

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 binds to the catalytic domain of TMPRSS6 but does not bind to the catalytic triad of TMPRSS6.

2. The isolated antibody or antigen-binding fragment thereof of claim 1, 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.

3. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the TMPRSS6 substrate is hemojuvelin (HJV).

4. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof competes with hemojuvelin (HHV) for binding to TMPRSS6.

5. 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), wherein the HCDR3 has an amino acid sequence selected from a HCDR3 sequence listed in Table 1.

6. The antibody or antigen-binding fragment thereof of claim 5, wherein:
(a) the HCDR1 domain has an amino acid sequence selected from SEQ ID NOs: 4, 24, 34, 44, 64, 84, or 102;

- (b) the HCDR2 domain has an amino acid sequence selected from SEQ ID NOs: 6, 26, 36, 46, 66, 86, or 104;
- (c) the HCDR3 domain has an amino acid sequence selected from SEQ ID NOs: 8, 28, 38, 48, 68, 88, or 106;
- (d) the LCDR1 domain has an amino acid sequence selected from SEQ ID NOs: 12, 52, 72, 92, or 110;
- (e) the LCDR2 domain has an amino acid sequence selected from SEQ ID NOs: 14, 54, or 74; and
- (f) the LCDR3 domain has an amino acid sequence selected from SEQ ID NOs: 16, 56, 76, 94, or 112.

7. The antibody or antigen-binding fragment thereof of claim 5, wherein the three heavy chain CDRs and three light chain CDRs comprise one of the following sets of CDRs:

- (a) SEQ ID NO: 4 (HCDR1), SEQ ID NO:6 (HCDR2), SEQ ID NO:8 (HCDR3), SEQ ID NO:12 (LCDR1), SEQ ID NO:14 (LCDR2), and SEQ ID NO:16 (LCDR3);
- (b) SEQ ID NO: 24 (HCDR1), SEQ ID NO:26 (HCDR2), SEQ ID NO:28 (HCDR3), SEQ ID NO:12 (LCDR1), SEQ ID NO:14 (LCDR2), and SEQ ID NO:16 (LCDR3);
- (c) SEQ ID NO: 34 (HCDR1), SEQ ID NO:36 (HCDR2), SEQ ID NO:38 (HCDR3), SEQ ID NO:12 (LCDR1), SEQ ID NO:14 (LCDR2), and SEQ ID NO:16 (LCDR3);
- (d) 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);
- (e) SEQ ID NO: 64 (HCDR1), SEQ ID NO:66 (HCDR2), SEQ ID NO:68 (HCDR3), SEQ ID NO:72 (LCDR1), SEQ ID NO:74 (LCDR2), and SEQ ID NO:76 (LCDR3);
- (f) SEQ ID NO: 84 (HCDR1), SEQ ID NO:86 (HCDR2), SEQ ID NO:88 (HCDR3), SEQ ID NO:92 (LCDR1), SEQ ID NO:14 (LCDR2), and SEQ ID NO:94 (LCDR3); or
- (g) 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).

8. The antibody or antigen-binding fragment thereof of claim 7, wherein the three heavy chain CDRs and three light chain CDRs comprise the following set of CDRs:

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).

9. The antibody or antigen-binding fragment thereof of claim 5 comprising the
HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 100/108.

10. The antibody or antigen-binding fragment thereof of claim 5, comprising the
HC/LC amino acid sequence pair of 114/116.

11. 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 about 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 about 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 about 703 nM, as measured in a surface plasmon resonance assay;
- (e) binds to cells expressing human TMPRSS6 with EC_{50} less than about 2.7 nM;
- (f) binds to cells expressing monkey TMPRSS6 with EC_{50} less than about 3.6 nM;
- (g) binds to cells expressing mouse TMPRSS6 with EC_{50} less than about 35 nM;
- (h) inhibits protease-dependent release of cell surface hemojuvelin in the presence of human TMPRSS6, e.g., inhibits human TMPRSS6, with percent inhibition greater than about 90%;
- (i) inhibits protease-dependent release of cell surface hemojuvelin in the presence of human TMPRSS6, e.g., inhibits human TMPRSS6 and exhibits an IC_{50} less than about 200 pM;
- (j) inhibits protease-dependent release of cell surface hemojuvelin in the presence of mouse TMPRSS6, e.g., inhibits mouse TMPRSS6, with percent inhibition greater than about 42%;
- (k) inhibits protease-dependent release of cell surface hemojuvelin in the presence of mouse TMPRSS6, e.g., inhibits mouse TMPRSS6 and exhibits an IC_{50} less than about 274 pM;

(l) inhibits human TMPRSS6 at 25°C and at 37°C with percent inhibition greater than about 65%;

(m) inhibits human TMPRSS6 at 25°C and at 37°C and exhibits an IC₅₀ less than about 10 nM;

(n) inhibits monkey TMPRSS6 at 25°C and at 37°C with percent inhibition greater than about 66%;

(o) inhibits monkey TMPRSS6 at 25°C and at 37°C and exhibits an IC₅₀ less than about 50 nM;

(p) inhibits mouse TMPRSS6 at 25°C and at 37°C with percent inhibition greater than about 58%;

(q) inhibits mouse TMPRSS6 at 25°C and at 37°C and exhibits an IC₅₀ less than about 35 nM;

(r) when administered to a subject in need thereof, decreases serum iron levels of the subject;

(s) when administered to a subject in need thereof, increases serum hepcidin levels of the subject;

(t) when administered to a subject in need thereof, increases mature red blood cell levels of the subject;

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

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

12. A pharmaceutical composition comprising an isolated antibody or antigen-binding fragment thereof that binds to TMPRSS6 according to claim 1 and a pharmaceutically acceptable carrier or diluent.

13. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a HCVR or a LCVR of an antibody or antigen-binding fragment thereof as set forth in claim 5.

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

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

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

17. Use of a therapeutically effective amount of an antibody or antigen-binding fragment thereof of claim 1 in the manufacture of a pharmaceutical composition for treating, preventing, or ameliorating at least one symptom or indication of a disease or disorder associated with iron overload in a subject in need thereof.

18. The use according to claim 17, wherein the disease or disorder is a congenital dyserythropoietic 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.

19. The use according to claim 18, wherein the disease or disorder is beta thalassemia.