSQSLX_5X_6SDGX_7TFLX_8 (SEQ ID NO: 108), in which X_5 can be A or E, X_6 can be T, S, E, or D, X_7 can be D, Y, or G, and X_8 can be E or H,

a light chain complementary determining region 2 (LC CDR2) set forth as X_9VSX_{10}RFS (SEQ ID NO: 109), in which X_9 can be E, D or A, and X_{10} can be N, S, T, E or H,

a light chain complementary determining region 3 (LC CDR3) set forth as X_{11}QX_{12}TX_{13}DP$X_{14}X_{15}$ (SEQ ID NO: 110), in which X_{11} can be F or M, X_{12} can be V or A, X_{13} can be H or Y, X_{14} can be M, L or V, and X_{15} 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.

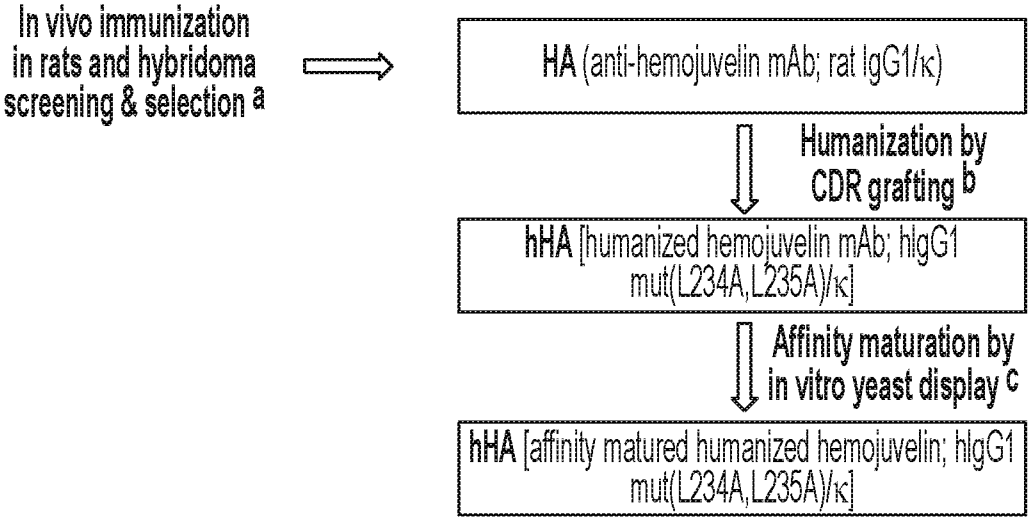

In vivo immunization in rats and hybridoma screening & selection a
HA (anti-hemojuvelin mAb; rat IgG1/κ)
Humanization by CDR grafting b
hHA [humanized hemojuvelin mAb; hIgG1 mut(L234A,L235A)/κ]
Affinity maturation by in vitro yeast display c
hHA [affinity matured humanized hemojuvelin; hIgG1 mut(L234A,L235A)/κ]

FIG. 1A

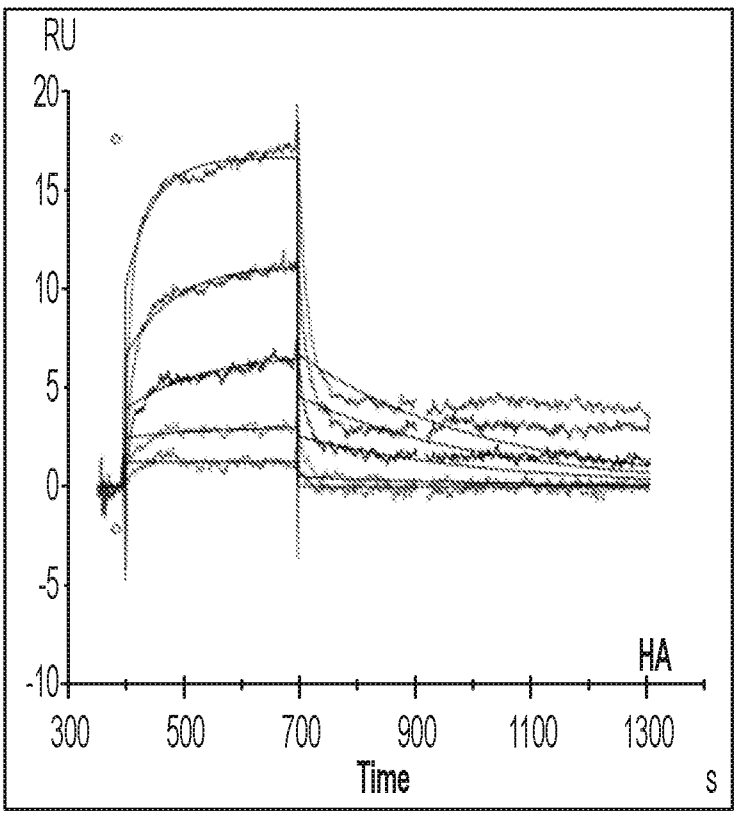

RU
20
15
10
5
0
-5
-10
HA
300
500
700
900
1100
1300
Time
s

FIG. 1B

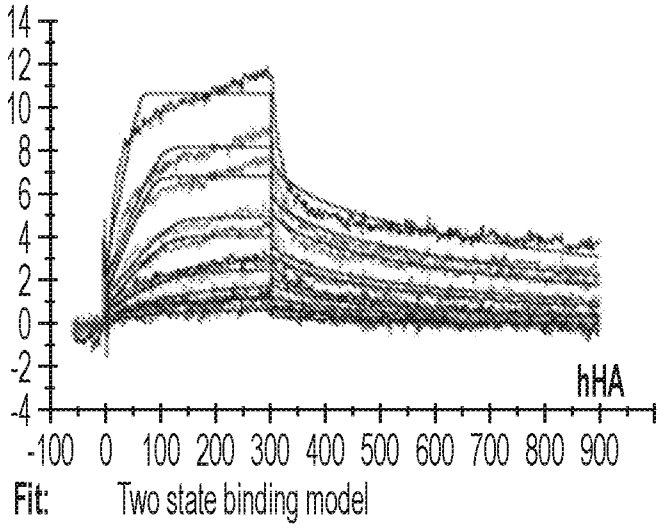

14
12
10
8
6
4
2
0
-2
-4
-100 0 100 200 300 400 500 600 700 800 900
hHA
Fit: Two state binding model

FIG. 1C

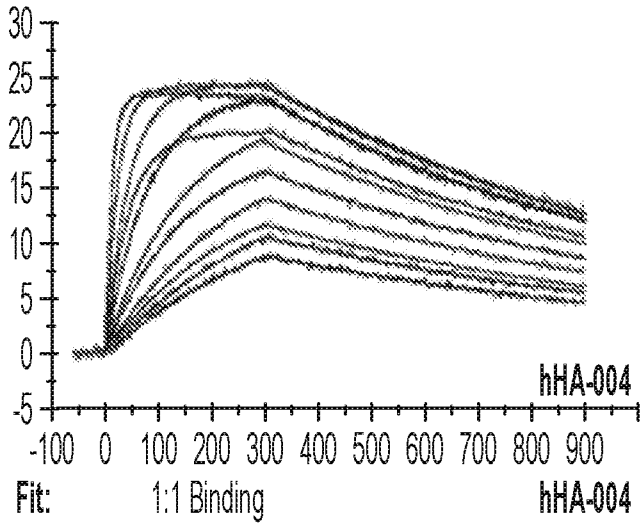

30
25
20
15
10
5
0
-5
-100 0 100 200 300 400 500 600 700 800 900
hHA-004
Fit: 1:1 Binding
hHA-004

FIG. 1D

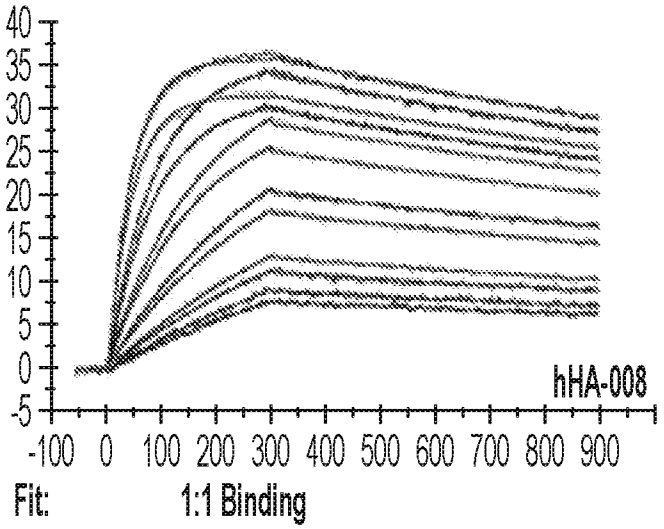

40
35
30
25
20
15
10
5
0
-5
-100 0 100 200 300 400 500 600 700 800 900
hHA-008
Fit: 1:1 Binding

FIG. 1E

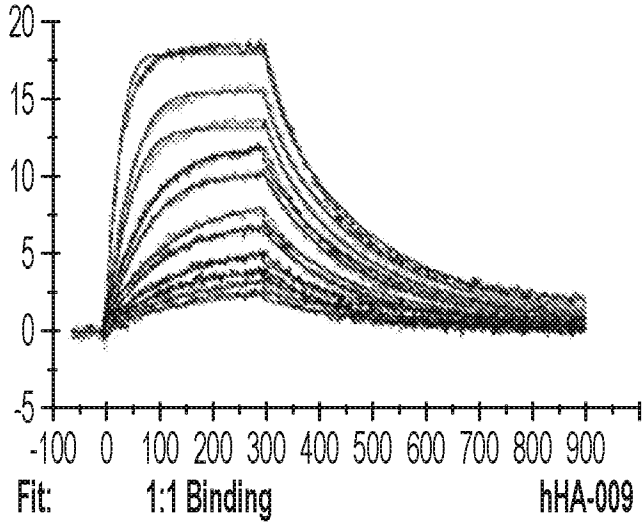

20
15
10
5
0
-5
-100 0 100 200 300 400 500 600 700 800 900
Fit: 1:1 Binding
hHA-009

FIG. 1F

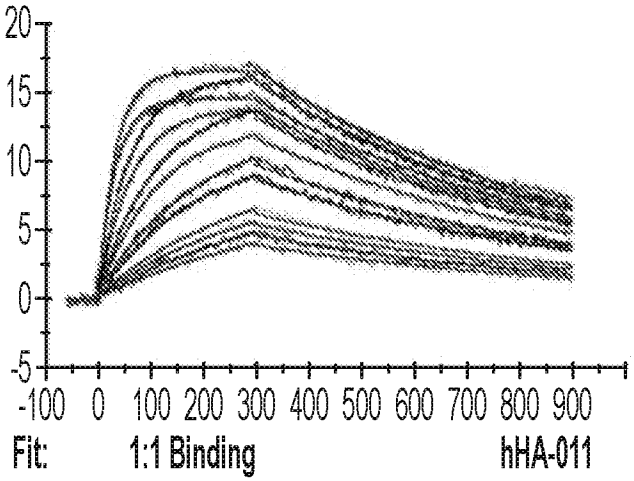

20
15
10
5
0
-5
-100 0 100 200 300 400 500 600 700 800 900
Fit: 1:1 Binding hHA-011

FIG. 1G

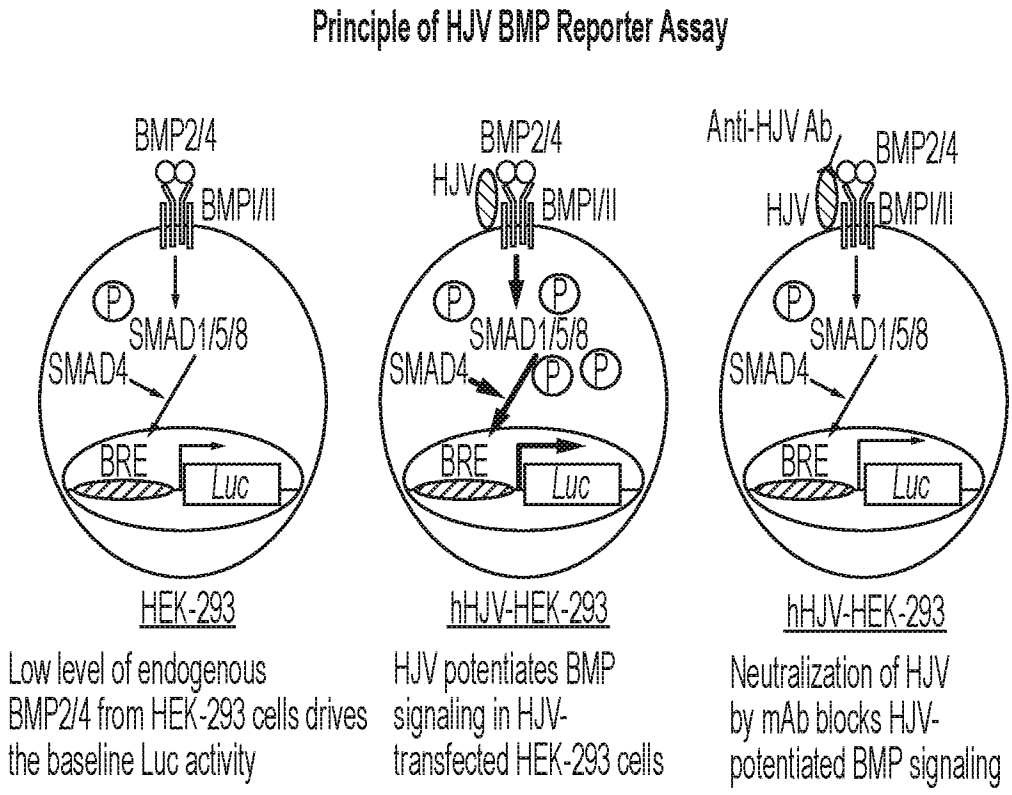

Principle of HJV BMP Reporter Assay
BMP2/4
BMPI/II
P
SMAD1/5/8
SMAD4
BRE
Luc
HEK-293
Low level of endogenous BMP2/4 from HEK-293 cells drives the baseline Luc activity
BMP2/4
HJV
BMPI/II
P
P
SMAD1/5/8
SMAD4
P
P
BRE
Luc
hHJV-HEK-293
HJV potentiates BMP signaling in HJV-transfected HEK-293 cells
Anti-HJV Ab
BMP2/4
HJV
BMPI/II
P
SMAD1/5/8
SMAD4
BRE
Luc
hHJV-HEK-293
Neutralization of HJV by mAb blocks HJV-potentiated BMP signaling

FIG. 2A

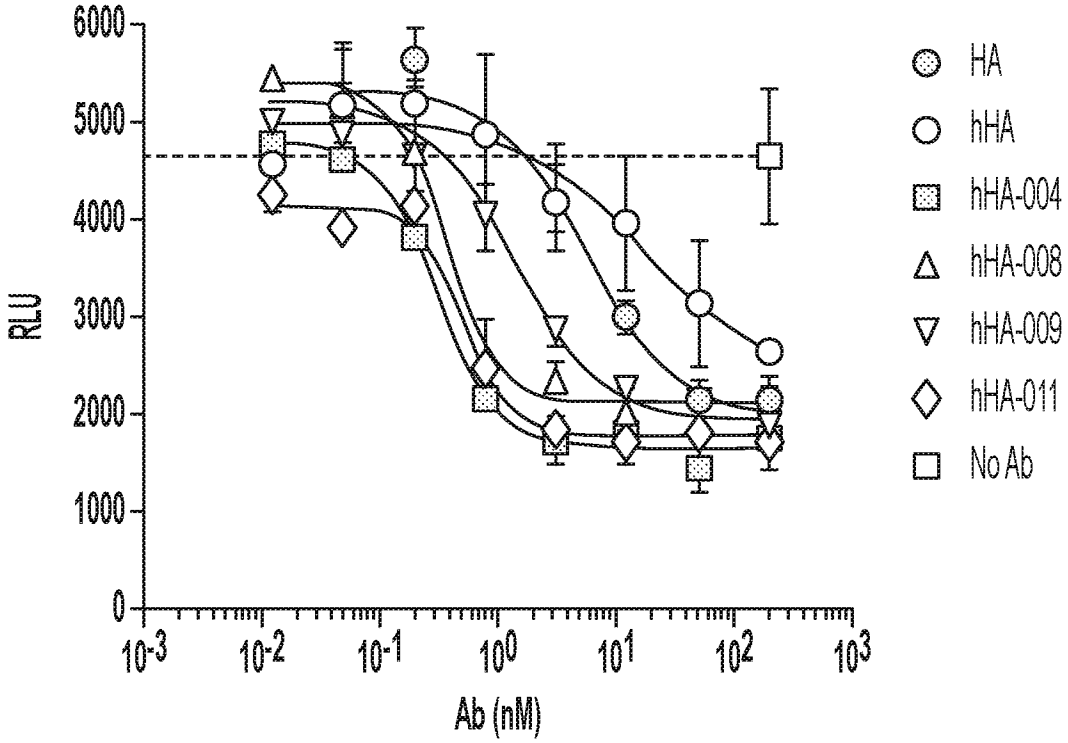

6000
5000
4000
3000
2000
1000
0
RLU
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
Ab (nM)
HA
hHA
hHA-004
hHA-008
hHA-009
hHA-011
No Ab

FIG. 2B

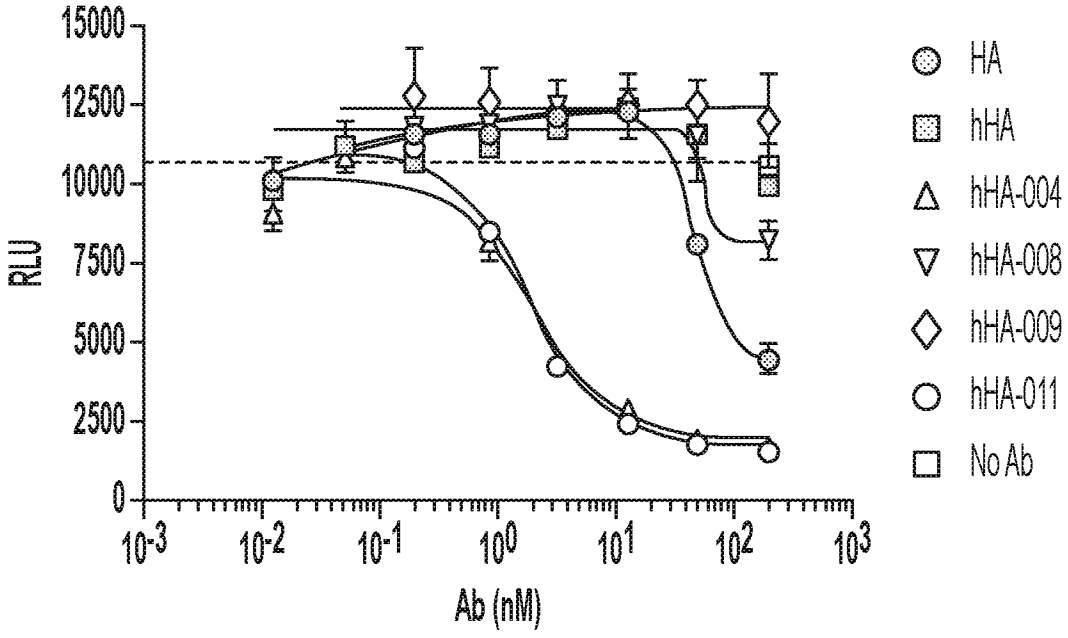

15000
12500
10000
7500
5000
2500
0
RLU
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
Ab (nM)
HA
hHA
hHA-004
hHA-008
hHA-009
hHA-011
No Ab

FIG. 2C

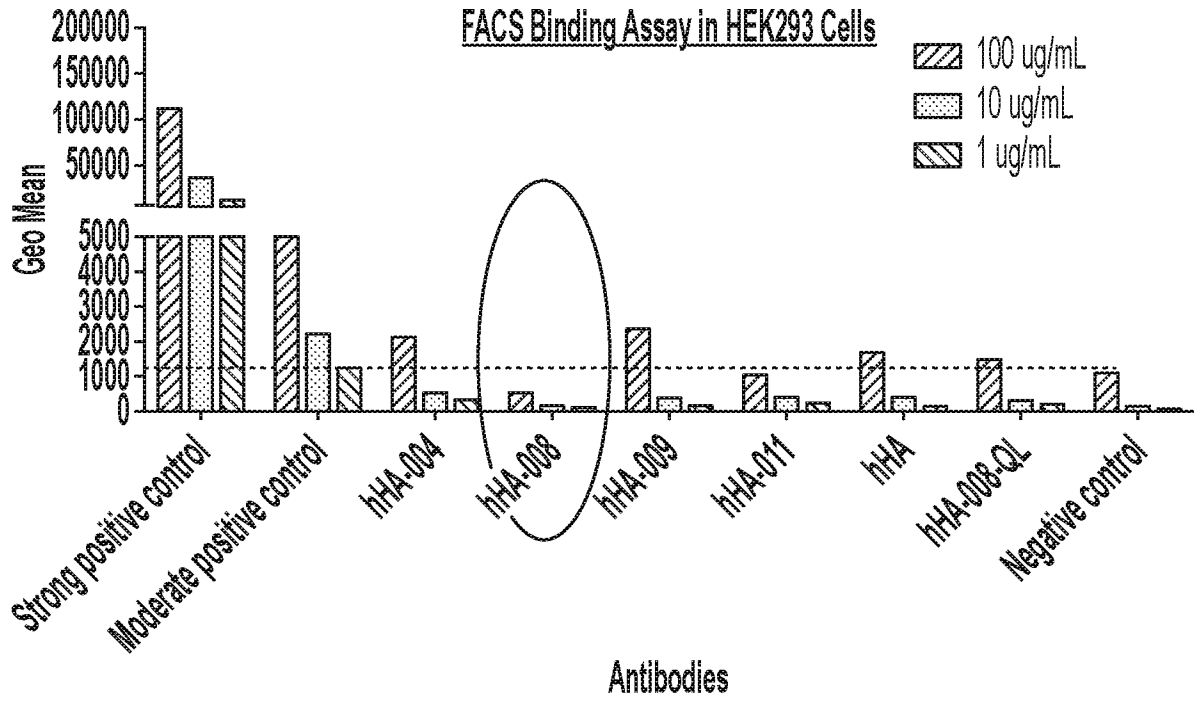

FACS Binding Assay in HEK293 Cells
100 ug/mL
10 ug/mL
1 ug/mL
Geo Mean
200000
150000
100000
50000
5000
4000
3000
2000
1000
0
Strong positive control
Moderate positive control
hHA-004
hHA-008
hHA-009
hHA-011
hHA
hHA-008-QL
Negative control
Antibodies

FIG. 3

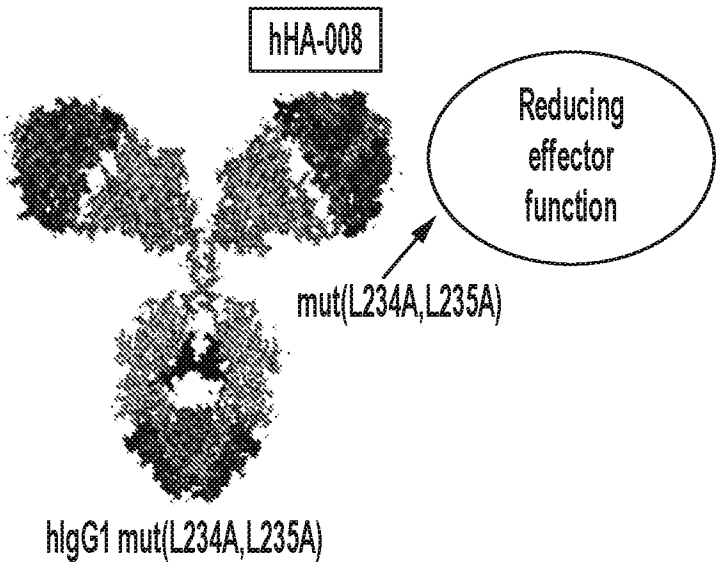

hHA-008
Reducing effector function
mut(L234A,L235A)
hIgG1 mut(L234A,L235A)

FIG. 4A

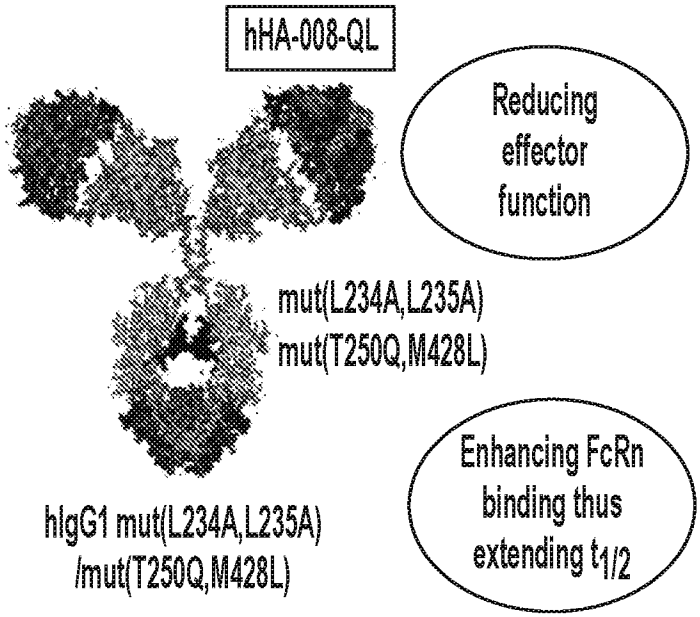

hHA-008-QL
Reducing effector function
mut(L234A,L235A)
mut(T250Q,M428L)
Enhancing FcRn binding thus extending t1/2
hIgG1 mut(L234A,L235A)
/mut(T250Q,M428L)

FIG. 4B

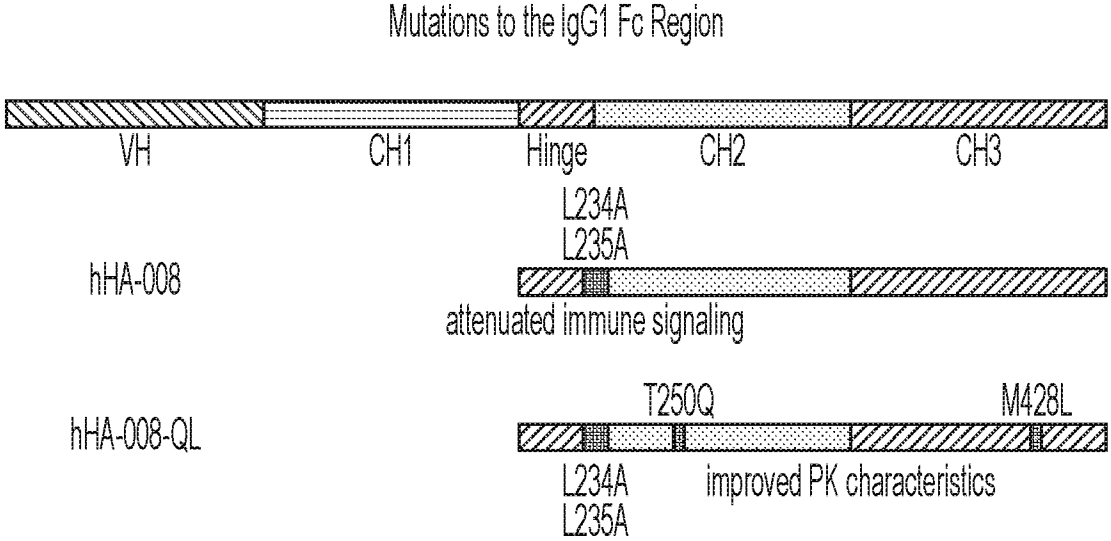

Mutations to the IgG1 Fc Region
VH
CH1
Hinge
CH2
CH3
L234A
L235A
hHA-008
attenuated immune signaling
T250Q
M428L
hHA-008-QL
L234A
L235A
improved PK characteristics

FIG. 4C

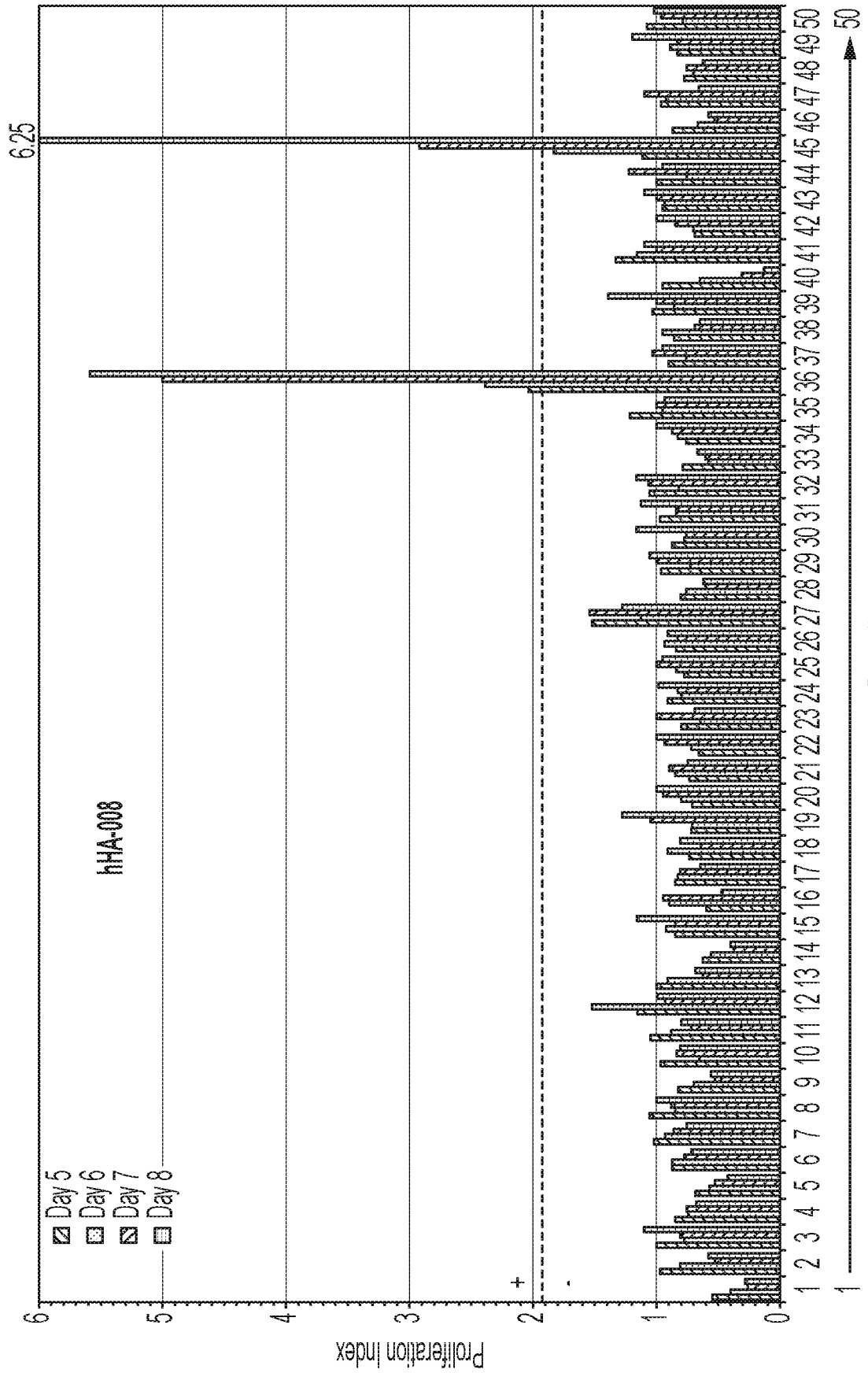


FIG. 5

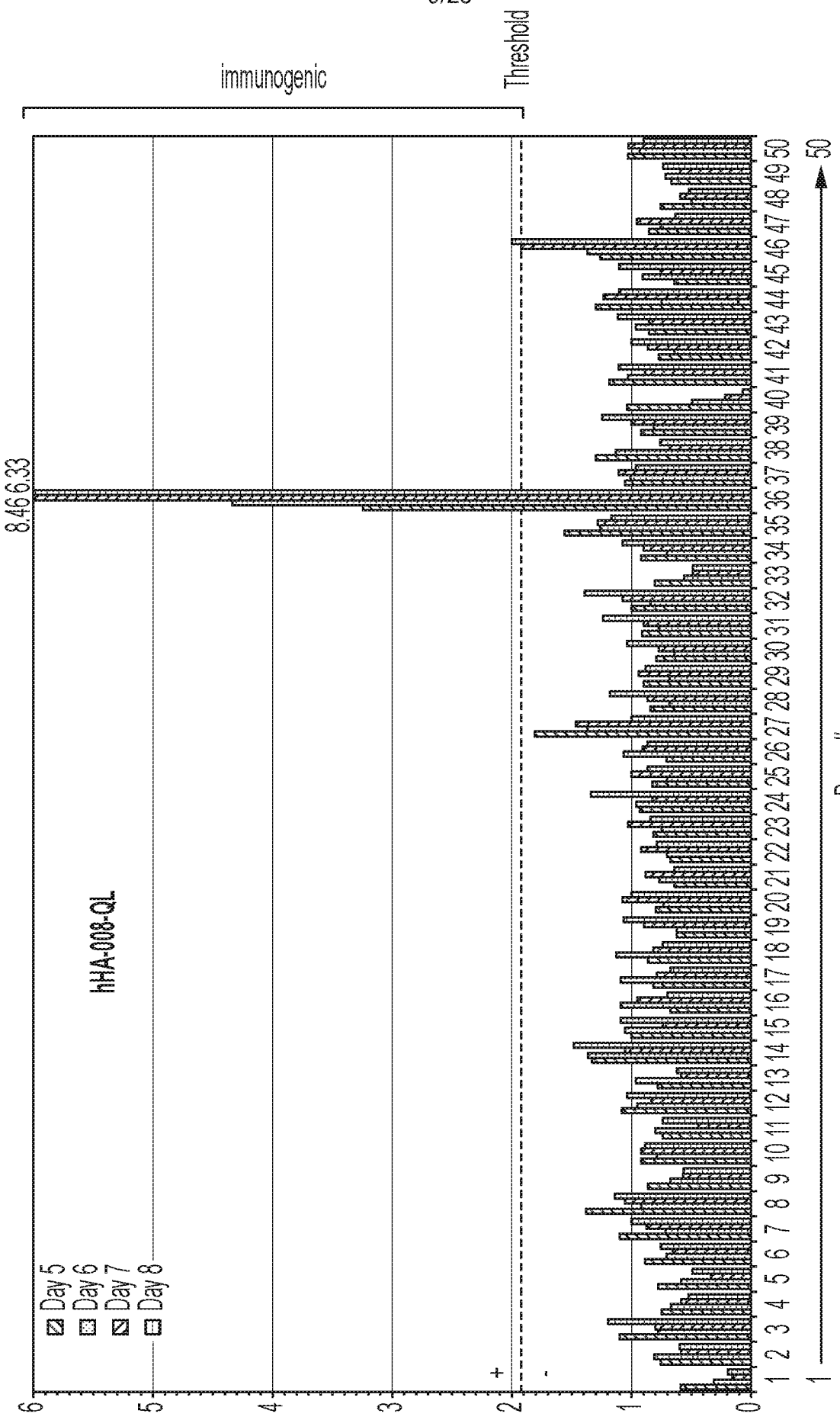


FIG. 5
CONTINUED

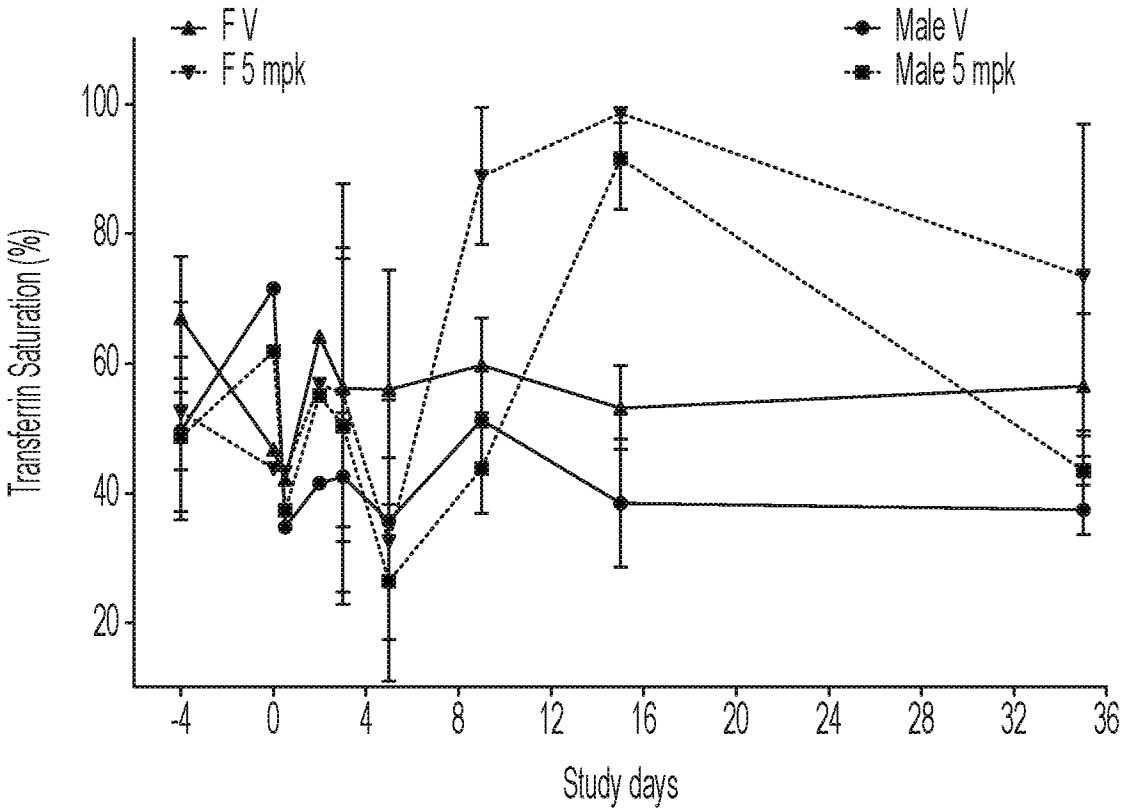

F V
F 5 mpk
Male V
Male 5 mpk
Transferrin Saturation (%)
100
80
60
40
20
-4
0
4
8
12
16
20
24
28
32
36
Study days

FIG. 6A

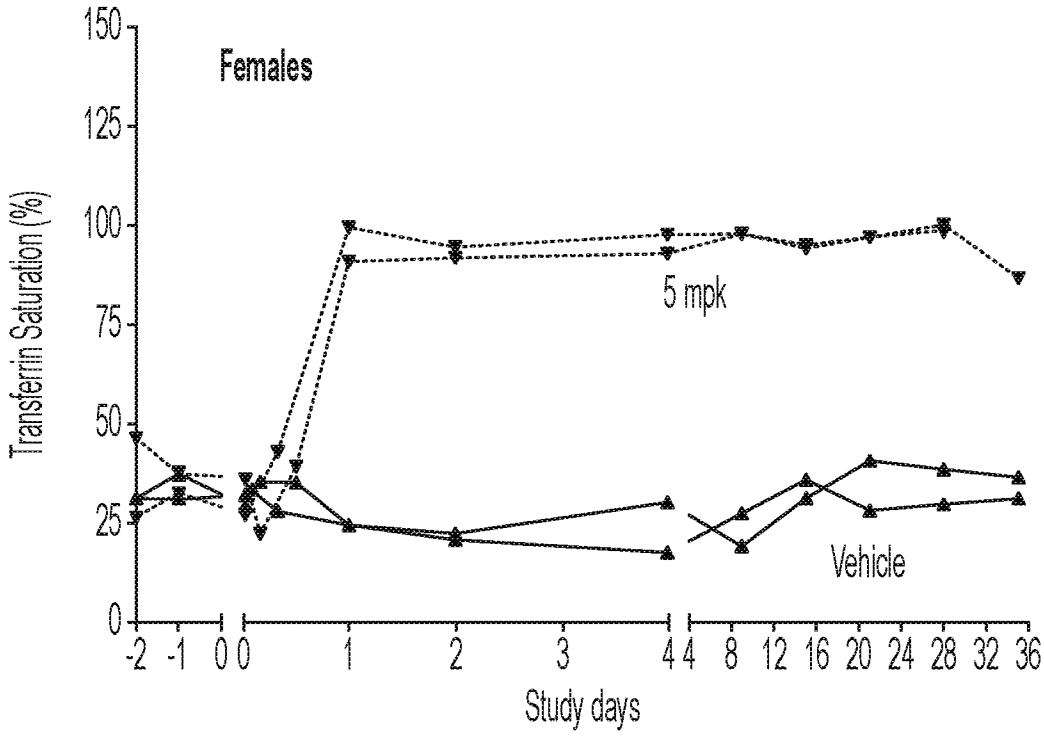

Females
Transferrin Saturation (%)
150
125
100
75
50
25
0
5 mpk
Vehicle
-2
-1
0
0
1
2
3
4
4
8
12
16
20
24
28
32
36
Study days

FIG. 6B

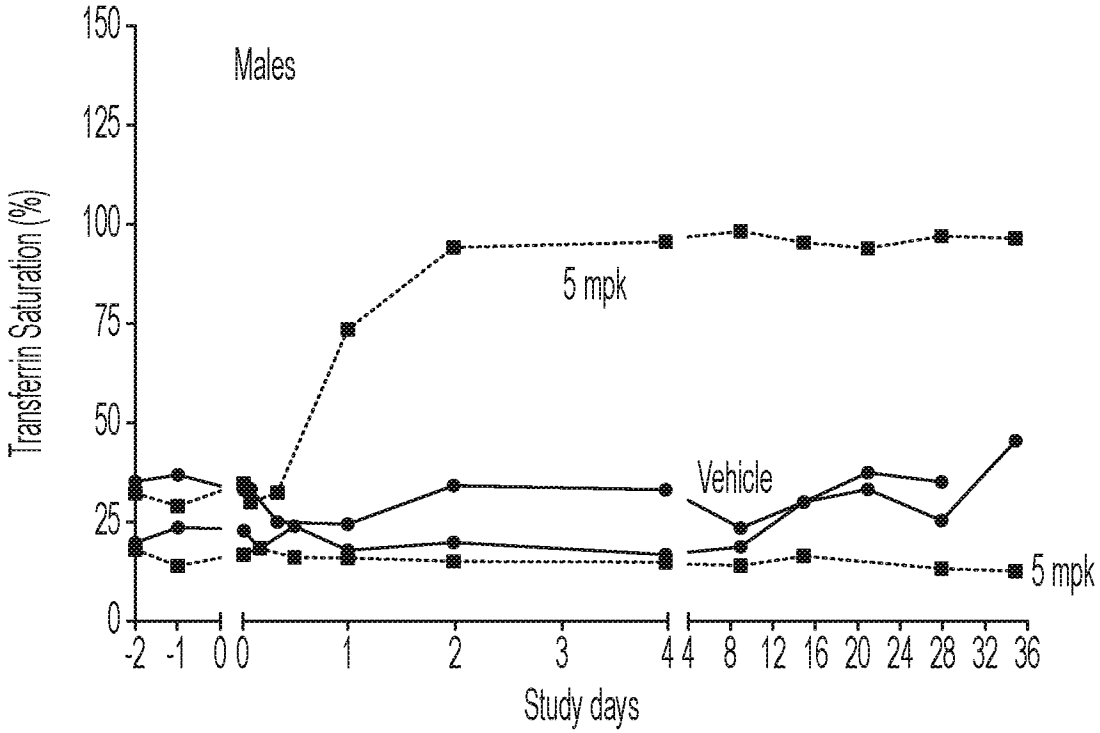

Males
Transferrin Saturation (%)
150
125
100
75
50
25
0
5 mpk
Vehicle
5 mpk
-2 -1 0 0 1 2 3 4 4 8 12 16 20 24 28 32 36
Study days

FIG. 6C

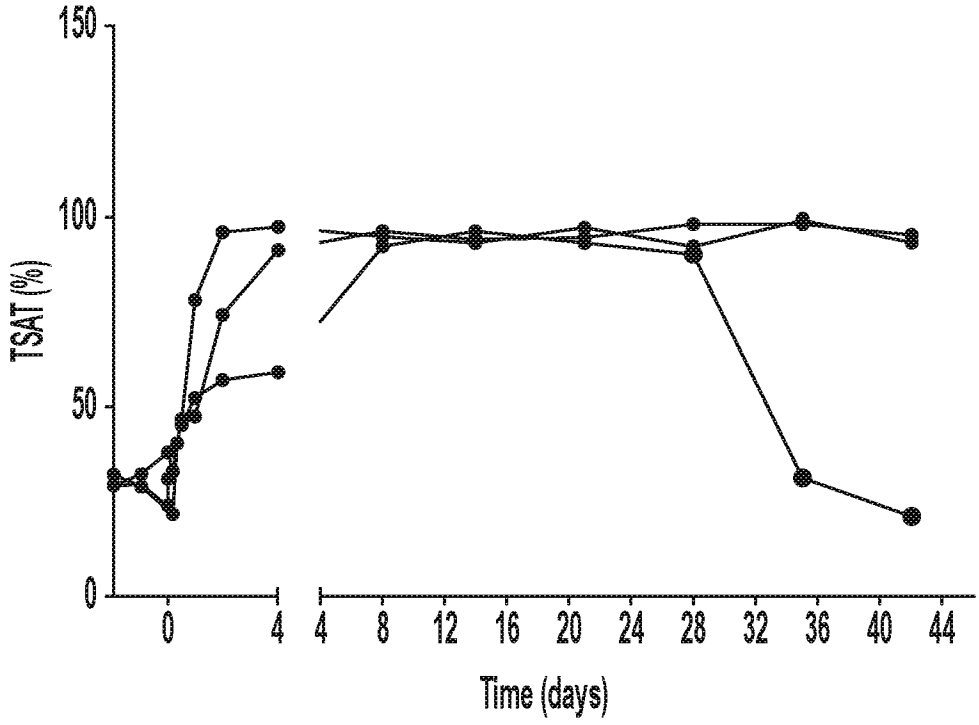

TSAT (%)
150
100
50
0
0 4 4 8 12 16 20 24 28 32 36 40 44
Time (days)

FIG. 7A

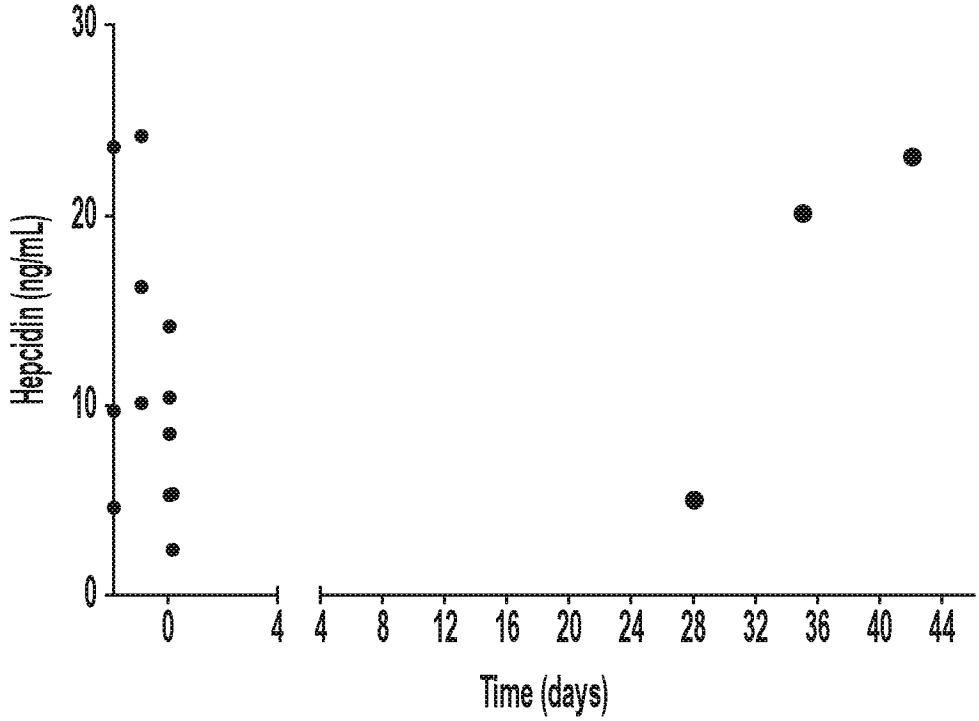

Hepcidin (ng/mL)
30
20
10
0
0
4
4
8
12
16
20
24
28
32
36
40
44
Time (days)

FIG. 7B

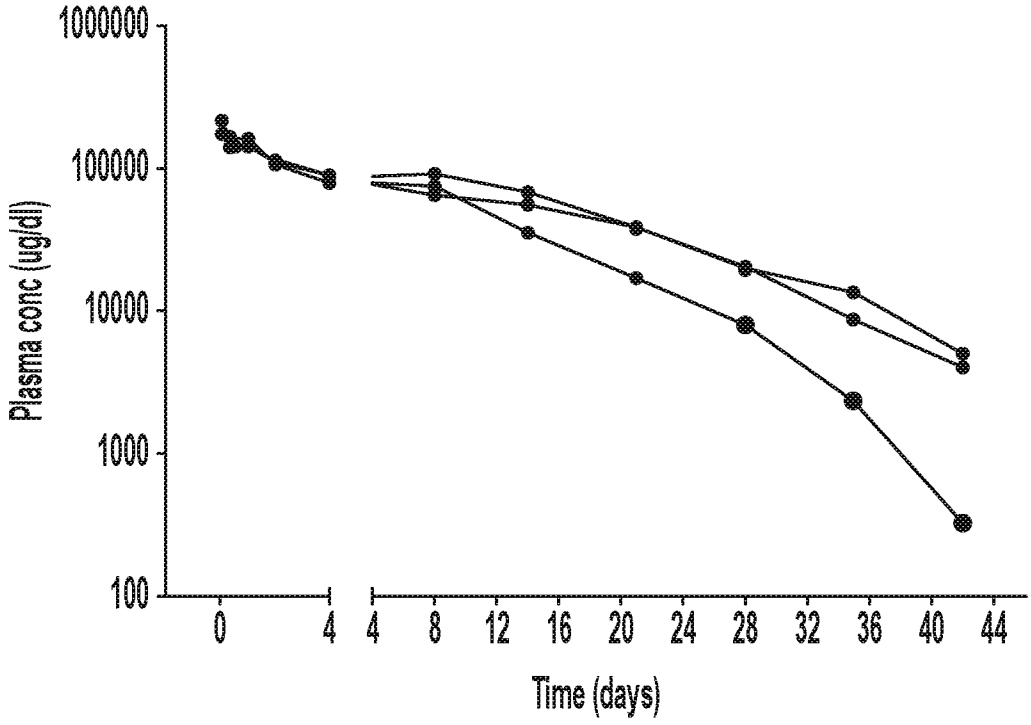

Plasma conc (ug/dl)
1000000
100000
10000
1000
100
0
4
4
8
12
16
20
24
28
32
36
40
44
Time (days)

FIG. 7C

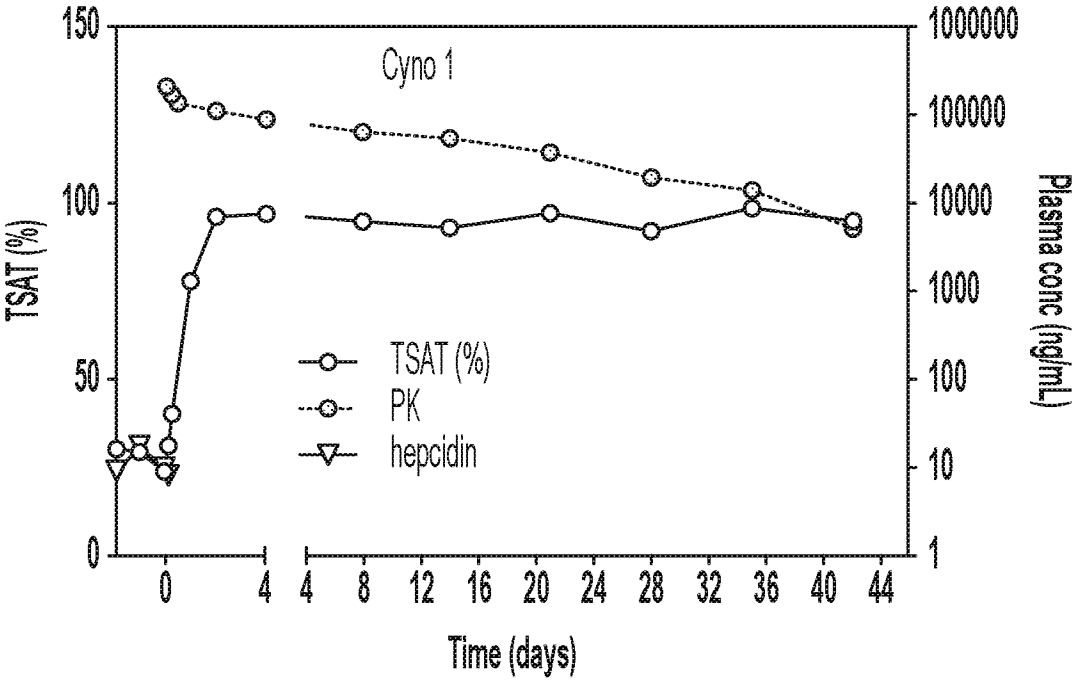

Cyno 1
TSAT (%)
PK
hepcidin
TSAT (%)
Plasma conc (ng/mL)
Time (days)
150
100
50
0
1000000
100000
10000
1000
100
10
1
0
4
4
8
12
16
20
24
28
32
36
40
44

FIG. 7D

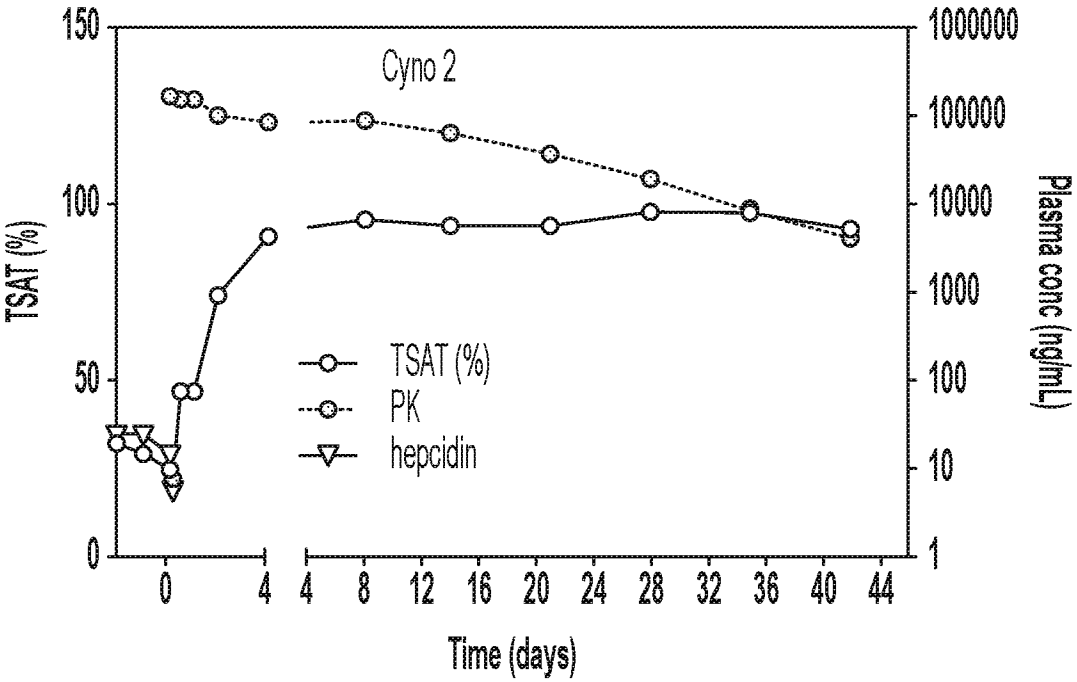

Cyno 2
TSAT (%)
PK
hepcidin
TSAT (%)
Plasma conc (ng/mL)
Time (days)
150
100
50
0
1000000
100000
10000
1000
100
10
1
0
4
4
8
12
16
20
24
28
32
36
40
44

FIG. 7E

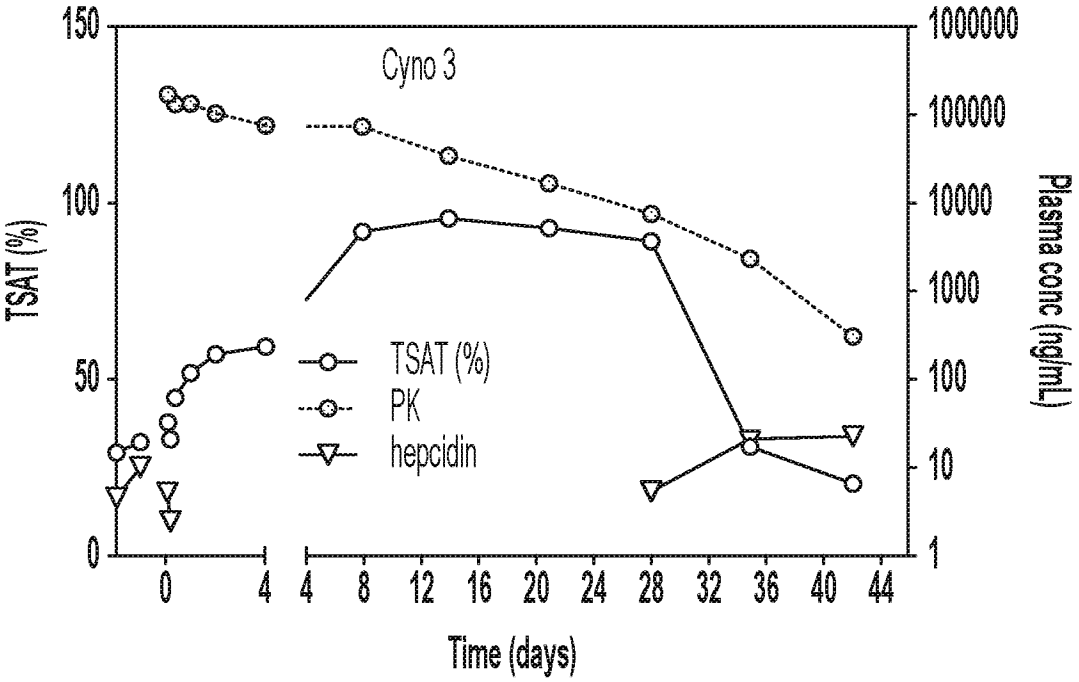

Cyno 3
TSAT (%)
PK
hepcidin
TSAT (%)
Plasma conc (ng/mL)
Time (days)
150
100
50
0
1000000
100000
10000
1000
100
10
1
0
4
4
8
12
16
20
24
28
32
36
40
44

FIG. 7F

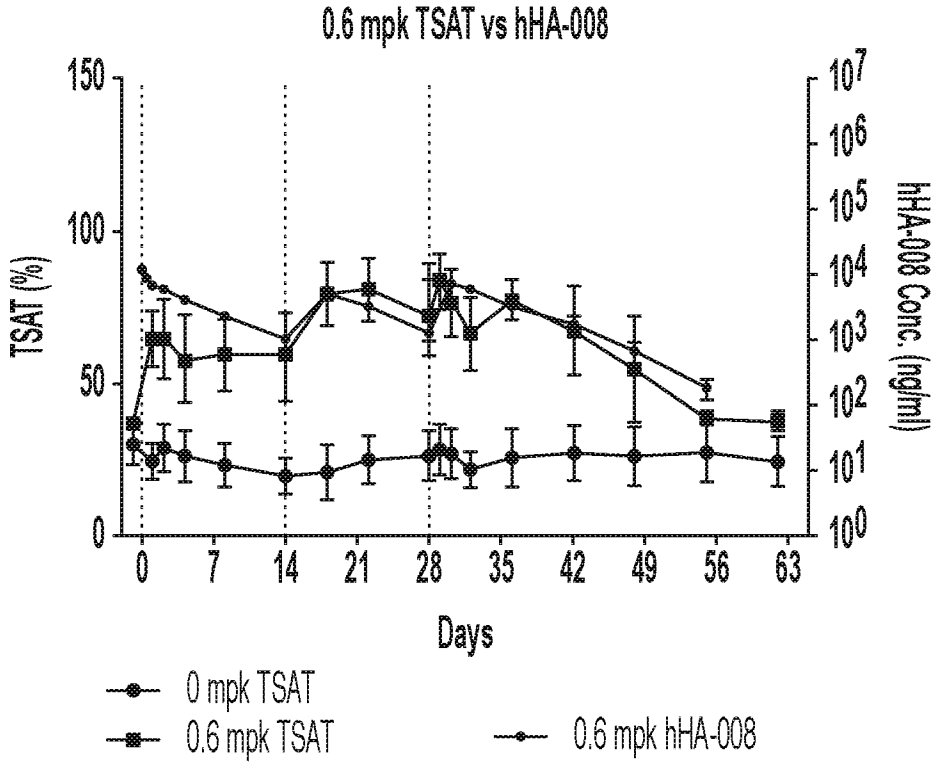

0.6 mpk TSAT vs hHA-008
TSAT (%)
hHA-008 Conc. (ng/ml)
Days
150
100
50
0
10^7
10^6
10^5
10^4
10^3
10^2
10^1
10^0
0
7
14
21
28
35
42
49
56
63
0 mpk TSAT
0.6 mpk TSAT
0.6 mpk hHA-008

FIG. 8A

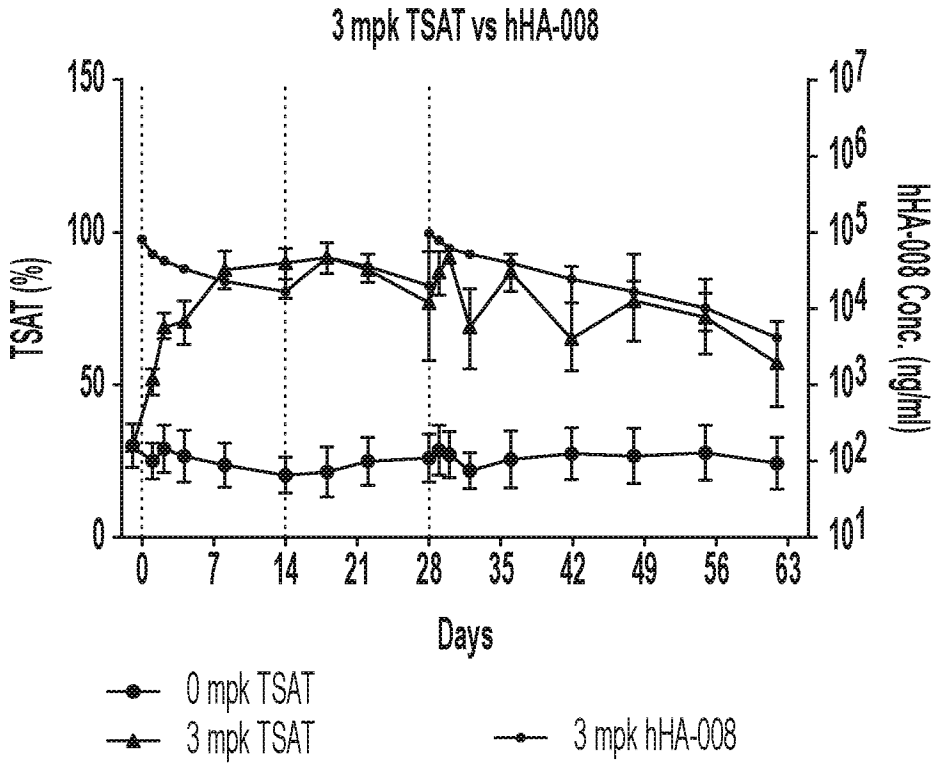

3 mpk TSAT vs hHA-008
TSAT (%)
hHA-008 Conc. (ng/ml)
Days
0 mpk TSAT
3 mpk TSAT
3 mpk hHA-008

FIG. 8B

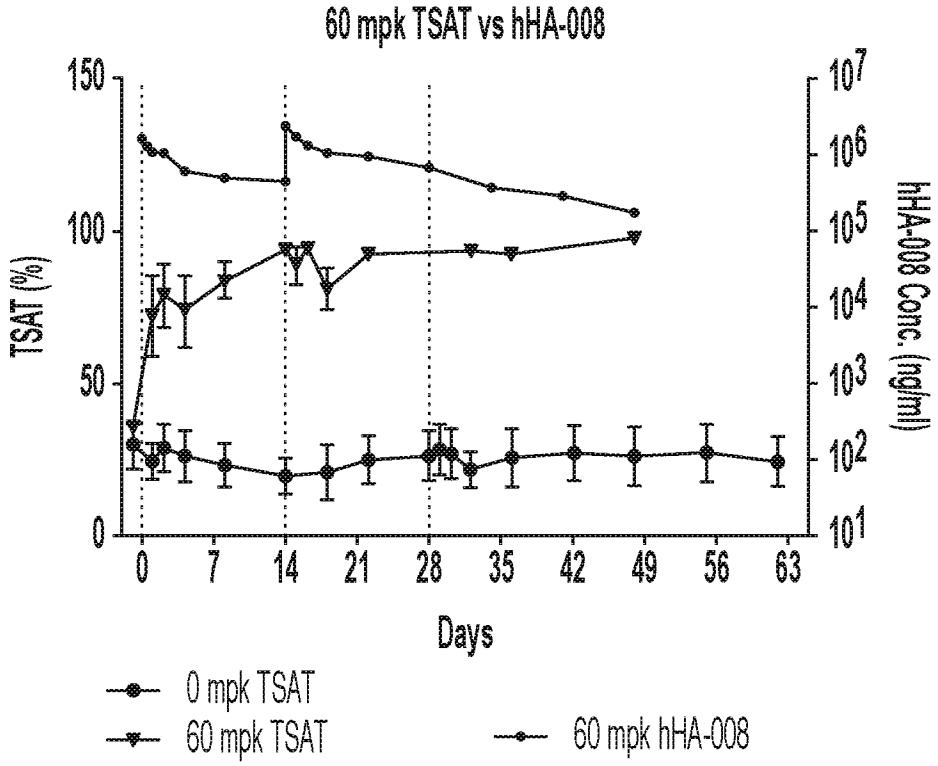

60 mpk TSAT vs hHA-008
TSAT (%)
hHA-008 Conc. (ng/ml)
Days
0 mpk TSAT
60 mpk TSAT
60 mpk hHA-008

FIG. 8C

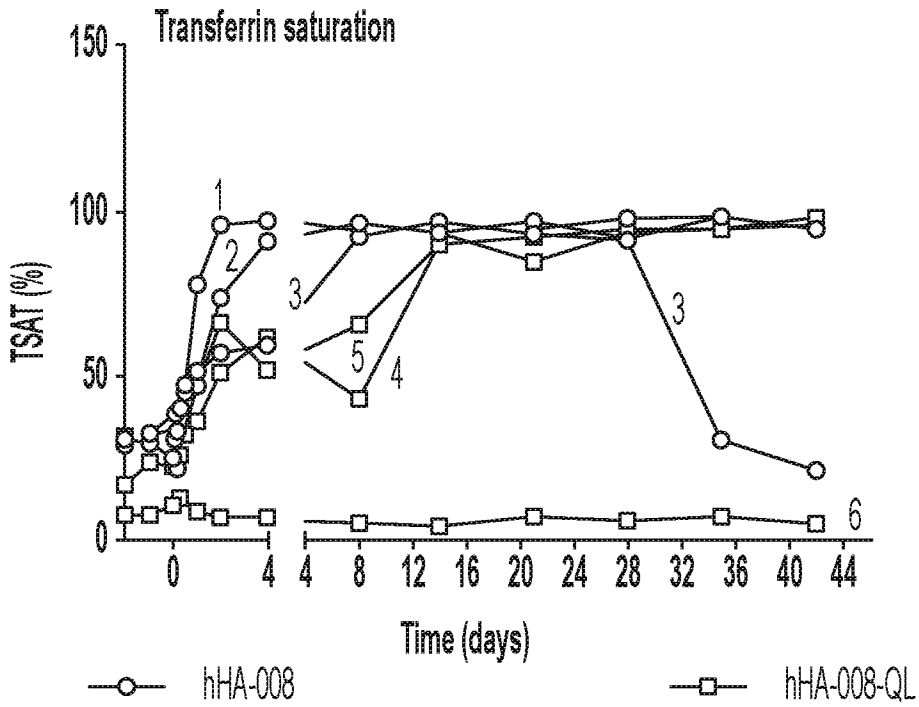

Transferrin saturation
150
100
50
0
TSAT (%)
1
2
3
5
4
3
6
0
4
4
8
12
16
20
24
28
32
36
40
44
Time (days)
hHA-008
hHA-008-QL

FIG. 9A

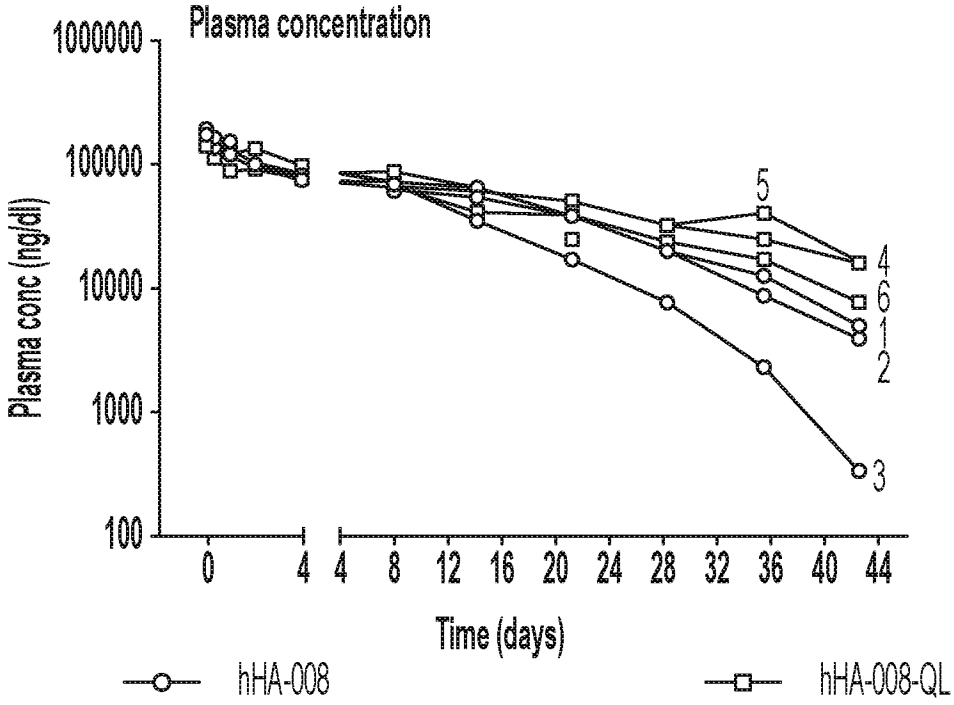

Plasma concentration
1000000
100000
10000
1000
100
Plasma conc (ng/dl)
5
4
6
1
2
3
0
4
4
8
12
16
20
24
28
32
36
40
44
Time (days)
hHA-008
hHA-008-QL

FIG. 9B

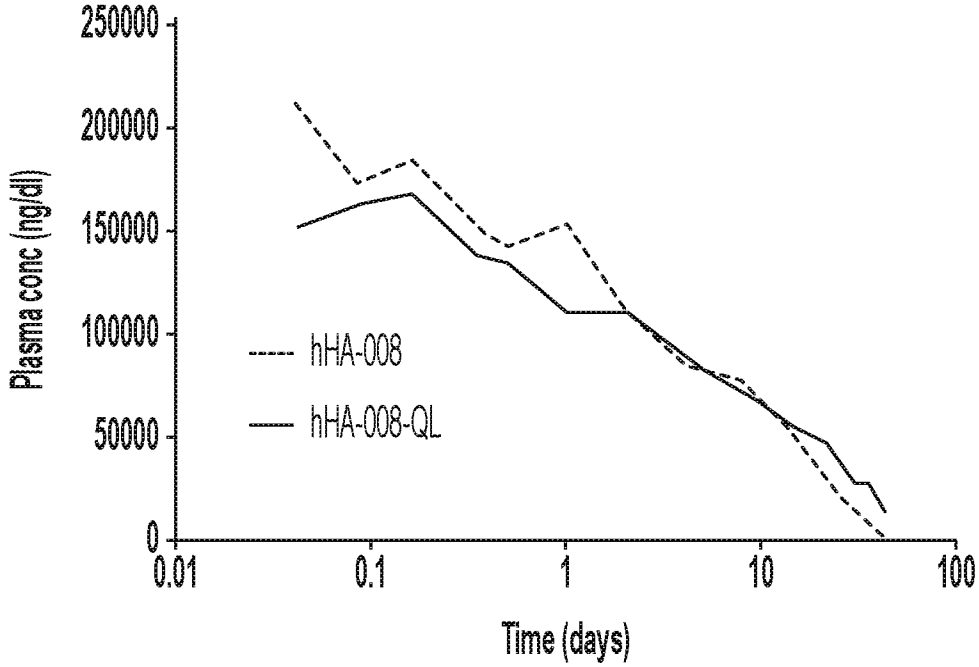

250000
200000
150000
100000
50000
0
Plasma conc (ng/dl)
hHA-008
hHA-008-QL
0.01
0.1
1
10
100
Time (days)

FIG. 9C

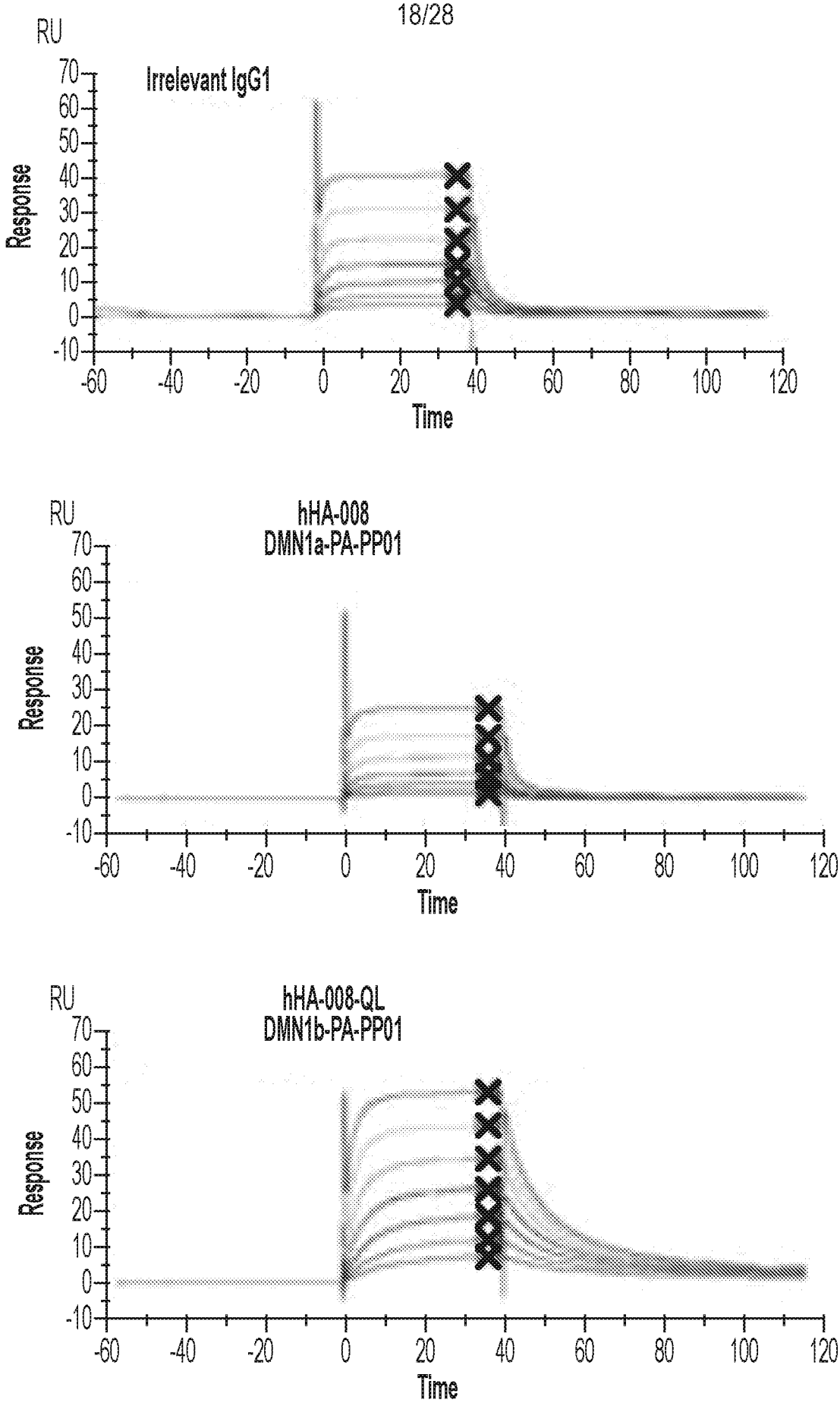

RU
Irrelevant IgG1
Response
Time
RU
hHA-008
DMN1a-PA-PP01
Response
Time
RU
hHA-008-QL
DMN1b-PA-PP01
Response
Time

FIG. 10A

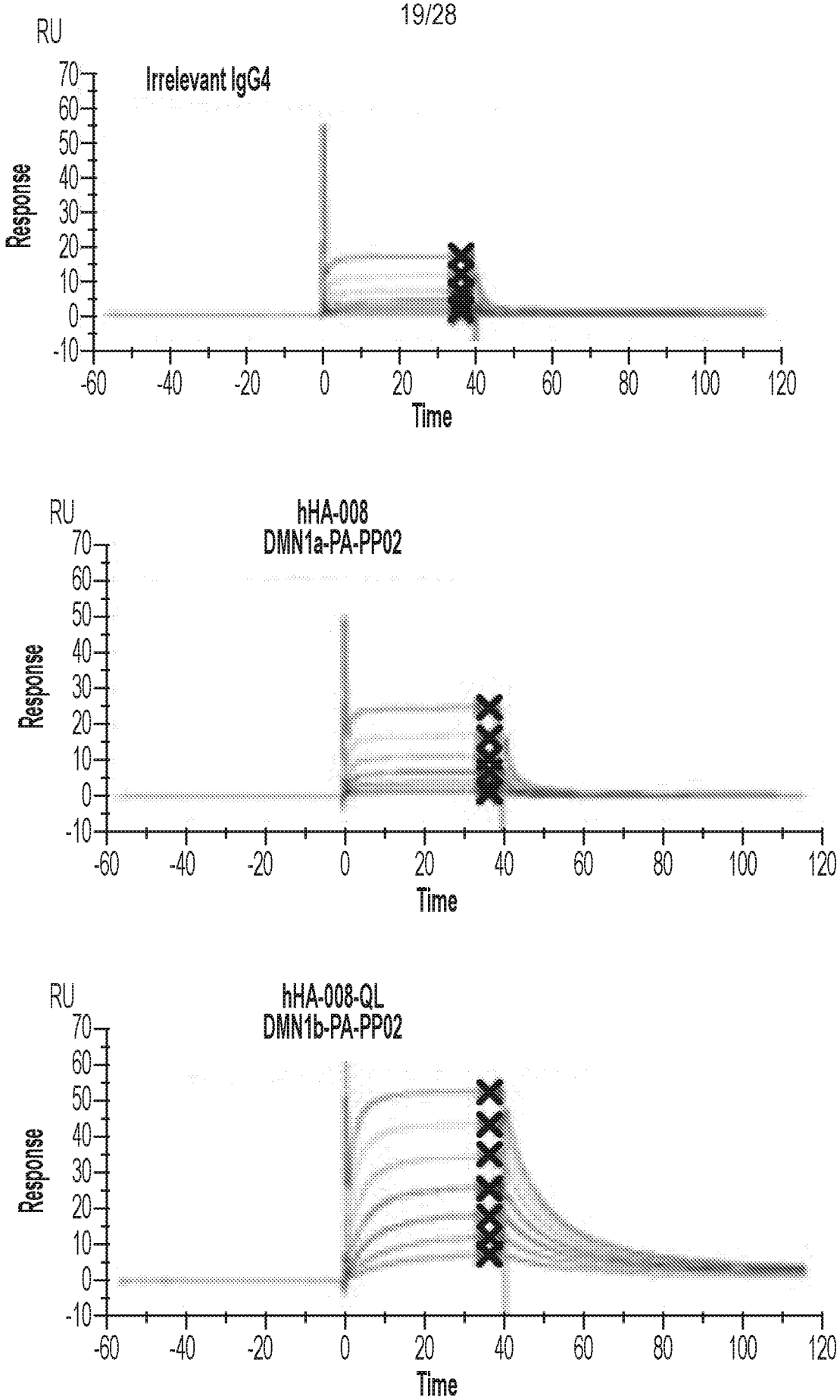
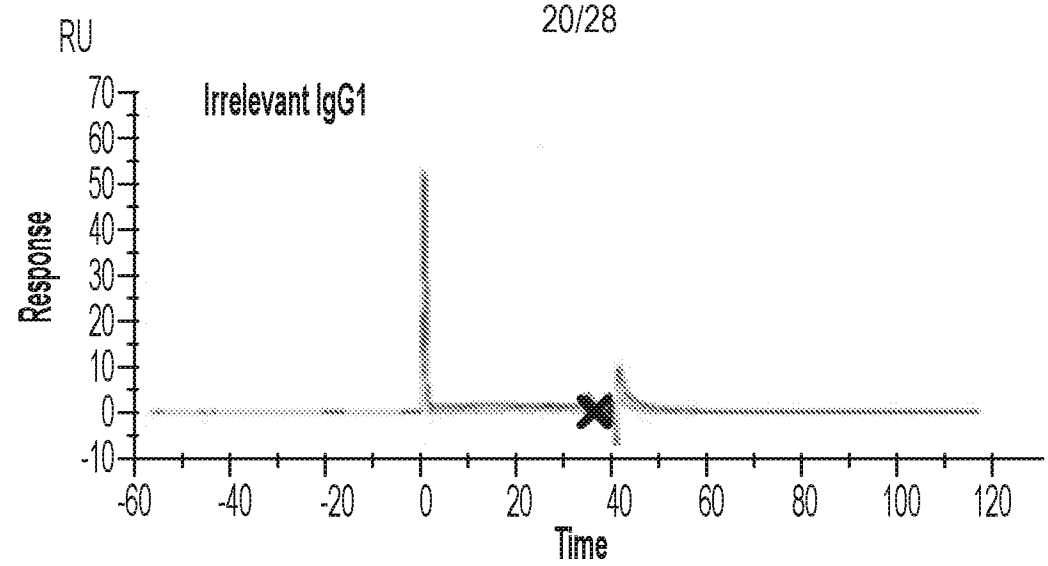
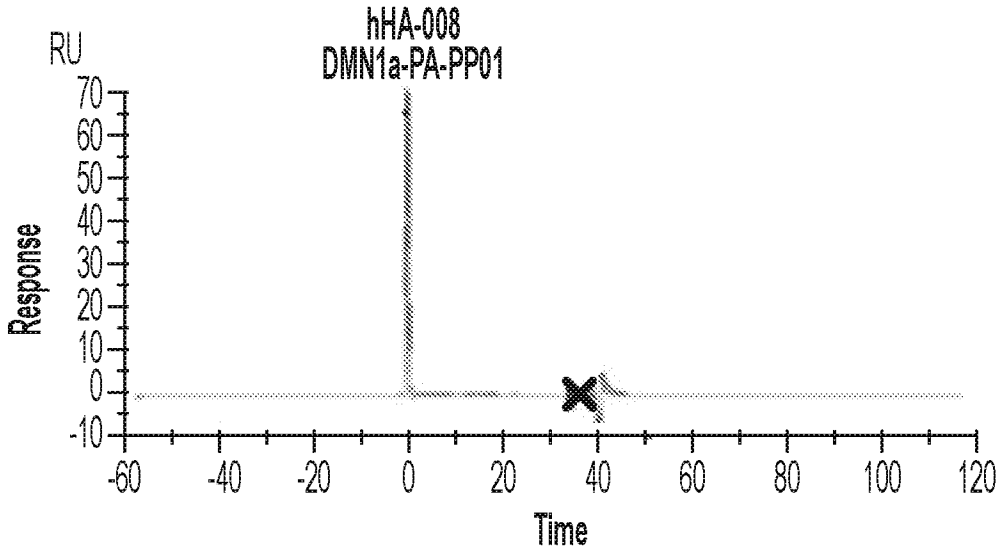


FIG. 10A
CONTINUED


RU
Irrelevant IgG1
Response
70
60
50
40
30
20
10
0
-10
-60
-40
-20
0
20
40
60
80
100
120
Time


RU
hHA-008
DMN1a-PA-PP01
Response
70
60
50
40
30
20
10
0
-10
-60
-40
-20
0
20
40
60
80
100
120
Time

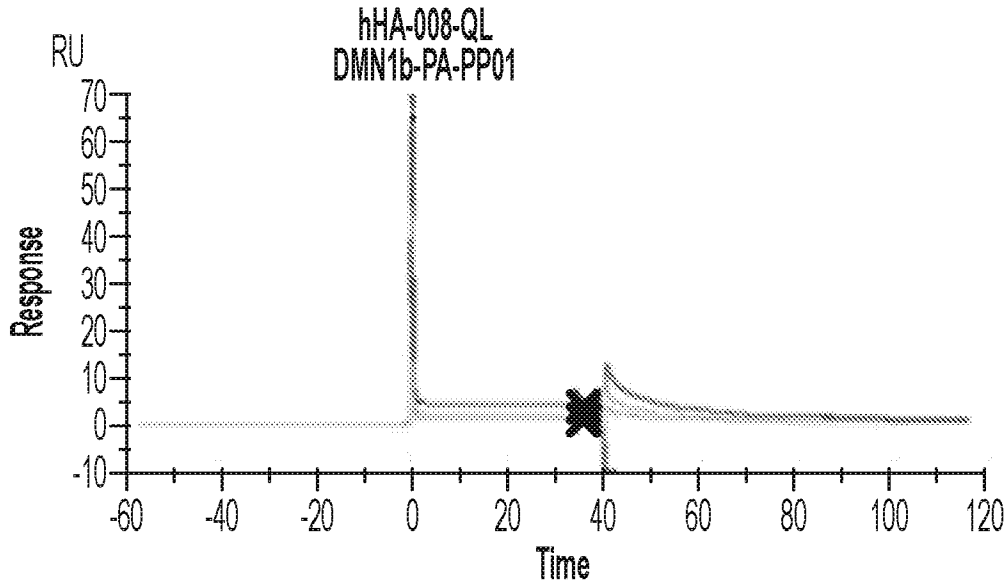

RU
hHA-008-QL
DMN1b-PA-PP01
Response
70
60
50
40
30
20
10
0
-10
-60
-40
-20
0
20
40
60
80
100
120
Time

FIG. 10B

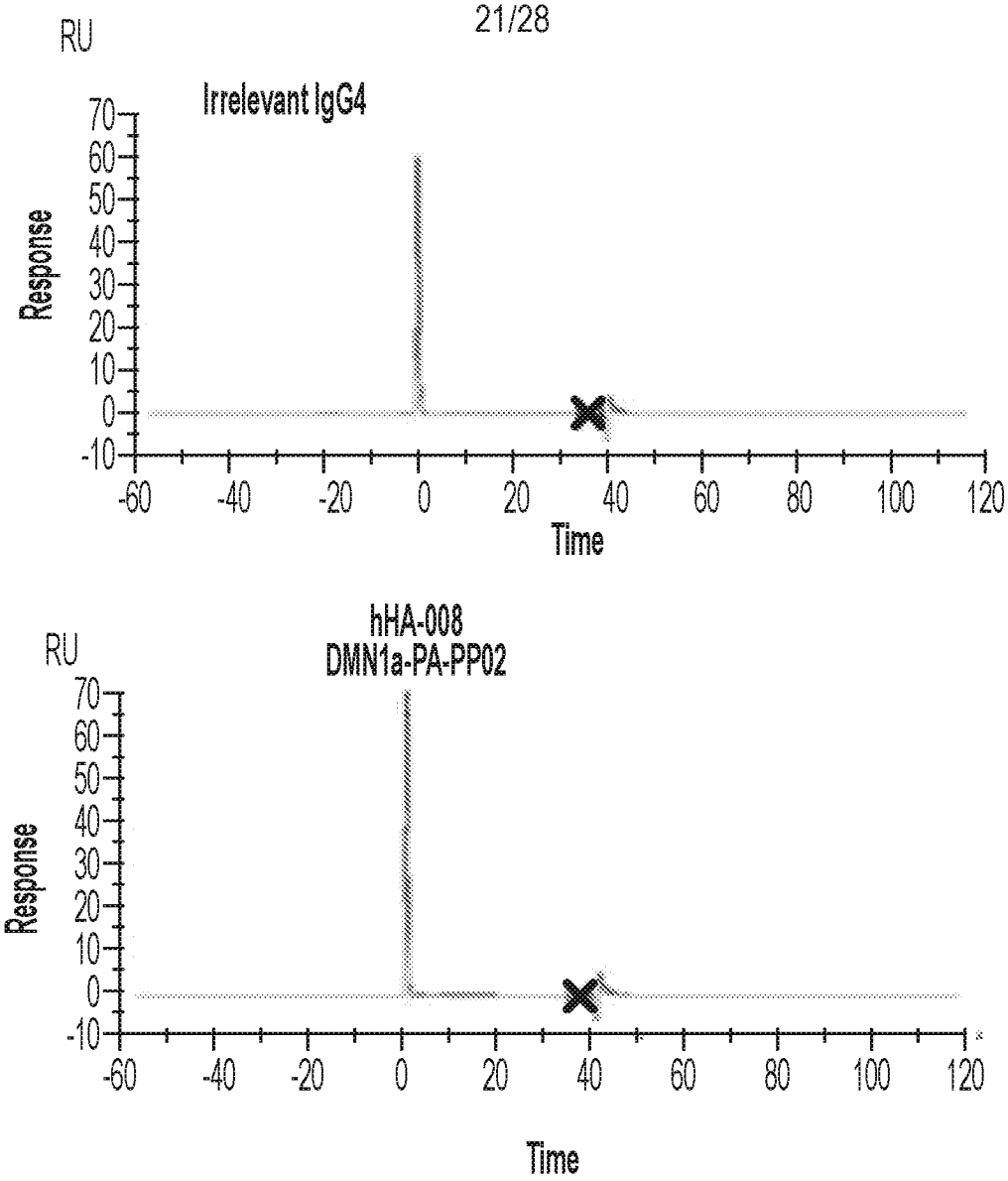


FIG. 10B
CONTINUED

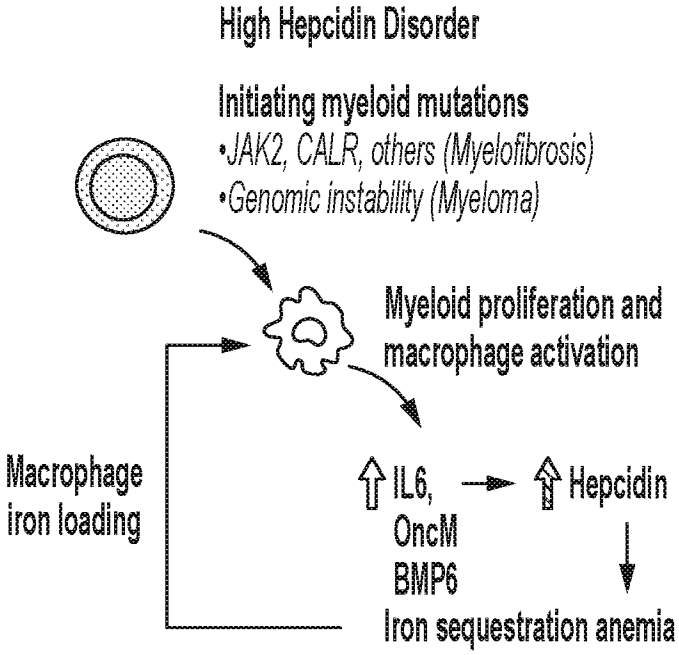

High Hepcidin Disorder
Initiating myeloid mutations
•JAK2, CALR, others (Myelofibrosis)
•Genomic instability (Myeloma)
Myeloid proliferation and macrophage activation
Macrophage iron loading
IL6, OncM BMP6
Hepcidin
Iron sequestration anemia

FIG. 11

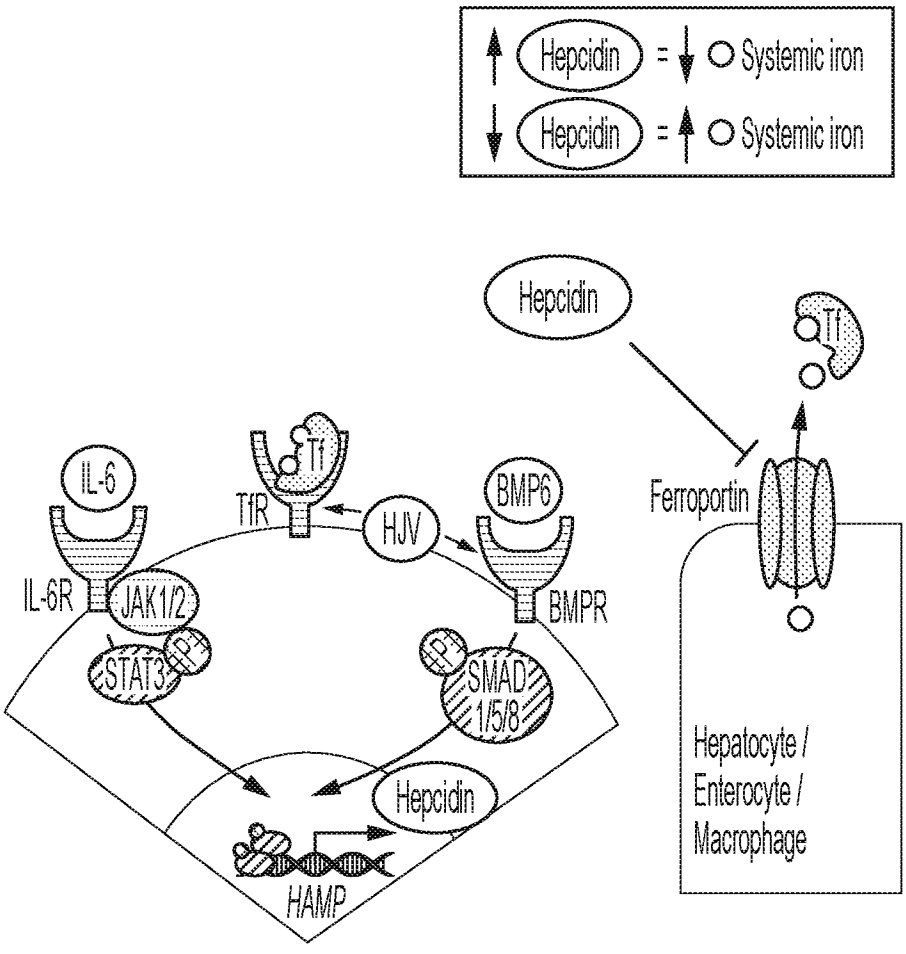

Hepcidin = Systemic iron
Hepcidin = Systemic iron
Hepcidin
Tf
IL-6
TfR
HJV
BMP6
Ferroportin
IL-6R
JAK1/2
BMPR
STAT3
SMAD 1/5/8
Hepcidin
HAMP
Hepatocyte / Enterocyte / Macrophage

FIG. 12

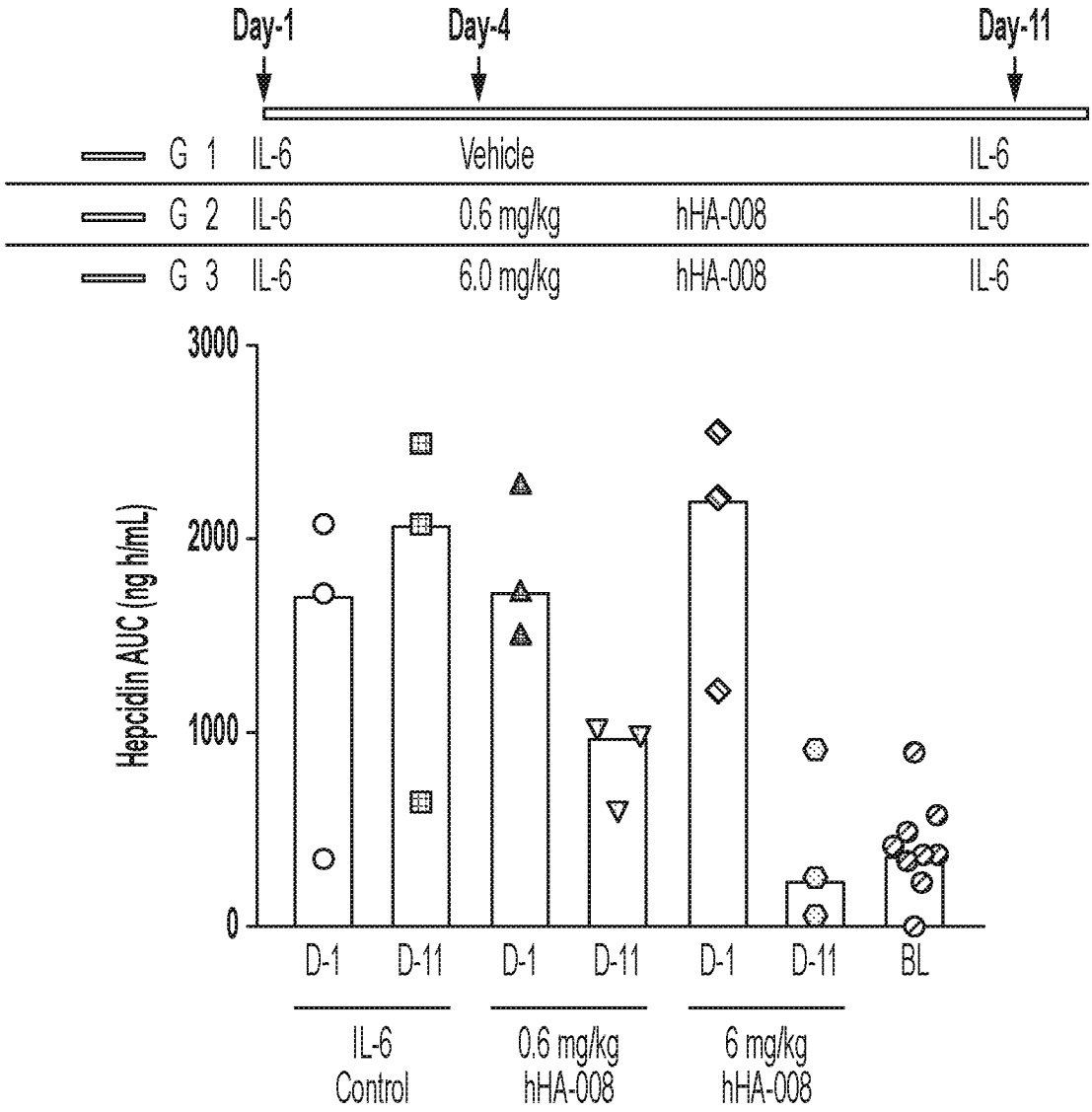

Day-1
Day-4
Day-11
G 1 IL-6 Vehicle IL-6
G 2 IL-6 0.6 mg/kg hHA-008 IL-6
G 3 IL-6 6.0 mg/kg hHA-008 IL-6
Hepcidin AUC (ng h/mL)
3000
2000
1000
0
D-1
D-11
D-1
D-11
D-1
D-11
BL
IL-6 Control
0.6 mg/kg hHA-008
6 mg/kg hHA-008

FIG. 13

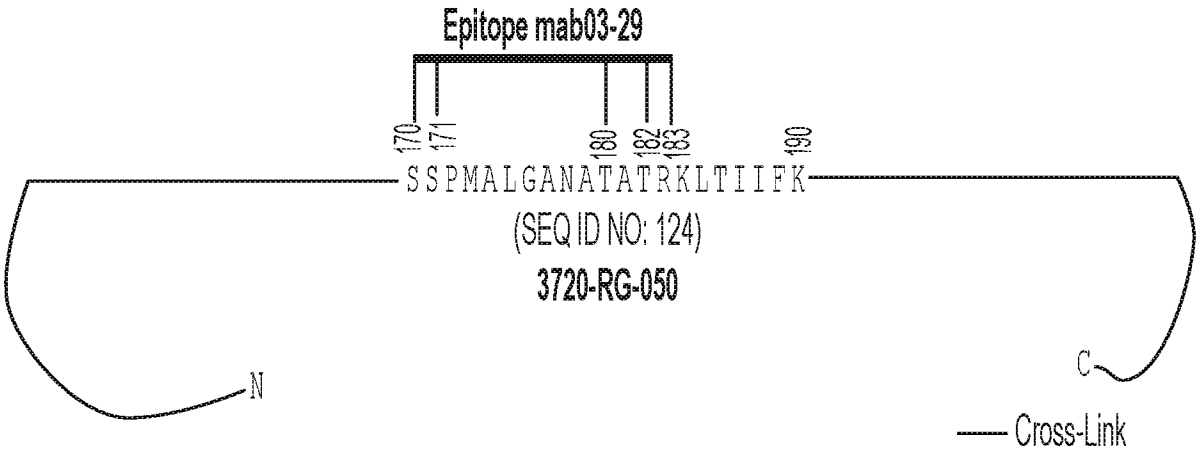


FIG. 14



FIG. 15A



FIG. 15B



FIG. 15C



FIG. 15D



FIG. 15E



FIG. 15F

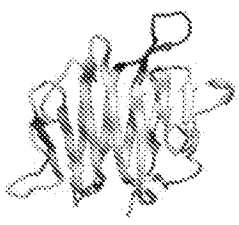


FIG. 15G



FIG. 15H



FIG. 15I



FIG. 15J

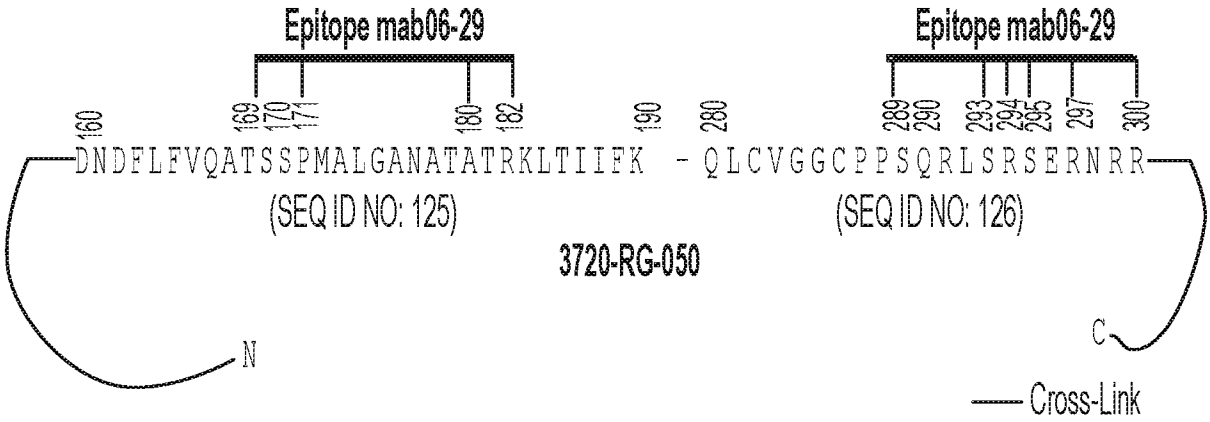


FIG. 16



FIG. 17A

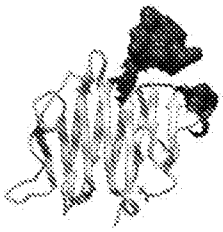


FIG. 17B



FIG. 17C



FIG. 17D



FIG. 17E

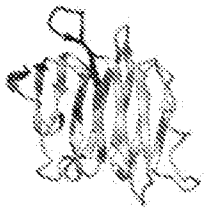


FIG. 17F

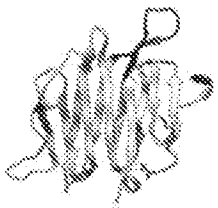


FIG. 17G



FIG. 17H



FIG. 17I



FIG. 17J

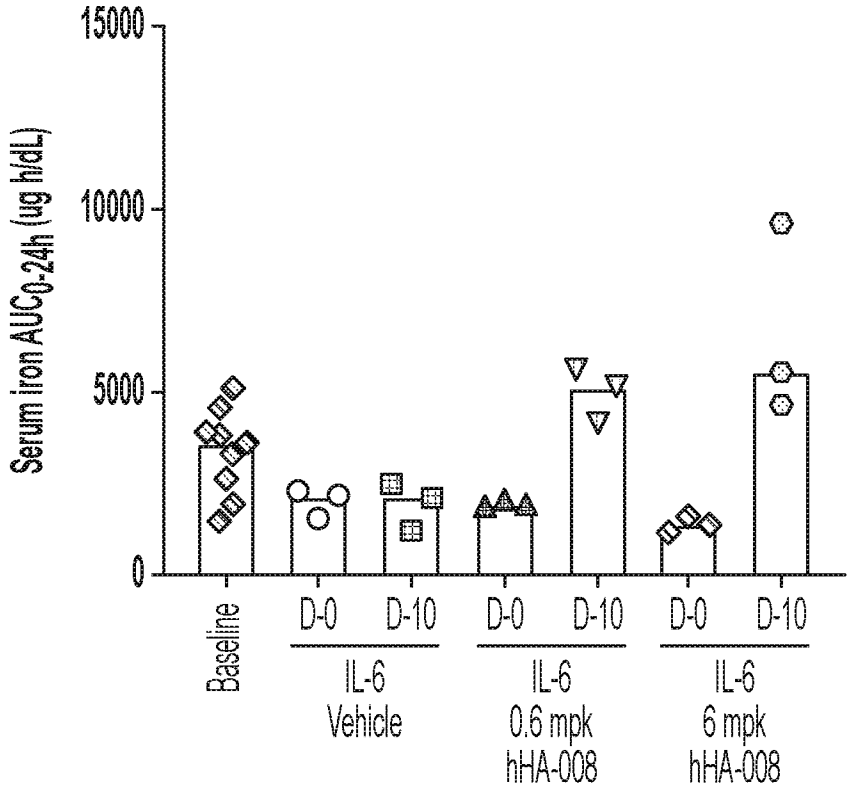

15000
10000
5000
0
Serum iron AUC0-24h (ug h/dL)
Baseline
D-0
D-10
D-0
D-10
D-0
D-10
IL-6
Vehicle
IL-6
0.6 mpk
hHA-008
IL-6
6 mpk
hHA-008

FIG. 18

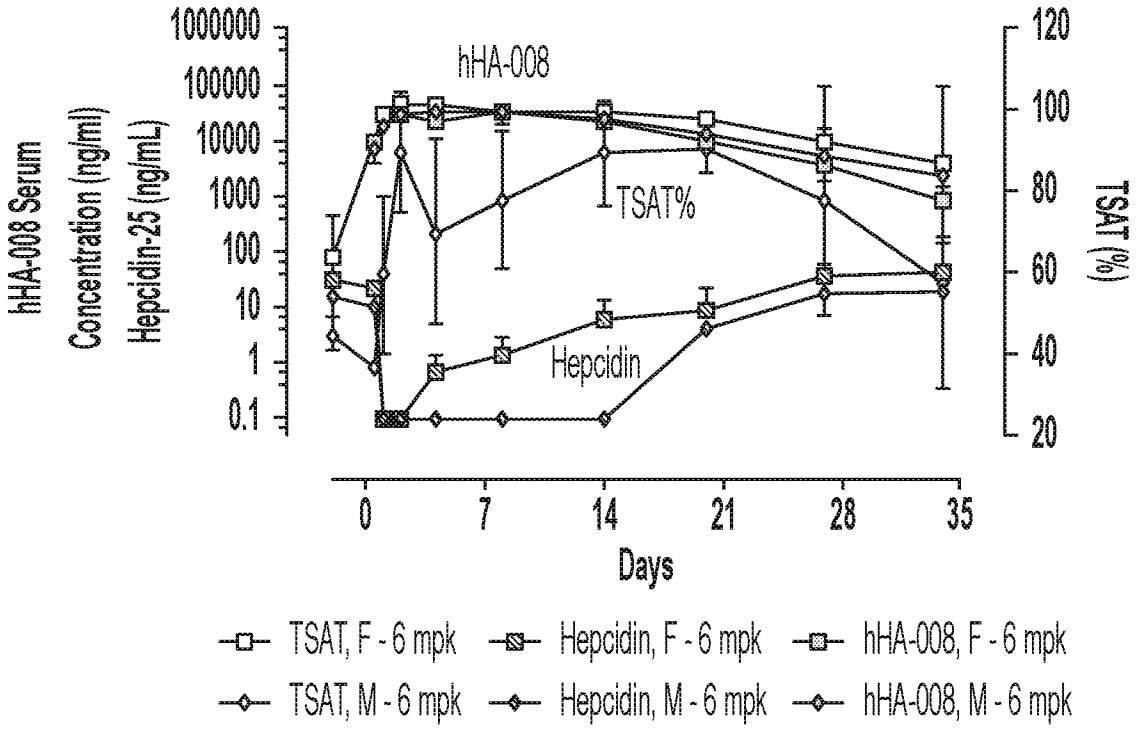

hHA-008 Serum
Concentration (ng/ml)
Hepcidin-25 (ng/mL)
1000000
100000
10000
1000
100
10
1
0.1
hHA-008
TSAT%
Hepcidin
120
100
80
60
40
20
TSAT (%)
0
7
14
21
28
35
Days
TSAT, F - 6 mpk
Hepcidin, F - 6 mpk
hHA-008, F - 6 mpk
TSAT, M - 6 mpk
Hepcidin, M - 6 mpk
hHA-008, M - 6 mpk

FIG. 19

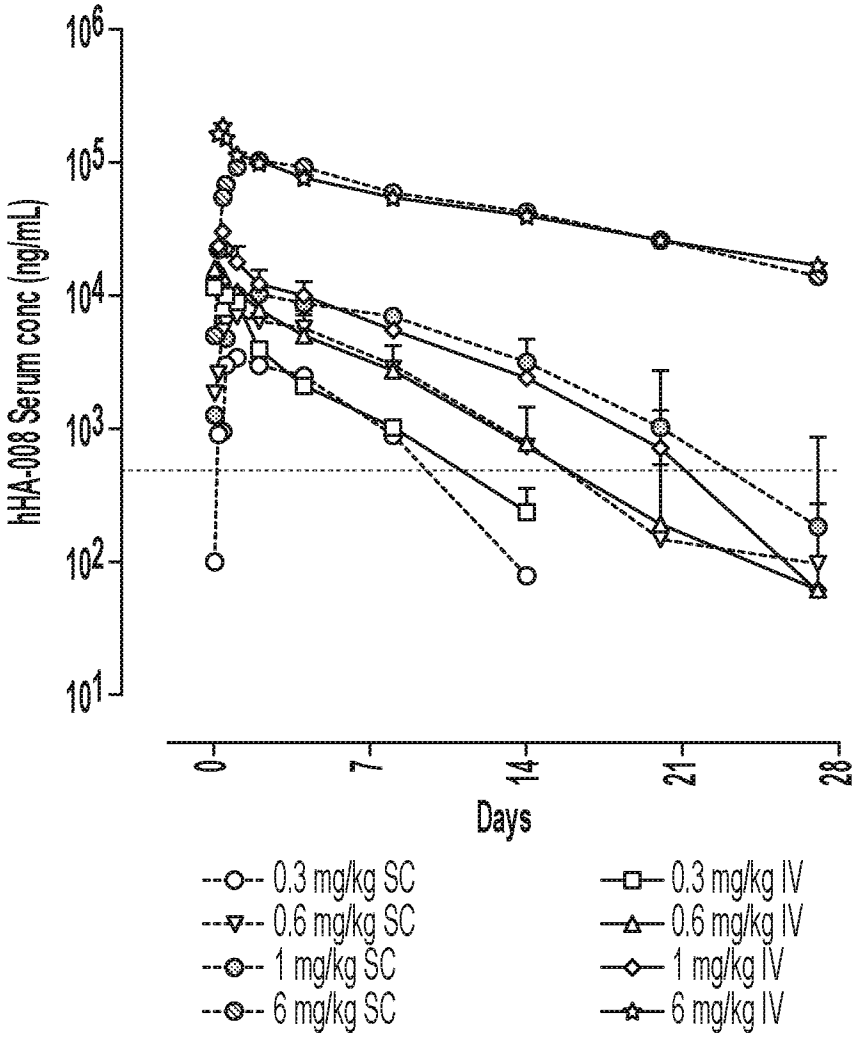


FIG. 20A

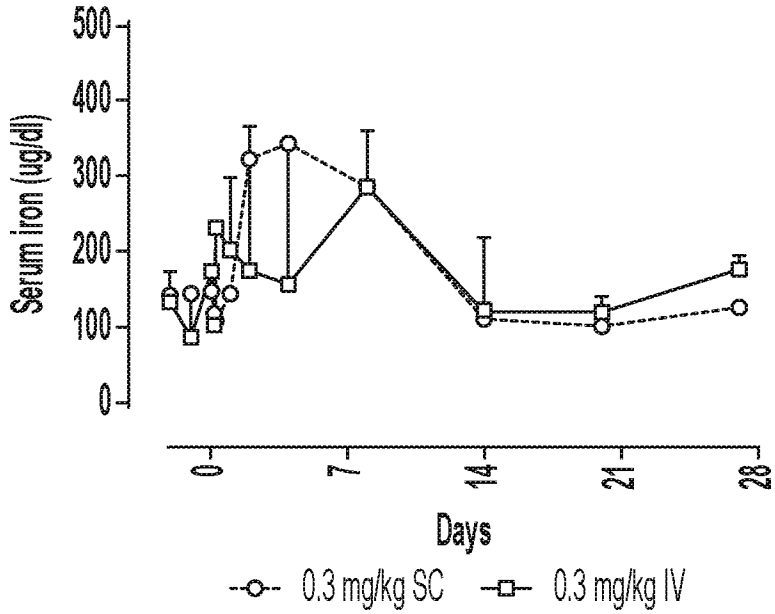


FIG. 20B

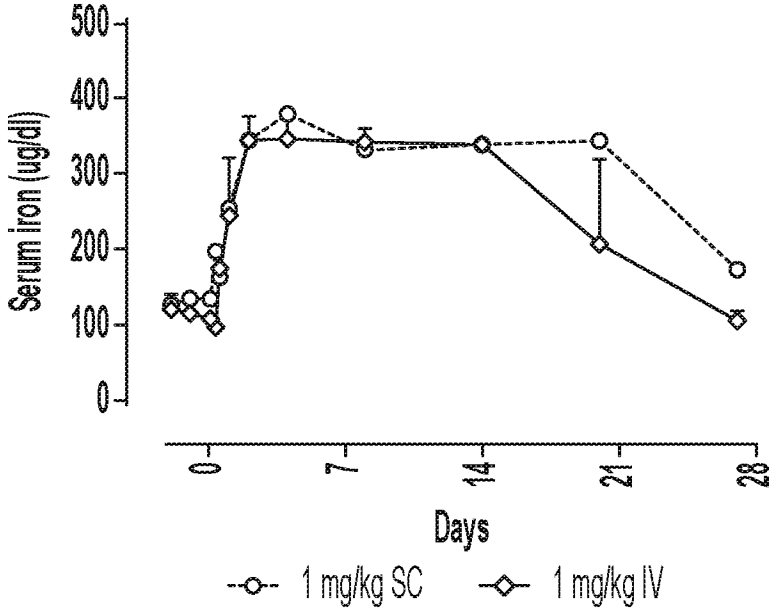


FIG. 20C

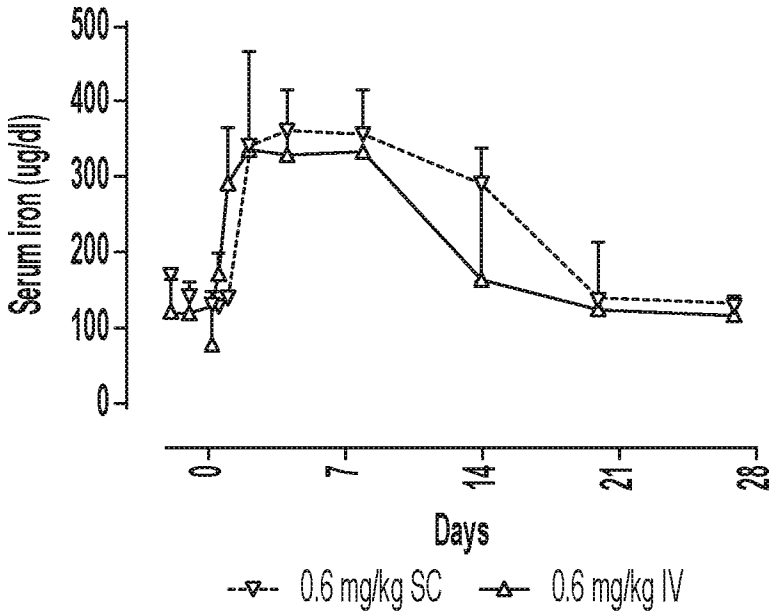


FIG. 20D

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US21/32343

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 39/395; C07K 16/28; A61P 35/00 (2021.01)

CPC - A61K 39/3955; C07K 16/28; A61P 35/00; A61K 2039/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2020/086736 A1 (SCHOLAR ROCK, INC.) 30 April 2020; paragraphs [158], [276], [313]-[314], [316], [320]-[321], [363]	1-4
Y	WO 2013/090635 A2 (ABBVIE DEUTSCHLAND GMBH & CO. KG) 20 June 2013; paragraphs [0004]-[0005], [0008], [0046]-[0048], [00107], [00109]	1-4
A	ZHOU. "Hepcidin Is Elevated in Primary and Secondary Myelofibrosis and Correlates with IL-6 and IL-2R but Is High in Patients Treated with Ruxolitinib" 1760. Blood. Vol. 132, Supplement 1.. Web. 29 November 2018; Entire Document; DOI: 10.1182/blood-2018-99-113661	1-4
A	KOVAC. "Anti-hemojuvelin antibody corrects anemia caused by inappropriately high hepcidin levels" e173-e176. Haematologica. Vol. 101, No. 5.. Web. May 2016; Entire Document; DOI: 10.3324/haematol.2015.140772	1-4
P,X	WO 2021/062163 A1 (DISC MEDICINE, INC.) 01 April 2021; Entire Document	1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 September 2021 (24.09.2021)	OCT 29 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

Form PCT/ISA/210 (second sheet) (July 2019)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US21/32343

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US21/32343

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-18, 30, 35-46, 52
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
-***-Please See Supplemental Page-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
-***-Please See Supplemental Page-***-

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

-***-Continued From Box No. III: Observations where unity of invention is lacking-***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-4, 19-29, 31-34, 47-51, an antibody comprising an HC CDR1 encompassing SEQ ID NO: 1 (HC CDR1), an HC CDR2 encompassing SEQ ID NO: 2 (HC CDR2), and an HC CDR3 encompassing SEQ ID NO: 3 (HC CDR3); and an LC CDR1 encompassing SEQ ID NO: 108, wherein X5 is A, X6 is T, X7 is D, and X8 is E (LC CDR1); an LC CDR2 encompassing SEQ ID NO: 18 (LC CDR2) and an LC CDR3 encompassing SEQ ID NO: 110, wherein X11 is F, X12 is V, X13 is H, X14 is M, and X15 is T (LC CDR3) are directed toward methods of treating subjects having myelofibrosis, and antibodies therefor, wherein the antibodies bind to human hemojuvelin.

The methods and antibodies will be searched to the extent they encompass an HC CDR1 encompassing SEQ ID NO: 1 (first exemplary HC CDR1) [wherein SEQ ID NO: 1 meets the first set of restrictions indicated in SEQ ID NO: 105], an HC CDR2 encompassing SEQ ID NO: 2 (first exemplary HC CDR2) [wherein SEQ ID NO: 2 meets the first set of restrictions indicated in SEQ ID NO: 106], and an HC CDR3 encompassing SEQ ID NO: 3 (first exemplary HC CDR3) [wherein SEQ ID NO: 3 meets the first set of restrictions indicated in SEQ ID NO: 107]; and an LC CDR1 encompassing SEQ ID NO: 108, wherein X5 is A, X6 is T, X7 is D, and X8 is E (first exemplary LC CDR1); an LC CDR2 encompassing SEQ ID NO: 18 (first exemplary LC CDR2) [wherein SEQ ID NO: 18 meets the first set of restrictions indicated in SEQ ID NO: 109] and an LC CDR3 encompassing SEQ ID NO: 110, wherein X11 is F, X12 is V, X13 is H, X14 is M, and X15 is T (first exemplary LC CDR3). Applicant is invited to elect additional antibody(ies), with, where applicable, specified set(s) of sequence(s) associated therewith, including specified set(s) of heavy and light chain(s), specified set(s) of heavy and light chain variable region(s), and specified set(s) of CDR(s), with specified SEQ ID NO: for each, or with specified substitution(s) at specified site(s) of a SEQ ID NO:, such that the sequence of each elected species is fully specified (i.e. no optional or variable residues or substituents), and where available as an option within at least one searchable claim, to be searched. Additional antibody(ies) and associated sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1-4 (each in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass an antibody comprising an HC CDR1 encompassing SEQ ID NO: 1 (HC CDR1), an HC CDR2 encompassing SEQ ID NO: 2 (HC CDR2), and an HC CDR3 encompassing SEQ ID NO: 3 (HC CDR3); and an LC CDR1 encompassing SEQ ID NO: 108, wherein X5 is A, X6 is T, X7 is D, and X8 is E (LC CDR1); an LC CDR2 encompassing SEQ ID NO: 18 (LC CDR2) and an LC CDR3 encompassing SEQ ID NO: 110, wherein X11 is F, X12 is V, X13 is H, X14 is M, and X15 is T (LC CDR3). Applicants must specify the searchable claims that encompass any additionally elected antibody(ies) and associated sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be an antibody comprising an HC CDR1 encompassing SEQ ID NO: 9 (HC CDR1) [wherein SEQ ID NO: 9 meets the second set of restrictions indicated in SEQ ID NO: 105], an HC CDR2 encompassing SEQ ID NO: 2 (HC CDR2), and an HC CDR3 encompassing SEQ ID NO: 3 (HC CDR3); and an LC CDR1 encompassing SEQ ID NO: 108, wherein X5 is A, X6 is T, X7 is D, and X8 is E (LC CDR1); an LC CDR2 encompassing SEQ ID NO: 18 (LC CDR2) and an LC CDR3 encompassing SEQ ID NO: 110, wherein X11 is F, X12 is V, X13 is H, X14 is M, and X15 is T (LC CDR3).

No technical features are shared between the antibody sequences of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including: 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 and inhibits 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; 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; 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.

However, these shared technical features are previously disclosed by WO 2020/086736 A1 to Scholar Rock, Inc (hereinafter 'Scholar'), in view of US 2013/0330343 A1 to AbbVie Deutschland GmbH & co. KG, et al. (hereinafter 'AbbVie').

Scholar discloses a method of treating a subject having myelofibrosis (a method of treating a subject having myelofibrosis; paragraph [321]), the method comprising: administering to the subject (the method comprising: administering to the subject; paragraph [321]), by subcutaneous administration (by subcutaneous administration; paragraph [0355]; Claim 59), an effective amount of the isolated antibody that binds to and inhibits human hemojuvelin (HJV) (an effective amount of the isolated antibody that binds to and inhibits human RGMc (hemojuvelin); paragraph [321]), wherein the antibody comprises: a heavy chain complementary determining region 1 (wherein the antibody comprises: a heavy chain complementary determining region 1; paragraph [67]), a heavy chain complementary determining region 2 (a heavy chain complementary determining region 2; paragraph [67]), and a heavy chain complementary determining region 3 (a heavy chain complementary determining region 3; paragraph [67]); and a light chain complementary determining region 1; paragraph [67]), a light chain complementary determining region 2 (a light chain complementary determining region 2; paragraph [67]), and a light chain complementary determining region 3 (a light chain complementary determining region 3; paragraph [67]); an isolated antibody that binds to human hemojuvelin (HJV), wherein the antibody comprises a VH and/or a VL (an isolated antibody that binds to human RGMc (hemojuvelin), wherein the antibody comprises a VH and/or a VL; paragraph [24]); a method of reducing hepcidin-25 in a subject (a

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from previous Supplemental Box-***-

method of reducing hepcidin-25 in a subject; paragraph [33]) having myelofibrosis (having myelofibrosis; paragraph [321]), the method comprising: administering to the subject an effective amount of the isolated antibody that binds to human hemojuvelin (HJV) (the method comprising: administering to the subject an effective amount of the isolated antibody that binds to human RGMc (hemojuvelin); paragraphs [33], [321])

Scholar does not disclose 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; and 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.

AbbVie discloses an antibody which binds to RGMc (an antibody which binds to RGMc; paragraph [0006]), wherein the antibody comprises an amino acid sequence of SEQ ID NO: 38 (wherein the antibody comprises an HCDR1 with SEQ ID NO: 11 (a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 38); paragraph [0006], SEQ ID NO: 11, wherein SEQ ID NO: 11 is 100% identical to residues 31-35 of SEQ ID NO: 38, and thus is '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 (and a LCDR1 (a light chain variable region) with SEQ ID NO: 20 (an amino acid sequence of SEQ ID NO: 39); paragraph [0006], wherein SEQ ID NO: 20 is identical to residues 24-39 of SEQ ID NO: 39 , and thus is 'an amino acid sequence of SEQ ID NO: 39'); and wherein the antibody comprises: a heavy chain complementary determining region 1 (HC CDR1) set forth as NYGMN (wherein the antibody comprises: a heavy chain complementary determining region 1 set forth as SEQ ID NO: 11 (NYGMN); paragraph [0006]; wherein SEQ ID NO: 11 is identical to the sequence NYGMN); a heavy chain complementary determining region 2 (HC CDR2) set forth as MIYYDSSEKHYADSVKG (wherein the antibody comprises: a heavy chain complementary determining region 2 set forth as SEQ ID NO: 12 (MIYYDSSEKHYADSVKG); paragraph [0006]; wherein SEQ ID NO: 12 is identical to the sequence MIYYDSSEKHYADSVKG); a heavy chain complementary determining region 3 (HC CDR3) set forth as GTTPDY (wherein the antibody comprises: a heavy chain complementary determining region 2 set forth as SEQ ID NO: 13 (GTTPDY); paragraph [0006], wherein SEQ ID NO: 13 is identical to the sequence GTTPDY); and/or a light chain complementary determining region 1 (LC CDR1) set forth as RSSQSLEESDGYTFLH (a light chain complementary determining region 1 set forth as SEQ ID NO: 20 (RSSQSLEESDGYTFLH); paragraph [0006], wherein SEQ ID NO: 20 is identical to the sequence RSSQSLEESDGYTFLH), a light chain complementary determining region 2 (LC CDR2) set forth as X9VSX10RFS (a light chain complementary determining region 2 set forth as SEQ ID NO: 21 (EVSTRFS); paragraph [0006], wherein SEQ ID NO: 21 is identical to the sequence EVSTRFS), and a light chain complementary determining region 3 (LC CDR3) set forth as FQATHDPLT (a light chain complementary determining region 3 set forth as SEQ ID NO: 22 (FQATHDPLT); paragraph [0006], wherein SEQ ID NO: 22 is identical to the sequence FQATHDPLT).

it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the disclosure of Scholar to have used an anti-human RGMc antibody comprising the sequences disclosed by AbbVie in order to identify and utilize a therapeutic antibody agent with superior affinity, lifetime, or other desirable pharmacokinetic parameters.

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Scholar and AbbVie references, unity of invention is lacking.

-***-Continued From Box III: Item IV-***-

Groups I+, Claims 1-4, 19-29, 31-34, 47-51, an antibody comprising an HC CDR1 encompassing SEQ ID NO: 1 (HC CDR1), an HC CDR2 encompassing SEQ ID NO: 2 (HC CDR2), and an HC CDR3 encompassing SEQ ID NO: 3 (HC CDR3); and an LC CDR1 encompassing SEQ ID NO: 108, wherein X5 is A, X6 is T, X7 is D, and X8 is E (LC CDR1); an LC CDR2 encompassing SEQ ID NO: 18 (LC CDR2) and an LC CDR3 encompassing SEQ ID NO: 110, wherein X11 is F, X12 is V, X13 is H, X14 is M, and X15 is T (LC CDR3)