

CLAIMS

What is claimed is:

1. An isolated antibody or antigen-binding fragment thereof that binds specifically to Transmembrane Protease Serine 6 (TMPRSS6) protein, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR); and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR); and

wherein the three heavy chain CDRs and three light chain CDRs comprise either one of the following sets of CDRs:

- (i) SEQ ID NO: 102 (HCDR1), SEQ ID NO:104 (HCDR2), SEQ ID NO:106 (HCDR3), SEQ ID NO:110 (LCDR1), SEQ ID NO:14 (LCDR2), and SEQ ID NO:112 (LCDR3); or
- (ii) SEQ ID NO: 44 (HCDR1), SEQ ID NO:46 (HCDR2), SEQ ID NO:48 (HCDR3), SEQ ID NO:52 (LCDR1), SEQ ID NO:54 (LCDR2), and SEQ ID NO:56 (LCDR3).

2. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein said antibody or antigen-binding fragment thereof binds to the catalytic domain of TMPRSS6 but does not bind to the catalytic triad of TMPRSS6.

3. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the three heavy chain CDRs and three light chain CDRs comprise the set of CDRs defined in (i), and wherein the antibody or antigen-binding fragment maintains TMPRSS6 in an inactive conformation that is capable of binding to but not cleaving a TMPRSS6 substrate.

4. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the three heavy chain CDRs and three light chain CDRs comprise the set of CDRs defined in (ii), wherein the antibody or antigen-binding fragment thereof competes with a TMPRSS6 substrate for binding to TMPRSS6.

5. The isolated antibody or antigen-binding fragment thereof of claim 3 or claim 4, wherein the TMPRSS6 substrate is hemojuvelin (HJV).

6. The antibody or antigen-binding fragment thereof of claim 1, wherein the three heavy chain CDRs and three light chain CDRs comprise the set of CDRs defined in (i), and wherein the antibody or antigen-binding fragment comprises the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 100/108.

7. The antibody or antigen-binding fragment thereof of claim 1, wherein the three heavy chain CDRs and three light chain CDRs comprise the set of CDRs defined in (i), and wherein the antibody or antigen-binding fragment comprises the HC/LC amino acid sequence pair of SEQ ID NOs: 114/116.

8. The antibody or antigen-binding fragment thereof of claim 1, wherein the three heavy chain CDRs and three light chain CDRs comprise the set of CDRs defined in (ii), and wherein the antibody or antigen-binding fragment comprises the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 42/50.

9. The antibody or antigen-binding fragment thereof of claim 1, wherein the three heavy chain CDRs and three light chain CDRs comprise the set of CDRs defined in (ii), and wherein the antibody or antigen-binding fragment comprises the HC/LC amino acid sequence pair of SEQ ID NOs: 58/60.

10. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody has one or more properties selected from:

(a) is a fully human monoclonal antibody;

- (b) binds to human TMPRSS6 at 25°C and at 37°C with a dissociation constant (K_D) of less than 21.2 nM, as measured in a surface plasmon resonance assay;
- (c) binds to monkey TMPRSS6 at 25°C and at 37°C with a K_D of less than 25.7 nM, as measured in a surface plasmon resonance assay;
- (d) binds to mouse TMPRSS6 at 25°C and at 37°C with a K_D of less than 703 nM, as measured in a surface plasmon resonance assay;
- (e) binds to cells expressing human TMPRSS6 with EC_{50} less than 2.7 nM;
- (f) binds to cells expressing monkey TMPRSS6 with EC_{50} less than 3.6 nM;
- (g) binds to cells expressing mouse TMPRSS6 with EC_{50} less than 35 nM;
- (h) inhibits protease-dependent release of cell surface hemojuvelin in the presence of human TMPRSS6, with percent inhibition greater than 90%;
- (i) inhibits protease-dependent release of cell surface hemojuvelin in the presence of human TMPRSS6, and exhibits an IC_{50} less than 200 pM;
- (j) inhibits protease-dependent release of cell surface hemojuvelin in the presence of mouse TMPRSS6, with percent inhibition greater than 42%;
- (k) inhibits protease-dependent release of cell surface hemojuvelin in the presence of mouse TMPRSS6, and exhibits an IC_{50} less than 274 pM;
- (l) inhibits human TMPRSS6 at 25°C and at 37°C with percent inhibition greater than 65%;
- (m) inhibits human TMPRSS6 at 25°C and at 37°C and exhibits an IC_{50} less than 10 nM;
- (n) inhibits monkey TMPRSS6 at 25°C and at 37°C with percent inhibition greater than 66%;
- (o) inhibits monkey TMPRSS6 at 25°C and at 37°C and exhibits an IC_{50} less than 50 nM;
- (p) inhibits mouse TMPRSS6 at 25°C and at 37°C with percent inhibition greater than 58%;
- (q) inhibits mouse TMPRSS6 at 25°C and at 37°C and exhibits an IC_{50} less than 35 nM;
- (r) when to be administered to a subject in need thereof, decreases serum iron levels of the subject;
- (s) when to be administered to a subject in need thereof, increases serum hepcidin levels of the subject;
- (t) when to be administered to a subject in need thereof, increases mature red blood cell

levels of the subject;

(u) when to be administered to a subject in need thereof, increases mature red blood cell levels in the spleen and/or bone marrow of the subject;

(v) when to be administered to a subject in need thereof, increases hemoglobin levels of the subject; or

(w) when to be administered to a subject in need thereof, decreases transferrin saturation levels of the subject.

11. A pharmaceutical composition comprising an isolated antibody or antigen-binding fragment thereof that binds to TMPRSS6 according to any one of claims 1 to 10 and a pharmaceutically acceptable carrier or diluent.

12. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a HCVR and a LCVR of an antibody or antigen-binding fragment thereof as set forth in any one of claims 1 to 9.

13. A host cell comprising the polynucleotide molecule of claim 12.

14. A method of producing an antibody or antigen-binding fragment thereof that binds specifically to TMPRSS6, comprising culturing the host cell of claim 13 under conditions permitting production of the antibody or antigen-binding fragment thereof, and recovering the antibody or antigen-binding fragment thereof so produced.

15. The method of claim 14, further comprising formulating the antibody or antigen-binding fragment thereof as a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

16. Use of a therapeutically effective amount of an antibody or antigen-binding fragment thereof of any one of claims 1 to 81 in the manufacture of a pharmaceutical composition for treating, preventing, or ameliorating a disease or disorder associated with iron overload in a subject in need thereof, wherein the disease is selected from: a congenital

dyserythropoeitic anemia, Diamond-Blackfan anemia, alpha thalassemia, beta thalassemia, a transfusion-dependent hemolytic anemia, myelodysplastic syndrome, sickle cell disease, polycythemia vera, hereditary hemochromatosis, or chronic liver disease.

17. The use according to claim 16, wherein the disease or disorder is beta thalassemia.