

WHAT IS CLAIMED IS:

1. ~~A method of treating a hepcidin-mediated disorder, comprising:~~
administering Use of a therapeutically effective amount of an anti-IL-6 antibody
~~antagonist to a patient with a hepcidin-mediated disorder, in the manufacture of a~~
medicament for treating cardiovascular disease in a subject,
wherein the ~~patient has been determined to have~~ subject has at least one copy of the *TMPRSS6* rs855791 major allele.
2. ~~The method of claim 1, wherein the patient has previously been determined to have at least one copy of the *TMPRSS6* rs855791 major allele.~~
3. ~~The method of claim 1, further comprising the earlier step of:~~
~~determining that the patient has at least one copy of the *TMPRSS6* rs855791 major allele.~~
4. ~~The method of any one of claims 1–3, wherein the patient has elevated pre-treatment serum levels of IL-6.~~
5. ~~The method of any one of claims 1–4, wherein the patient has elevated pre-treatment serum levels of CRP.~~
6. ~~The method of any one of claims 1–5, wherein the hepcidin-mediated disorder is an anemia of chronic disease.~~
7. ~~The method of claim 6, wherein the patient is male and has a pre-treatment hemoglobin (Hb) level of less than 14 g/dl.~~
8. ~~The method of claim 7, wherein the patient has a pre-treatment Hb level of less than 13 g/dl.~~
9. ~~The method of claim 8, wherein the patient has a pre-treatment Hb level of less than 12 g/dl.~~

~~10. The method of claim 9, wherein the patient has a pre-treatment Hb level of less than 11 g/dl.~~

~~11. The method of claim 6, wherein the patient is female and has a pre-treatment Hb level of less than 12 g/dl.~~

~~12. The method of claim 11, wherein the patient has a pre-treatment Hb level of less than 11 g/dl.~~

~~13. The method of claim 12, wherein the patient has a pre-treatment Hb level of less than 10 g/dl.~~

~~14. The method of claim 13, wherein the patient has a pre-treatment Hb level of less than 9 g/dl.~~

~~15. The method of any one of claims 6-10, wherein the patient is male and has a pre-treatment hematocrit of less than 40%.~~

~~16. The method of claim 15, wherein the patient has a pre-treatment hematocrit of less than 35%.~~

~~17. The method of claim 16, wherein the patient has a pre-treatment hematocrit of 30-34%.~~

~~18. The method of any one of claims 6, 11-14, wherein the patient has a pre-treatment hematocrit of less than 36%.~~

~~19. The method of claim 18, wherein the patient has a pre-treatment hematocrit of less than 30%.~~

~~20. The method of claim 19, wherein the patient has a pre-treatment hematocrit of 26-29%.~~

~~21. The method of any one of claims 6-20, wherein the patient has received at least one pre-treatment administration of an ESA.~~

~~22. — The method of claim 6, wherein the patient has received at least one pre-treatment administration of an ESA and has a normal Hb level or normal hematocrit.~~

~~23. — The method of any one of claims 6 — 20, wherein the patient has received at least one pre-treatment administration of an iron supplement.~~

~~24. — The method of claim 6, wherein the patient has received at least one pre-treatment administration of an iron supplement and has a normal Hb level or normal hematocrit.~~

~~25. — The method of any one of claims 6 — 20, wherein the patient has received at least one pre-treatment transfusion of blood or packed red blood cells.~~

~~26. — The method of claim 6, wherein the patient has received at least one pre-treatment transfusion of blood or packed red blood cells and has a normal Hb level or normal hematocrit.~~

~~27. — The method of any one of claims 6 — 26, wherein the IL-6 antagonist is administered at a dose, on a schedule, and for a period sufficient to increase the patient's Hb levels above pre-treatment levels.~~

~~28. — The method of any one of claims 6 — 27, wherein the IL-6 antagonist is administered at a dose, on a schedule, and for a period sufficient to increase the patient's hematocrit above pre-treatment levels.~~

~~29. — The method of claim 21 or 22, wherein the IL-6 antagonist is administered at a dose, on a schedule, and for a period sufficient to allow reduction in the patient's dose of ESA without reduction in the patient's Hb levels below levels present immediately pre-treatment.~~

~~30. — The method of claim 21 or 22, wherein the IL-6 antagonist is administered at a dose, on a schedule, and for a period sufficient to allow reduction in the patient's dose of ESA without reduction in the patient's hematocrit below levels present immediately pre-treatment.~~

31. ~~— The method of any one of claims 21, 22, 29, or 30, wherein the IL-6 antagonist is administered at a dose, on a schedule, and for a period sufficient to allow at least a 10% reduction in the patient's dose of ESA as compared to pre-treatment ESA dose.~~

32. ~~— The method of claim 31, wherein the IL-6 antagonist is administered at a dose, on a schedule, and for a period sufficient to allow at least a 20% reduction in the patient's dose of ESA as compared to pre-treatment ESA dose.~~

33. ~~— The method of claim 32, wherein the IL-6 antagonist is administered at a dose, on a schedule, and for a period sufficient to allow at least a 50% reduction in the patient's dose of ESA as compared to pre-treatment ESA dose.~~

34. ~~— The method of any one of claims 6—33, wherein the IL-6 antagonist is administered at a dose, on a schedule, and for a period sufficient to reverse functional iron deficiency.~~

2. The use of claim 1, wherein the cardiovascular disease is atherosclerosis.

3. The use of claim 2, wherein the cardiovascular disease is inflammatory.

35.4. The method use of any one of claims 6—34 claim 1, wherein the chronic disease is subject has chronic kidney disease (CKD).

36.5. The method use of claim 35 4, wherein the patient subject has KDOQI stage 1 chronic kidney disease, KDOQI stage 2 chronic kidney disease, KDOQI stage 3 chronic kidney disease, KDOQI stage 4 chronic kidney disease, or KDOQI stage 5 chronic kidney disease.

6. The use of claim 4, wherein the subject has KDOQI stage 2 chronic kidney disease.

7. The use of claim 4, wherein the subject has KDOQI stage 3 chronic kidney disease.

8. The use of claim 4, wherein the subject has KDOQI stage 4 chronic kidney disease.

37.9. The ~~method~~ use of claim 36 ~~4~~, wherein the ~~patient~~ subject has KDOQI stage 5 chronic kidney disease.

~~38. The method of claim 35, wherein the patient has cardiorenal syndrome (CRS).~~

~~39. The method of claim 38, wherein the patient has CRS Type 4.~~

~~40. The method of any one of claims 35—39, wherein the patient has received at least one pre-treatment dialysis treatment.~~

~~41. The method of any one of claims 35—40, wherein the IL-6 antagonist is administered at a dose, on a schedule, and for a period sufficient to reduce cardiovascular (CV) mortality as compared to age-matched and disease-matched historical controls.~~

~~42. The method of any one of claims 6—34, wherein the chronic disease is a chronic inflammatory disease.~~

~~43. The method of claim 42, wherein the chronic inflammatory disease is rheumatoid arthritis (RA).~~

~~44. The method of claim 43, wherein the patient has a pre-treatment DAS28 score of greater than 5.1.~~

~~45. The method of claim 43, wherein the patient has a pre-treatment DAS28 score of 3.2 to 5.1.~~

~~46. The method of claim 43, wherein the patient has a pre-treatment DAS28 score of less than 2.6.~~

~~47. The method of claim 43, wherein the patient's pre-treatment RA is moderately active to severely active.~~

~~48. The method of any one of claims 43—47, wherein the patient has received at least one pre-treatment administration of methotrexate.~~

~~49. — The method of any one of claims 43 — 48, wherein the patient has received at least one pre-treatment administration of a TNF α antagonist.~~

~~50. — The method of claim 49, wherein the TNF α antagonist is selected from the group consisting of etanercept, adalimumab, infliximab, certolizumab, and golimumab.~~

~~51. — The method of any one of claims 43 — 47, wherein the patient has received at least one pre-treatment administration of an IL-6 antagonist.~~

~~52. — The method of claim 51, wherein the pre-treatment IL-6 antagonist is tocilizumab.~~

~~53. — The method of claim 51, wherein the pre-treatment IL-6 antagonist is tofacitinib.~~

~~54. — The method of any one of claims 51 — 53, wherein the treatment IL-6 antagonist is MEDI5117.~~

~~55. — The method of claim 42, wherein the chronic inflammatory disease is selected from the group consisting of juvenile idiopathic arthritis, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, inflammatory bowel disease, Crohn's disease, and ulcerative colitis.~~

~~56. — The method of any one of claims 6 — 34, wherein the chronic disease is cancer.~~

~~57. — The method of claim 56, wherein the cancer is selected from the group consisting of: solid tumors, small cell lung cancer, non-small cell lung cancer, hematological cancer, multiple myeloma, leukemias, chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), lymphomas, Hodgkin's lymphoma and hepatic adenoma.~~

~~58. — The method of any one of claims 6 — 34, wherein the chronic disease is a chronic infection.~~

~~59. The method of any one of claims 6—34, wherein the chronic disease is congestive heart failure (CHF).~~

~~60. The method of any one of claims 1—5, wherein the hepcidin-mediated disorder is iron-refractory iron-deficiency anemia (IRIDA).~~

~~61. The method of any one of claims 1—5, wherein the hepcidin-mediated disorder is acute coronary syndrome.~~

~~62. The method of claim 61, wherein the patient has suffered a myocardial infarction (MI) within the 60 days preceding the first administration of an IL-6 antagonist.~~

~~63. The method of claim 62, wherein the patient has suffered an MI within the 30 days preceding the first administration of an IL-6 antagonist.~~

~~64. The method of claim 63, wherein the patient has suffered an MI within the 48 hours preceding the first administration of an IL-6 antagonist.~~

~~65. The method of claim 64, wherein the patient has suffered an MI within the 24 hours preceding the first administration of an IL-6 antagonist.~~

~~66. The method of any one of claims 61—65, wherein the IL-6 antagonist is administered at a dose, on a schedule, and for a period sufficient to improve myocardial contractility as compared to pre-treatment levels.~~

~~67. The method of any one of claims 61—66, wherein the IL-6 antagonist is administered at dose, on a schedule, and for a period sufficient to improve cardiac ejection fraction as compared to pre-treatment levels.~~

~~68. The method of any one of claims 61—67, wherein the IL-6 antagonist is administered at dose, on a schedule, and for a period sufficient to reduce cardiac fibrosis as compared to pre-treatment levels.~~

~~69. The method of any one of claims 1—5, wherein the hepcidin-mediated disorder is Castleman's Disease.~~

~~70. — A method for improving treatment of a hepcidin-mediated disorder, the method comprising:~~

~~discontinuing administration of an IL-6 antagonist to a patient with a hepcidin-mediated disorder,~~

~~wherein the patient has been determined to be homozygous for the *TMPRSS6*-rs855791 minor allele.~~

~~71. — The method of claim 70, wherein the patient has previously been determined to be homozygous for the *TMPRSS6*-rs855791 minor allele.~~

~~72. — The method of claim 70, further comprising the earlier step of determining that the patient is homozygous for the *TMPRSS6*-rs855791 minor allele.~~

~~73. — A method of treating an IL-6 mediated inflammatory disorder in a patient without anemia of chronic inflammation, comprising:~~

~~administering a therapeutically effective amount of an IL-6 antagonist to a patient with an IL-6 mediated inflammatory disorder without anemia,~~

~~wherein the patient has been determined to have at least one copy of the *TMPRSS6*-rs855791 major allele.~~

~~74. — The method of claim 73, wherein the patient has previously been determined to have at least one copy of the *TMPRSS6*-rs855791 major allele.~~

~~75. — The method of claim 73, further comprising the earlier step of determining that the patient has at least one copy of the *TMPRSS6*-rs855791 major allele.~~

~~76. — The method of any one of claims 1—75, wherein the patient has elevated pre-treatment serum levels of IL-6.~~

~~77. — The method of claim 76, wherein the patient has a pre-treatment serum IL-6 level of greater than 2.5 pg/ml.~~

~~78. — The method of claim 77, wherein the patient has a pre-treatment serum IL-6 level of greater than 5 pg/ml.~~

~~79. The method of claim 78, wherein the patient has a pre-treatment serum IL-6 level of greater than 7.5 pg/ml.~~

~~80. The method of claim 79, wherein the patient has a pre-treatment serum IL-6 level of greater than 10 pg/ml.~~

~~81. The method of claim 80, wherein the patient has a pre-treatment serum IL-6 level of greater than 12.5 pg/ml.~~

~~82. The method of any one of claims 76—81, wherein the IL-6 antagonist is administered at a dose, on a schedule, and for a period sufficient to reduce the free IL-6 levels in the patient's serum below pre-treatment levels.~~

~~83. The method of claim 82, wherein the IL-6 antagonist is administered at a dose, on a schedule, and for a period sufficient to reduce the free IL-6 levels by at least 10% as compared to pre-treatment levels.~~

~~84. The method of claim 83, wherein the IL-6 antagonist is administered at a dose, on a schedule, and for a period sufficient to reduce the free IL-6 levels in the patient's serum by at least 20% as compared to pre-treatment levels.~~

~~85. The method of claim 84, wherein the IL-6 antagonist is administered at a dose, on a schedule, and for a period sufficient to reduce the free IL-6 levels in the patient's serum by at least 50% as compared to pre-treatment levels.~~

~~86. The method of any one of claims 1—85, wherein the patient has elevated pre-treatment levels of C-reactive protein (CRP).~~

10. The use of claim 3, wherein the inflammation in the subject is characterized by elevated levels of serum IL-6 and/or CRP relative to a reference level.

11. The use of claim 3, wherein the therapeutically effective amount of the anti-IL-6 antibody is an amount effective to neutralize inflammation.

87.12. The ~~method use~~ of claim 86 3, wherein the ~~patient~~ subject has a pre-treatment CRP level greater than 2 mg/ml.

88. — The method of claim 87, wherein the patient has a pre-treatment CRP level of ~~greater than 3 mg/ml.~~

89. — The method of claim 88, wherein the patient has a pre-treatment CRP level of ~~greater than 5 mg/ml.~~

90. — The method of claim 89, wherein the patient has a pre-treatment CRP level of ~~greater than 7.5 mg/ml.~~

91. — The method of claim 90, wherein the patient has a pre-treatment CRP level of ~~greater than 10 mg/ml.~~

92.13. The ~~method use~~ of ~~any one of claims 86 — 91~~ claim 3, wherein the ~~IL-6 antagonist medicament is to be~~ administered at a dose, on a schedule, and for a period sufficient to reduce the ~~patient's~~ subject's CRP levels below pre-treatment levels.

93.14. The ~~method use~~ of claim 92 13, wherein the ~~IL-6 antagonist medicament is to be~~ administered at a dose, on a schedule, and for a period sufficient to reduce the ~~patient's~~ subject's CRP levels by at least ~~50%~~ 50 percent as compared to pre-treatment levels.

94. — The method of any one of claims 1 — 93, wherein the patient has been determined to have at least one copy of the *TMPRSS6* rs855791 major allele using a TaqMan® real time PCR assay.

95. — The method of any one of claims 1 — 94, wherein the IL-6 antagonist is an anti-IL-6 antibody, or antigen-binding fragment or derivative thereof.

96. — The method of claim 95, wherein the anti-IL-6 antibody or antigen-binding fragment or derivative has a K_D for binding human IL-6 of less than 100 nM.

97. — The method of claim 96, wherein the antibody or antigen-binding fragment or derivative has a K_D for binding human IL-6 of less than 50 nM.

~~98. The method of claim 97, wherein the antibody or antigen binding fragment or derivative has a K_D for binding human IL-6 of less than 10 nM.~~

~~99. The method of claim 98, wherein the antibody or antigen binding fragment or derivative has a K_D for binding human IL-6 of less than 1 nM.~~

~~100. The method of any one of claims 95—99, wherein the anti-IL-6 antibody or antigen binding fragment or derivative has an elimination half life following intravenous administration of at least 7 days.~~

~~101. The method of claim 100, wherein the anti-IL-6 antibody or antigen binding fragment or derivative has an elimination half life following intravenous administration of at least 14 days.~~

~~102. The method of claim 101, wherein the anti-IL-6 antibody or antigen binding fragment or derivative has an elimination half life following intravenous administration of at least 21 days.~~

~~103. The method of claim 102, wherein the anti-IL-6 antibody or antigen binding fragment or derivative has an elimination half life following intravenous administration of at least 30 days.~~

~~104. The method of any one of claims 95—103, wherein the IL-6 antagonist is a full length monoclonal anti-IL-6 antibody.~~

~~105. The method of claim 104, wherein the antibody is an IgG1 or IgG4 antibody.~~

~~106. The method of claim 105, wherein the antibody is an IgG1 antibody.~~

~~107. The method of any one of claims 95—106, wherein the anti-IL-6 antibody or antigen binding fragment or derivative is fully human.~~

~~108. The method of any one of claims 95—106, wherein the anti-IL-6 antibody or antigen binding fragment or derivative is humanized.~~

~~109.15.~~ The ~~method use~~ of ~~any one of claims 95—108~~ claim 1, wherein the anti-IL-6 antibody ~~or antigen-binding fragment or derivative~~ comprises all six variable region CDRs of MED5117.

~~110.16.~~ The ~~method use~~ of claim ~~109~~ 15, wherein the anti-IL-6 antibody comprises the VH and VL of MED5117.

~~111.17.~~ The ~~method use~~ of claim ~~110~~ 16, wherein the anti-IL-6 antibody is MED5117.

18. The use of claim 17, wherein the cardiovascular disease is atherosclerosis and inflammatory;

wherein the subject has chronic kidney disease selected from KDOQI stage 3 chronic kidney disease, KDOQI stage 4 chronic kidney disease and KDOQI stage 5 chronic kidney disease;

wherein the subject has a pre-treatment CRP level greater than 2 mg/L; and

wherein the medicament is to be administered at a dose, on a schedule, and for a period sufficient to reduce the subject's CRP levels by at least 50 percent as compared to pre-treatment levels.

~~112.—The method of any one of claims 95—108, wherein the anti-IL-6 antibody or antigen-binding fragment or derivative comprises all six variable region CDRs of an antibody selected from the group consisting of siltuximab, gerilimumab, sirukumab, elazakizumab, olokizumab, elsilimomab, VX30 (VOP R003; Vaccinex), EB-007 (EBI-029; Eleven Bio), ARGX-109 (ArGEN X), FM101 (Femta Pharmaceuticals, Lonza) and ALD518/BMS-945429 (Alder Biopharmaceuticals, Bristol Myers Squibb).~~

~~113.—The method of claim 112, wherein the anti-IL-6 antibody or antigen-binding fragment or derivative comprises the heavy chain V-region and light chain V-region from an antibody selected from the group consisting of siltuximab, gerilimumab, sirukumab, elazakizumab, olokizumab, VX30 (VOP R003; Vaccinex), EB-007 (EBI-029; Eleven Bio), ARGX-109 (ArGEN X), FM101 (Femta Pharmaceuticals, Lonza) and ALD518/BMS-945429 (Alder Biopharmaceuticals, Bristol Myers Squibb). In particular embodiments, the anti-IL-6 antibody is an antibody selected from the group consisting of siltuximab,~~

~~gerilimzumab, sirukumab, elazakizumab, olokizumab, VX30 (VOP-R003; Vaccinex), EB-007 (EBI-029; Eleven Bio), ARGX-109 (ArGEN X), FM101 (Femta Pharmaceuticals, Lonza) and ALD518/BMS-945429 (Alder Biopharmaceuticals, Bristol Myers Squibb).~~

~~114. The method of claim 113, wherein the anti IL-6 antibody or antigen-binding fragment or derivative is an antibody selected from the group consisting of siltuximab, gerilimzumab, sirukumab, elazakizumab, olokizumab, VX30 (VOP-R003; Vaccinex), EB-007 (EBI-029; Eleven Bio), ARGX-109 (ArGEN X), FM101 (Femta Pharmaceuticals, Lonza) and ALD518/BMS-945429 (Alder Biopharmaceuticals, Bristol Myers Squibb). In particular embodiments, the anti IL-6 antibody is an antibody selected from the group consisting of siltuximab, gerilimzumab, sirukumab, elazakizumab, olokizumab, VX30 (VOP-R003; Vaccinex), EB-007 (EBI-029; Eleven Bio), ARGX-109 (ArGEN X), FM101 (Femta Pharmaceuticals, Lonza) and ALD518/BMS-945429 (Alder Biopharmaceuticals, Bristol Myers Squibb).~~

~~115. The method of any one of claims 95-103, wherein the IL-6 antagonist is a single domain antibody, a VHH Nanobody, an Fab, or a scFv.~~

~~116. The method of any one of claims 1-94, wherein the IL-6 antagonist is an anti-IL-6R antibody, or antigen-binding fragment or derivative thereof.~~

~~117. The method of claim 116, wherein the anti-IL-6R antibody, antigen-binding fragment, or derivative is tocilizumab.~~

~~118. The method of claim 116, wherein the anti-IL-6R antibody, antigen-binding fragment, or derivative is vobarilizumab.~~

~~119. The method of any one of claims 1-94, wherein the IL-6 antagonist is a JAK-inhibitor.~~

~~120. The method of claim 119, wherein the JAK inhibitor is selected from the group consisting of tofacitinib (Xeljanz), decernotinib, ruxolitinib, upadacitinib, baricitinib, filgotinib, lestaurtinib, pacritinib, peficitinib, INCB-039110, ABT-494, INCB-047986 and AC-410.~~

~~121. The method of any one of claims 1—94, wherein the IL-6 antagonist is a STAT3 inhibitor.~~

~~122. The method of any one of claims 95—118, wherein the IL-6 antagonist is administered parenterally.~~

~~123. The method of claim 122, wherein the IL-6 antagonist is administered subcutaneously.~~

~~124. The method of any one of claims 119—120, wherein the IL-6 antagonist is administered orally.~~